CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-541/S-006

MEDICAL REVIEWS

SNDA MEDICAL REVIEW

NDA #: 20-541

ARIMIDEX

Applicant: Zeneca Pharmaceuticals

Date Submitted: November 01, 1999

MEDICAL OFFICER REVIEW OF A SNDA

Title

Anastrozole is indicated for the first -line treatment of advanced breast cancer in postmenopausal women

1.0 General Information

1.1.1	**NDA #**	20-541/S006
1.1.2	**Medical Reviewer**	Oluwole O. Odujinrin MD
1.1.3	**Submission (date):**	November 01,1999
1.1.4	**Review completed**	August 29, 2000

1.2 **Drug name**

1.2.1	Generic name	ARIMIDEX
1.2.2	Proposed trade name	ANASTROZOLE
1.2.3	Chemical name	1,3-Benzenediacetonitrile, α, α, α', α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)
1.2.4	Molecular formula	$C_{17}H_{19}N_5$
1.2.5	Molecular weight	293.4

1.3 **Sponsor**

Zeneca Pharmaceuticals
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

1.4 **Pharmacologic Category** Aromatase inhibitor

1.5 **Proposed Indication**

Anastrozole is indicated for the first line treatment of advanced breast cancer in postmenopausal women

1.6 **Dosage Form(s) and Route(s) of Administration**

Anastrozole is supplied as a 1mg tablet for once daily oral dosage. Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethyleneglycol, povidone, sodium starch glycolate, and titanium dioxide.

1.7 **NDA Drug Classification**

Standard

1.8 **Important Related Drugs**

Letrozole
Aromasin (exemestine)

1.9 **Related INDS AND NDAS**

IND filed on 1 April 1992 for ZD1033 (ARIMIDEX TM) filed by Zeneca Inc, Wilmington, DE, for treatment of advanced breast cancer.

NDA (20-541) filed on 28 March 1995 for Anastrozole (ZD1033, ARIMIDEX TM) by Zeneca Inc, Wilmington, Delaware, for the treatment of advanced breast cancer. Anastrozole was approved for marketing on 27 December 1995.

1.10 **Foreign Marketing:**

Anastrozole is marketed in 77 countries

2.0 Table of Contents

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

3.0 Material Reviewed /Clinical Data Sources/Administrative Review

3.1 Sources

3.1.1 sNDA submissions

The sNDA was submitted on November 1, 1999 and consisted of a combination of paper and electronic documentation:
11 volumes (Volumes 6.1 to 6.11)
2 CD-ROMs
1 CD-ROM, ISO 9660 format representing Volumes 6.12 to 6.62.
1-CD ROM, .ISO 9660 format 4 Month Safety Update Report Submitted Feb.18, 2000

3.1.1.1 Key volume numbers

sNDA report item	VOLUME
Detailed index to the application	6.1
Label -Nonannotated	6.1
Summaries:	
Label -Annotated	6.2
Pharmacology	6.2
Foreign Marketing History	6.2
CMC	6.3
Clinical Trial Formula	6.3
Chemistry	
Non Clinical pharmacology and Toxicology	6.4
Human pharmacolokinetics /Bioavailability	6.5
Clinical Data	6.12-6.59
Case Report Tabulations (Data Sets)	6.61
Case Report Forms (for deaths and withdrawals)	6.62

3.1.2

FDA-Adverse Reporting System (AERS), Statistical Summary Report on Arimidex

3.2 Administrative review

3.2.1 FDA and Sponsor (Zeneca) discussions

There were several contacts between Zeneca and the FDA regarding the submission. These contacts included 2 meetings (teleconferences), and many telephone and written communications. A summary of the major contacts and agreements is presented below.

26 January 1996. The FDA accepted the clinical trial program presented by Zeneca to evaluate the efficacy and tolerability of anastrozole 1 mg daily versus tamoxifen 20 mg

daily in the first-line treatment of advanced breast cancer in postmenopausal women. Based on FDA comments, the protocols for Trials 0030 and 0027 were amended to reflect the following criteria:

- For time to progression, the lower 1-sided 95% confidence limit for the tamoxifen:anastrozole hazard ratio should be 0.8 or greater to demonstrate equivalence.
- For objective response, the lower one-sided 95% confidence limit for the difference in response rates (anastrozole-tamoxifen) should be -10% or greater to demonstrate equivalence.
- The definition of objective response should include complete and partial responses only.
- The number of patients with stable disease for 24 or more weeks should be described
- separately.
- The number of patients considered to experience clinical benefit should comprise those who achieve an objective response, and those who have stable disease for 24 or more weeks.
- The same criteria for complete response should be used for all patients.

6 October 1997 and 29 January 1998
Because of recruitment difficulties in Trial 0030, the FDA and Zeneca agreed that recruitment in both trials could be stopped when Trial 0027 had achieved the target recruitment of 660 patients. It was also agreed that data from each trial would be analyzed independently. The FDA indicated that the results obtained from the 2 trials should be supportive of each other, and that a combined analysis of the data would be accepted if the statistical validity of doing so could be demonstrated. The Agency agreed that the first-line Supplemental New Drug Application (sNDA) would not include adjuvant data from Trial 0029 (ATAC)

3 August 1998, data from trials of anastrozole as second-line therapy for advanced breast cancer, or data from patients receiving anastrozole on a 'compassionate-use' or 'named-patient' basis

9 February 1999. It was agreed that serious post-marketing adverse events would be summarized in the sNDA, and any clinically significant difference in safety profile between the second- and first-line program would be discussed in the Integrated Summary of Safety Information (ISS).

3.2.2 Protocol amendments to Trial 0030

During the conduct of the first-line clinical trial program, 3 protocol amendments to Trial 0030 were submitted to the IND.

27 August 1996 (Serial No. 100). The first protocol amendment was submitted to the FDA. This incorporated the following FDA comments:

- increase the total number of patients to 660;

- include a new statistical section;
- include objective response rate as a primary, rather than secondary, end point,
- "hormonal treatment" should replace 'tamoxifen treatment' as a covariate in the statistical models.

2 March 1998 (Serial No. 155). The second protocol amendment allowed the use of concomitant bisphosphonate therapy.

17 July 1998 (Serial No. 167) The third protocol amendment added clarification to the statistical methods. The changes included the addition of 2 interpretations of duration of response; duration of clinical benefit as a secondary end point; and, age as covariate in the statistical models.

3.2.3 Pre-NDA meetings (20 May 1999 and 12 August 1999)

5 March 1999 (Serial No. 211) a Briefing Document was submitted to the FDA. This document described the content of the sNDA, and the proposed format of the electronic submission.

23 July 1999, a second Briefing Document (Serial No. 240) provided a summary of the statistical and safety results from Trials 0030 and 0027. On the basis of these documents, a statistical teleconference and several communications (dated 25 May 1999 [Serial No. 229], 4 June 1999, 9 August 1999, 10 August 1999 [Serial No. 243], and 11 August 1999), the FDA indicated that the data from the first-line clinical program supported the submission of a sNDA.

The relevant agreements are highlighted below.

- Human Pharmacokinetics and Bioavailability section:
- The review copy will consist of a paper copy of the Human Pharmacokinetics and Bioavailability (HPB) section, and a PDF file containing the trial reports, and a summary of the tables and figures. The FDA agreed that the tamoxifen bioequivalence trial results (Trial 6157/002) could be submitted within 60 days of the review period.
- Outlines for the Integrated Summaries of Effectiveness Data and Safety Information:
- The FDA considered the outlines for the Integrated Summary of Effectiveness Data (ISE) and ISS acceptable. Zeneca agreed to clarify in the sNDA the term 'advanced' and to identify for review the patients with Stage III disease.
- Case report forms and tabulations
- Case report forms (CRFs) will be provided for all deaths occurring within 30 days of trial treatment. Zeneca will provide CRFs for all patients that withdrew from the trials as a result of an adverse event occurring either during, or 14 days after stopping, trial treatment. For the small trials (A-15-12, 0032 and 1033NY/0001) only CRF tabulations describing demography and adverse events will be provided.
- Electronic submission:
- It was agreed that Zeneca would refer to the January 1999 FDA guidance for industry ('Providing regulatory Submissions in Electronic Format-NDAs') for the preparation of Items 1,8, 10, 11 and 12 in electronic format for archival purposes. In addition, the FDA requested a paper copy of the trial reports (including tables and protocols) for the 2 pivotal trials, the annotated labels and CRFs from each of these trials, data sets and the SAS programming codes for the efficacy analyses.

4.0 Chemistry/Manufacturing Controls

The composition, manufacturing formula , specifications and test methods for Arimidex 1 mg commercial tablet is as previously described in NDA 20-541. For additional information, please see the Chemistry review by S.Kim Ph.D and Biopharmaceutics review .

5.0 Animal Pharmacology/Toxicology

Please see Pharmacology /Toxicology review by Margaret Brower Ph.D

6.0 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Arimidex is a selective non-steroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol levels has been shown to produce a beneficial effect in women with breast cancer. In postmenopausal women, Arimidex at a daily dose of 1 mg produced estradiol suppression c

Arimidex does not possess progestogenic, androgenic or estrogenic activity. Daily doses of Arimidex up to 10 mg do demonstrate no effect on cortisol or aldosterone secretion, measured before or after standard ACTH challenge testing. Corticoid supplements therefore do not appear to be needed.

Pharmacokinetic Properties

Absorption of anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions). Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Food slightly decreases the rate but not the extent of absorption. The small change in the rate of absorption is not expected to result in a clinically significant effect on steady-state plasma concentrations during once daily dosing of Arimidex tablets. Approximately 90 to 95% of plasma anastrozole steady-state concentrations are attained after 7 daily doses. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Pharmacokinetics have not been studied in children.

Anastrozole is only 40% bound to plasma proteins.

Anastrozole is extensively metabolized by postmenopausal women with less than 10% of the dose excreted in the urine unchanged within 72 hours of dosing. Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. The metabolites are excreted primarily via the urine. Triazole, a major metabolite in plasma and urine, does not inhibit aromatase.

The apparent oral clearance of anastrozole in volunteers with stable hepatic cirrhosis or renal impairment was in the range observed in healthy volunteers.

Toxicity

Acute toxicity

In acute toxicity studies in rodents the median lethal dose of anastrozole was greater than 100 mg/kg/day by the oral route and greater than 50 mg/kg/day by the intraperitoneal route.

Chronic toxicity

Multiple dose toxicity studies utilized rats and dogs. No no-effect levels were established for anastrozole in the toxicity studies, but those effects that were observed at the low dose (1mg/kg/day) and mid doses (dog 3 mg/kg/day; rat 5 mg/kg/day) were related to either the pharmacological or enzyme inducing properties of anastrozole, and were unaccompanied by toxic or degenerative changes.

Mutagenicity

Genetic toxicology studies with anastrozole show that it is not a mutagen or a clastogen.

Reproductive toxicology

Oral administration of anastrozole to pregnant rats and rabbits caused no teratogenic effects at doses up to 1.0 and 0.2 mg/kg/day respectively.

Those effects that were seen (placental enlargement in rats and pregnancy failure in rabbits) were related to the pharmacology of the compound.

Carcinogenicity

No carcinogenicity studies have been conducted using anastrozole.

Racial Differences

Additional clinical pharmacokinetic data were presented in this document supplemental to those in NDA 20-541. These studies further show that the pharmacokinetics of anastrozole are linear and that there are no differences in the pharmacokinetics and pharmacodynamics of anastrozole between Japanese and Western women.

Drug-Drug Interaction

Additionally, data from the anastrozole/warfarin interaction trial show that anastrozole has no clinically significant effect on the pharmacokinetics and pharmacodynamics of warfarin.

7.0 Summary of Clinical Studies

The sNDA submission was based on 2 principal studies, 1033IL/0030 and 1033IL/0027 which were combined into one report.

Trial title: A Randomized, Clinical phase: IIIb Double-blind, Double-dummy multicenter, multinational Trial to Compare the Efficacy and Safety of ARIMIDEX] (ZD1033 1 mg Daily) with Tamoxifen (20 mg Daily) as First-line Therapy for Advanced Breast Cancer in Postmenopausal Women (1033IL/0027)

OBJECTIVES

The primary objectives of this trial were to compare anastrozole with tamoxifen based on the following measures: time to progression, objective-response rate, and tolerability. The secondary objectives of this trial were to compare the 2 treatment groups based on the following measures: time to treatment failure, time to death (survival), duration of response, duration of clinical benefit, and health economics.

METHODS

Design: Patients were randomized according to one level of stratification: soft tissue and/or lung disease only(Stratum A), and all other disease combinations (Stratum B). Patients were given their randomized treatment until, in the opinion of the investigator, there was sufficient objective evidence of disease progression to stop treatment.

Population: A total of 668 postmenopausal women with advanced breast cancer entered this trial.

Key inclusion criteria: Postmenopausal women who had locally advanced or metastatic breast cancer and were eligible to be given first-line hormonal therapy; hormone receptor status (estrogen and/or progesterone receptor) positive or unknown; measurable or evaluable advanced disease; given informed consent to participate in the trial.

Key exclusion criteria: Previous systemic therapy for advanced breast cancer; drug-maintained menopausal status; relevant history of any severe concomitant disease (including life-threatening visceral disease); any significantly abnormal laboratory test at baseline that would have placed the patient at unusual risk or confound the trial results; history of systemic malignancy other than breast cancer (except basal cell/squamous cell carcinoma of the skin or cancer of the cervix which had been satisfactorily controlled); estimated survival time of less than 3 months from trial start; treatment with a non-approved or experimental drug in the 3 months preceding randomization; unlikely to comply with the trial requirements (eg, confused, infirm, alcoholics); considered to be at risk of transmitting any infection through blood or other body fluids.

Dosage: Patients were given once-daily oral doses of either anastrozole (1 mg) and tamoxifen placebo, or tamoxifen (20 mg) and anastrozole placebo. Treatment continued until disease progression, or until the patient withdrew from treatment for any other reason, in which case they were monitored for time to progression.

Key assessments:

Efficacy: Breast cancer history was recorded and disease state evaluated, this evaluation included identification and measurement of lesions to be monitored during treatment and

assessment of non-measurable disease.During treatment, patients were seen every 4 weeks for the first 24 weeks of trial treatment, every 12 weeks thereafter, and at the time of withdrawal (for any reason). The size of measurable lesions and changes in non-measurable disease were recorded. On the basis of these assessments, an overall objective response (complete response, partial response, stable disease, or disease progression) was assigned for each visit.

Safety: Physical examination findings, adverse events, and laboratory measurements were recorded throughout the trial. Assessments continued until disease progression was assigned (according to the investigator's opinion) irrespective of whether trial treatment was withdrawn. Safety assessments were continuous throughout the trial. After withdrawal of trial treatment, patients were monitored at 6-month intervals for survival until death. In addition, patients who were withdrawn from trial treatment because of an adverse event had tumor assessments every 3 months until disease progression. All adverse events that resulted in withdrawal were monitored until resolution; all adverse events that resulted in death were monitored until the patient died. evidence of disease progression to stop treatment.

RESULTS

Demography: A total of 668 patients from 83 centers world-wide entered the trial; 340 patients were randomized to receive anastrozole (1 mg) and 328 were randomized to receive tamoxifen (20 mg). Overall, the majority (91.3 %) of patients were Caucasian. The mean age for all patients was 66 years (range 34 to 92 years). After taking into account patients who were misallocated trial treatment and patients who did not receive any trial medication, 336 patients were given anastrozole and 329 patients were given tamoxifen. The withdrawal rates and reasons for withdrawal were similar between the 2 treatment groups (235/336 [69.9%] patients with anastrozole treatment and 241/329 [73.3%] patients with tamoxifen treatment). The majority (58.6%) of patients withdrew because of disease progression.

Efficacy: The 2 primary efficacy end points in this clinical trial were time to progression and objective-response rate.

Supportive and other Studies Conducted:

No other studies conducted by the sponsor were included in the report of this supplemental sNDA.

8.0 Clinical Study:

APPEARS THIS WAY
ON ORIGINAL

8.1. Protocol 1033IL/0027

8.1.1.1 RATIONALE

Estrogen manipulation is an established approach to the treatment of advanced breast cancer. Tamoxifen (NOLVADEX), an anti-estrogen that binds to estrogen receptors in tumor cells and blocks the action of estrogen, is considered to be the therapy of choice in most clinical situations requiring endocrine therapy to palliate advanced disease. However, depending on tissue, species, and menopausal status, tamoxifen can act as a partial estrogen-agonist..

The development of selective, potent, non-steroidal aromatase inhibitors may provide another option in the treatment of advanced breast cancer in post-menopausal women. These compounds function by blocking the peripheral conversion of androgens to estrogens, thus causing a fall in serum estradiol and estrone concentrations and depriving tumors of the stimulatory effects of estrogen.

Since anastrozole has no known intrinsic estrogenic activity, it is considered biologically plausible that the drug could be efficacious and well tolerated as a first-line treatment for advanced breast cancer. It could therefore serve as an alternative therapy to tamoxifen, if it can be demonstrated that it is at least as efficacious as tamoxifen

8.1.1.2 OBJECTIVES

The primary objectives of this trial were to compare anastrozole with tamoxifen as first line treatment of postmenopausal women with advanced breast cancer, based on the following measures:

- time to progression
- objective-response rate
- tolerability

The secondary objectives of this trial were to compare the 2 treatment groups based on the following measures:

- time to treatment failure
- time to death (survival)
- duration of response
- duration of clinical benefit

8.1.1.3 Design

A randomized, double-blind, double-dummy, multicenter trial. Patients were randomized in a 1:1 ratio to oral treatment with anastrozole (1 mg once daily) plus tamoxifen placebo, or tamoxifen (20 mg once daily) plus anastrozole placebo. Placebos were added to protect the double-blind because the anastrozole and tamoxifen tablets were not similar in appearance. Randomization of patients included one level of stratification: soft tissue and/or lung disease only (Stratum A) and all other disease combinations (Stratum B). For

patients with only locally advanced soft tissue disease, eligibility for inclusion in the trial was based on the investigator's assessment of the patient as unsuitable for treatment with radiotherapy or surgery.

8.1.2 Protocol amendments

There were four protocol amendments in these trials

- 8 December 1995: was a treatment crossover amendment that applied to Switzerland only. Once a patient had progressed, she could be entered into a treatment crossover trial (run by the Swiss Group for Clinical Cancer Research)
- 15 July 1996: allowed for an increase in patient enrolment from 426 to 660 patients
- 29 December 1997: allowed for concomitant treatment with bisphosphonates in those countries where this medication had been registered for the treatment of bone metastases related to breast cancer.
- 26 March 1998: allowed for statistical and clinical modifications, as well as changes in trial personnel.

8.1.3 Protocol

8.1.3.1 Population

The estimation of sample size was based on the primary efficacy end points of time to progression and objective-response rate. The trial was powered to demonstrate non inferiority, as defined by the confidence intervals, for each of these end points. 660 patients were randomized to treatment in this trial (330 in each treatment group). The first patient was recruited on 21 August 1995, and the last patient on 1 July 1998. The data cut-off date (the date on which the final patient visit data was generated for the analysis) was set at 10 March 1999. The database was locked 1 month after this data cut-off date with unblinding of the treatment groups only occurring after this lock had been performed. The minimum follow-up time was 8 months

8.1.3.2 Inclusion / Exclusion Criteria

Inclusion Criteria

Women with

1) histologic diagnosis of locally advanced or metastatic breast cancer
2) suitable candidates for hormonal therapy as first-line therapy for advanced disease (patients may have been given adjuvant chemotherapy or hormonal therapy, but patients who had been given tamoxifen as adjuvant therapy must have had an interval of at least 12 months between stopping tamoxifen treatment and entering this trial)
3) post-menopausal status, defined as:
   (i) women aged 50 years or over who have not menstruated during the preceding 12 months or who have follicle stimulating hormone (FSH) levels within the post-menopausal range;
   (ii) women under the age of 50 years who have FSH levels within the post-menopausal range

(4) hormone receptor status (estrogen receptor and/or progesterone receptor) positive or unknown
(5) measurable or evaluable disease
(6) informed consent for participation (documented preferably in writing although witnessed verbal consent was acceptable)
(7) WHO performance status score of 0,1, or 2

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the trial:
(1) previous systemic therapy for advanced breast cancer
(2) women who had drug-maintained menopausal status
(3) presence of life-threatening visceral disease, defined as:
  (i) extensive hepatic involvement;
  (ii) any degree of intra-cranial or leptomeningeal involvement;
  (iii) pulmonary lymphangitic spread (patients with small discrete pulmonary parenchymal metastases were eligible provided they were free of respiratory symptoms)
(4) history of systemic malignancy other than breast cancer with the exception of basal cell/squamous cell carcinoma of the skin or cancer of the cervix that had bee satisfactorily controlled and off therapy for >5years.
(5) estimated survival of less than 3 months from the start of trial therapy based on investigator's clinical judgement
(6) liver function tests (i.e, aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) greater than 3 times the upper limit of the reference range
(7) any other significantly abnormal laboratory test result at baseline that would place the patient at unusual risk or confound the results of the trial
(8) treatment with a non-approved or experimental drug within the preceding 3 months before randomization
(9) a relevant history of any severe concomitant disease that would place the patient at unusual risk or confound the results of the trial
(10) lack of compliance, for whatever reason with trial requirements (eg, confusion, infirmity, alcoholism),
(11) patients considered by the investigator to be at risk of transmitting any infection through blood or other body fluids including the agents for acquired-immune deficiency syndrome (AIDS) or other sexually transmitted disease or hepatitis
12). Any other systemic treatment for breast cancer.
13) Treatment with other drugs that affect sex-hormone status or breast cancer including estrogen hormone replacement therapy, concurrently or within 4 weeks before randomization.

8.1.3.3 Withdrawal criteria

Patients were withdrawn from trial treatment at the investigator's discretion if any of the following occurred:
(1) disease progression
(2) patient at risk due to mismatch with selection criteria
(3) inappropriate patient compliance
(4) a serious or unexpected adverse event
(5) patient unwilling or unable to continue
(6) investigator considered it would be in the patient's best interest not to continue.

If any other systemic treatment for breast cancer was used, the trial treatment had to be withdrawn. Treatment with other drugs that affect sex-hormone status or breast cancer response was not allowed once the patient had entered the trial. Administration of any of these treatments constituted a reason for withdrawal of the patient from the trial treatment
Following withdrawal of trial treatment, details of further treatments (ie, the number and proportion of patients who were given radiotherapy, chemotherapy, or hormonal therapy until data cut-off), were recorded for all patients.

8.1.3.4 Assignment to treatment

Patient eligibility was established by trial site personnel before randomization to treatment. Randomization to trial treatment with anastrozole or tamoxifen. was assigned according to predetermined computer-generated randomization schemes prepared separately for each center by Zeneca personnel. The randomization schemes incorporated 2 levels of stratification:

Stratum A :soft tissue and/or lung disease only
Stratum B :all other disease combinations

Within each level, a patient was assigned to the next sequential patient number at a given center and trial treatment was dispensed for that patient number.
Once a patient number was assigned, that number was not used again and a patient was not randomized more than once.

8.1.4 Study Therapy

8.1.4.1 Formulation

Packaging and distribution of both treatments was identical. Treatments were packaged in bottles containing 112 tablets which were sufficient for 12 weeks of treatment and a 4-week surplus. A 12-week trial supply consisted of 1 carton containing 2 bottles. Each carton contained either 1 bottle of anastrozole and 1 bottle of tamoxifen placebo, or 1 bottle of anastrozole placebo and 1 bottle of tamoxifen. Both anastrozole and tamoxifen were stored in a secure dry location at room temperature, protected from temperatures above 30 degrees Centigrade. Tamoxifen was also protected from light.

8.1.4.2 Dosage Schedule
Patients were given a 12-week supply at Visits 1, 4 and 7 and at every visit thereafter until withdrawal from trial treatment.

8.1.4.3 Treatment-blinding technique
The trial used both active and placebo anastrozole, and active and placebo tamoxifen tablets to maintain blindness to trial treatment.
Each carton containing bottles of trial treatment had a 2-part label: a permanently affixed portion and a tear-off portion that was removed when the drug was dispensed to the patient.

8.1.5 Concomitant treatment
Use of bisphosphonates was permitted during the trial following a protocol amendment
Radiotherapy for control of bone pain or other reasons was permitted also following. protocol amendment.
The concomitant administration of any other treatment (except anticancer agents) was not restricted.
Prior cancer treatments (chemotherapy, radiotherapy, hormonal therapy) and all drugs given to, or taken by, the patient at entry into the trial or during the trial were to be documented on the appropriate CRF.

8.1.6 Efficacy assessments

8.1.6.1 Primary end points
Primary efficacy variables were
- time to progression
- objective-response rate (calculated from objective response).

8.1.6.2 Secondary end points
Secondary efficacy variables were
- time to treatment failure,
- time to death (survival),
- duration of response,
- duration of clinical benefit, (analgesic use, bone pain, performance status and health economics)

8.1.6.3 Methods of disease assessment

8.1.6.3.1 Time to progression
Time to progression was defined as the number of days from the date of randomization to the date of objective disease progression or death from any cause, whichever was earlier.

The date of objective disease progression was defined as the first visit date for which progression was determined by an algorithm based on Union Internationale Contre le Cancer (UICC) criteria

8.1.6.3.2 Objective response

(a) Objective tumor assessments

When present, local and regional disease of the skin and lymph nodes, and skeletal, pulmonary, and intra-abdominal metastases were assessed before and during trial treatment. At each site of tumor involvement, at least 1 lesion was monitored. If any given site contained more than 1 lesion, the investigator decided how many lesions were monitored based on his or her clinical judgement. The selected lesion(s) were monitored throughout the trial until objective disease progression occurred.

(i) Measurement of local and regional disease

If skin metastases were present, a maximum of 3 of the largest lesions were selected for measurement, and the longest diameter and greatest perpendicular diameter of the lesions were measured. Up to 3 superficial lymph nodes with clear evidence of tumor involvement (indicated by either at least 1 diameter greater than or equal to 2 cm or the presence of malignant cells on cytological examination) were selected, and the longest diameter and greatest perpendicular diameter measured.

(ii) Assessment of bone metastases

A radionuclide bone scan was performed before trial treatment to screen for possible bone metastases. If the baseline scan was negative for metastases, the scan was repeated every 12 months until objective disease progression; if positive for metastases, the scan was repeated every 6 months until objective disease progression. Lesions identified on the bone scan were examined radiographically. Radiographic examination of confirmed metastatic lesions was repeated every 12 weeks during treatment, and additionally at withdrawal (for any reason) from trial treatment. Additional bone scans and/or skeletal radiographs were performed at other visits, if clinically indicated.

Up to 4 measurable bone lesions and up to 6 non-measurable (evaluable) lesions were monitored radiographically throughout the trial, until objective disease progression occurred. The largest, bidimensionally assessable, primarily osteolytic bone lesions were selected, and the largest diameter and greatest perpendicular diameter measured.

(iii) Assessment of pulmonary metastases

A chest radiograph was obtained before trial treatment began to determine whether pulmonary metastases were present. If none was seen, the examination was repeated every 24 weeks until disease progression and at withdrawal from trial treatment for any reason. When pulmonary or mediastinal metastases were detected, chest radiography was repeated every 12 weeks. Up to 4 measurable pulmonary lesions surrounded by aerated lung tissue were measured. The longest diameter and the greatest perpendicular diameter were recorded. For lesions only partially surrounded by aerated tissue, the longest diameter demarcated by aerated tissue was recorded. Pleural effusion was evaluated by comparing chest radiographs, thoracentesis results, or both, from baseline assessments with those obtained during trial treatment.

(iv) Assessment of liver and abdominal metastases

When liver and abdominal metastases were suspected, a CAT scan, magnetic resonance imaging (MRI), or ultrasound scan of the liver and abdomen was performed before trial treatment began. If liver metastases were found, the scan was repeated every 12 weeks until objective disease progression, and additionally at withdrawal from trial treatment. The longest diameter and greatest perpendicular diameter of up to 4 lesions were measured. If no liver or abdominal metastases were suspected at trial entry, a CAT, MRI, or ultrasound scan of the liver and abdomen was performed at subsequent visits only if clinically indicated.

(v) Assessment of brain metastases

A cranial CT or MRI scan with enhancement was performed at baseline, and at subsequent visits if clinically indicated

(b) Assignment of objective response

The assignment of objective response included the evaluation of both measurable and non-measurable disease. Measurable disease was based on UICC criteria. Metastatic lesions measurable in 1 or 2 dimensions using physical or radiographic methods (including CAT scan) were regarded as measurable. However, osteolytic bone lesions were also considered measurable.

Single metastatic lesions smaller than 0.5 cm, malignant pleural effusion or ascites, a positive bone scan, and osteoblastic or in trabecular bone lesions were classified as non-measurable disease. Lesions classified as non-measurable constituted evaluable disease.

(i) Assignment of visit response in measurable disease

At each visit, measurable disease was assigned a response of complete response (CR), partial response (PR), stable disease (SD), or disease progression (PROG), based on the recorded dimensions of measurable lesions. The response category was assigned by an algorithm generated by Zeneca.

Once a response of PROG was assigned, it was carried forward for all subsequent visits. Any lesion exposed to radiotherapy, and bone lesions exposed to bisphosphonates, were considered to have become unevaluable. Enlargements of such lesions could contribute to the assignment of PROG, and such lesions were required to have disappeared in order for CR to be assigned. However, any shrinkage of such lesions could not contribute to an assignment of CR or PR.

(ii) Assignment of visit response in non-measurable disease

For non-measurable disease, the investigator assigned a response of CR, SD, or PROG. The category of PR was not allowed because this category is difficult to evaluate objectively in non-measurable lesions.

(iii) Assignment of overall visit response

For each patient, the algorithm assigned an overall objective response for each visit, taking into account the visit response in both measurable and non-measurable disease. The categories of response (CR, PR, SD, PROG, and not evaluable (NE) are defined as follows:

Complete response (CR): Complete disappearance of all known disease; clear improvement of bone lesions on bone scan or skeletal radiographs; evidence of re-

ossification of all lytic bone lesions; freedom from all cancer-related symptoms; and absence of new lesions.

Partial response (PR): No new lesions appeared and either of the following criteria were met:

(i) a decrease of 50% or more from the pre-treatment value in the sum of the products of the 2 perpendicular diameters measured for bidimensionally assessable lesions, or

(ii) a decrease of 30% or more from the pre-treatment value in the sum of the longest diameters for unidimensionally assessable lesions. The investigator assigned a PR only for patients who had measurable disease; PR is difficult to evaluate objectively for non-measurable disease.

Stable disease (SD): No disease progression or; there was insufficient evidence for CR or PR; or either

(i) no significant change, defined as a decrease in size of less than 50% for bidimensional lesions, less than 30% for unidimensional lesions, or lesions with slight enlargement but less than 25% increase in size, or

(ii) increased pain due to tumor flare in the first 2 to 3 months of trial treatment. Because the assessment of tumor flare is subjective and was not reported uniformly by all investigators, tumor flare cases were determined as follows:

- any case which the investigator noted as tumor flare was considered to be tumor flare
- the blinded database was reviewed for all adverse events considered to be drug-related by the investigator.
- Those cases with appropriate signs or symptoms (eg, pain, bone pain, hypercalcaemia, worsening of soft tissue lesion) that occurred within the first 3 months of trial treatment, reversed after a time while still being given trial treatment, and corresponded to a known lesion were also considered tumor flare.

Disease progression (PROG): was an appearance of any new lesions; an increase of 25% or more in the sum of the areas of existing bidimensional lesions, or sum of linear diameters of unidimensional lesions; late hypercalcaemia; or the investigator assigned PROG in non-measurable disease.

Not evaluable (NE): if all lesions assessed (measurable and non-measurable) were considered unevaluable due to exposure to radiotherapy or bisphosphonates (providing a response of PROG had not already been assigned). If no lesions (measurable or non-measurable) were assessed at the visit, a response of missing was recorded.

(iv) Assignment of best objective response

Best objective response was assigned by combining the overall visit responses for each patient. The categories of best objective response (CR, PR, SD .24 weeks, SD <24 weeks, and PROG) are defined below.

Complete response: A best response of CR was assigned if a patient had 2 overall visit responses of CR at least 28 days apart (providing the second of these assessed the entire disease, ie, not just local/regional assessments). An overall response of CR could only be assigned if all disease (measurable and non-measurable) had completely resolved.

Partial response

A best response of PR was assigned if:

- a patient had at least 2 overall visit responses of CR or PR at least 28 days apart (providing the second of these assessed the entire disease, ie, not just local/regional assessments), and
- a best objective response of CR could not be assigned

Stable disease 24 weeks (SD .24)

A best response of SD >24 was assigned if:

- a patient had at least 1 overall visit response of CR, PR, or SD at least 168 days after randomization, and
- a best objective response of CR or PR could not be assigned.

Stable disease <24 weeks (SD <24)

A best objective response of SD <24 was assigned to a patient with evaluable disease if a response of CR, PR, or PROG could not be assigned and the patient had been followed for less than 168 days after randomization.

Disease progression

A best objective response of PROG was assigned if a patient had an overall visit response of PROG before a best objective response of CR, PR, or SD could be assigned.

Time to treatment failure

Treatment failure was defined as the earliest occurrence of disease progression or withdrawal of trial treatment for any reason including death from any cause. Time to treatment failure was calculated as the number of days from the date of randomization to the date of treatment failure. Any patient who did not receive any trial treatment was assigned a time to treatment failure of 0 days.

Duration of response

Duration of response was measured for responding patients (any patient who had a best objective response of CR or PR) and was defined in 2 ways as: (i) the number of days from the date of randomization to the date of first determined progression or death from any cause; and (ii) the number of days from the date of first documentation of response to the date of progression or death from any cause.

Duration of clinical benefit

Duration of clinical benefit was measured for patients who showed clinical benefit (any patient who had a best objective response of CR, PR, or SD >24 weeks) from the date of randomization to the date of first determined progression or death from any cause.

Time to death (survival)

The survival status of patients was recorded every 6 months after their disease progressed, or after withdrawal for any reason, until death. Time to death (survival) was from the date of randomization to the date of death from any cause.

Populations analyzed

The primary efficacy analyses of all the end points included all randomized patients and compared the treatment groups based on randomized treatment, regardless of whether this treatment was actually received (ITT approach). In addition, the secondary efficacy analyses (excluding patients with significant protocol violations and deviations) were performed for time to progression and objective-response rate to assess whether the conclusions from the primary efficacy analyses were robust ('per-protocol' approach).

Statistical analysis

The equivalence of the 2 treatments, in terms of the primary and secondary end points, was assessed using non-inferiority criteria.

(a) Primary efficacy end points

The primary objective of this trial was achieved if non-inferiority of anastrozole to tamoxifen was obtained for both primary end points (time to progression and objective-response rate). Testing to demonstrate non-inferiority was performed using the lower 1-sided 95% confidence limit.

(i) Time to progression

Time to progression was summarized by randomized trial treatment using the Kaplan-Meier method. Kaplan-Meier plots and Kaplan-Meier estimates of median time to progression were presented for each treatment group. Cox's regression model was used to evaluate whether anastrozole was non-inferior to tamoxifen in 2 ways:

- an adjusted analysis with treatment factor and baseline prognostic variables. Factors for age (>65 years), previous hormonal treatment, estrogen- and progesterone-receptor status at entry, and extent of disease at entry were included in the model. The randomization was stratified for the extent of disease at entry, but the values for this variable were determined from the data (rather than the stratification arm) due to a proportion of patients being misallocated.
- an unadjusted analysis with treatment factor only.

Conclusions were based on the adjusted analysis, but any differences in the results of the 2 analyses were explored. Any interactions of treatment-by-baseline prognostic variables were investigated.

(ii) Objective-response rate

The best objective response of CR, PR, SD >24 weeks, SD <24 weeks, or PROG was summarized by randomized trial treatment for all patients. In addition, the best objective response was summarized by extent of disease at entry.

The objective-response rate (ie, the proportion of responders) was compared between the treatment groups using the same adjusted and unadjusted analyses as were used to assess time to progression.

Conclusions were based on the adjusted analysis, but any differences in the results of the 2 analyses were explored. The interactions of treatment-by-baseline prognostic variables were investigated.
The formal comparisons between the treatments were estimated using the odds ratio (anastrozole:tamoxifen) together with the lower 1-sided 95% confidence limit for the odds ratio. These results were then used to calculate the difference in response rate (anastrozole-tamoxifen) and if the lower 1-sided confidence limit for this difference was no less than -10%, it was concluded that anastrozole was non-inferior to tamoxifen.
The effect of center and treatment-by-center interaction was not investigated because the recruitment at most centers was low, which would have caused problems with computational convergence.

(b) Secondary end points
The secondary end points were time to treatment failure, time to death (survival), duration of response (time to progression or death from any cause in responding patients), and duration of clinical benefit. Statistical analysis to demonstrate that anastrozole was non-inferior to tamoxifen was performed at the 1-sided 5% significance level for time to treatment failure only.
(i) Time to treatment failure
Time to treatment failure was summarized by randomized trial treatment using the Kaplan-Meier method. Kaplan-Meier plots and Kaplan-Meier estimates of median time to treatment failure were presented for each treatment group.
Cox's regression model was used to evaluate whether anastrozole was non-inferior to tamoxifen. Again, conclusions were based on the adjusted analysis but any differences in the results of the 2 analyses were explored.
The difference between the 2 treatments was estimated using the previously described hazard ratio methodology. Any patient who had not reached treatment failure at the time of data cut-off, or who had been lost to follow-up, was right-censored at the date of their last disease assessment.
(ii) Duration of response and duration of clinical benefit
Duration of response (for responders only) and duration of clinical benefit were summarized for each treatment group using a Kaplan-Meier plot and Kaplan-Meier estimates of the median duration but no formal statistical analysis was planned. Any patient who had not progressed at the time of the data cut-off date was right-censored in the analysis at the date of the last disease assessment.

(iii) Time to death (survival)
Time to death (survival) was summarized by randomized trial treatment using the Kaplan-Meier method.

8.1.7 Safety assessments

8.1.7.1 Adverse events

Methods of assessment

(a) All adverse events

Any detrimental change in the patient's condition during trial treatment and during the 14 days following cessation of trial treatment, unless related to breast cancer progression, was considered an adverse event All adverse events (serious and non-serious) were followed to resolution.

(b) Serious adverse events

Serious adverse events were defined as:

- any adverse event leading to death
- any life-threatening, disabling, or permanently incapacitating event
- any event that required or prolonged hospitalization
- any occurrence of a congenital anomaly, the development of new cancers (other than
- breast cancer and its metastases), or overdose
- any event that required medical or surgical intervention to preclude permanent
- impairment of a body function or permanent damage to a body structure.

All assessments were repeated when a patient was withdrawn from the trial treatment. After withdrawal due to reasons other than disease progression, patients were followed-up with full assessments until objective progression. After objective progression, patients were contacted every 6 months (until death) for survival information.

8.1.7.2 Clinical and laboratory assessments

The schedule of disease assessments is as indicated in Table 1

Table 1 Trial plan to show timing of events and disease assessments

Week	0 Baseline	4	8	12	16	20	24	36	48
Demography, history, ECG, BP, pulse	X								
Physical examination/weight	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X			X			X	X	X
Assessment of local regional disease	X	X	X	X	X	X	X	X	X
Bone scan	X						X*		X
Skeletal X-ray	X			X			X*	X*	X*
Chest X-ray	X			X*			X*	X	X*
Adverse events		X	X	X	X	X	X	X	X
Drug dispensed	X			X			X	X	X

*Required if baseline is positive

Methods of assessment

Laboratory test results were examined in 3 ways:

(i) group means,
(ii) individual values crossing a threshold of significance,
(iii) adverse events.

Blood samples for hematologic and biochemical tests were obtained before treatment began and every 12 weeks thereafter until objective progression, and at the time of withdrawal from trial treatment.

The parameters determined were:

- hematology: hemoglobin concentration, total white blood cell and platelet counts
- hepatic biochemistry: total bilirubin, alkaline phosphatase, AST, ALT, gamma-glutamyl transferase (GGT), and albumin
- renal biochemistry: creatinine and urea
- other biochemistry tests: electrolytes: sodium, potassium, calcium and inorganic phosphorus
- lipids: total cholesterol, triglycerides, apolipoprotein A, apolipoprotein B,
- lipoprotein A, high density lipoprotein (HDL), and low density lipoprotein (LDL)
- glucose.

History, Physical examination and electrocardiogram

Demographic information (age, height, weight, and ethnic origin) was recorded before the patient was randomized to trial treatment.

A medical history was recorded before the patient was randomized to trial treatment.

A physical examination was performed before the patient was randomized to trial treatment and at all subsequent visits.

Blood pressure and heart rate were assessed at baseline and as clinically indicated.

A 12-lead electrocardiogram (ECG) was performed at baseline and thereafter as clinically indicated

Duration of trial treatment
Duration of trial treatment was defined for each patient as the number of days from the date of first dose until the date of last dose. The last date of contact was assigned to any patient who was not withdrawn from trial treatment.

Duration of follow-up
Duration of follow-up was defined as the number of days from the date of randomization to the date of last contact for any patients who were last known to be alive.

8.1.8 Statistical considerations

Interim analyses
An interim analysis was carried out to provide an early indication of clinical benefit to support the on-going adjuvant clinical trial program for anastrozole. The analysis was performed when at least 15 patients had been randomized to each treatment group within Stratum A (soft tissue and/or lung disease only), each of whom had at least 12 weeks of follow-up. There was no effect on the trial blinding.
The interim analysis was performed on 32 patients in Stratum A who had at least 12 weeks of follow-up (15 randomized to anastrozole and 17 randomized to tamoxifen). The rate of clinical benefit was compared between the treatment groups using logistic regression.
The comparison of the treatments was estimated using the odds ratio together with the 95% confidence limit for the odds ratio. As the trial was designed to assess the 1-sided alternative hypothesis, the 95% confidence limit used for this end point was a 1-sided interval and no p-value was quoted.

Multiple testing
The primary objective of this trial will be achieved if the non-inferiority of anastrozole to tamoxifen was obtained on both time to progression and objective-response rate. These 2 primary efficacy end points were considered composite variables due to their high correlation.

8.1 9. Results

8.1.9.1. **Patient Disposition,**

8.1.9.1.1 Comparability

Table 2 summarizes demographic details for all patients at entry.
A total of 668 patients were randomized to trial treatment 340 (50.9%) patients were randomized to anastrozole and 328 (49.1%) were randomized to tamoxifen The mean age for all patients who were randomized to anastrozole was 67 years (range 34 to 91years). Versus 66 years (range 41 to 92 years)for tamoxifen.. The age distribution was similar between the 2 treatment groups; however, slightly more patients in each treatment group

were aged 65 years or more. The distribution of body mass index was similar between the 2 treatment groups. The majority (91.3%) of patients were Caucasian.

Table 2 **Demographic characteristics**

	Anastrozole 1 mg	**Tamoxifen 20 mg**	
Age (years)	**(n = 340) (%)**	**(n = 328) (%)**	**(n = 668) (%)**
Mean(Range)	67(34 to 91)	66(41 to 92)	66(34 to 92
<65	160 (47.1)	160 (48.8)	320 (47.9)
>65	180 (52.9)	168 (51.2)	348 (52.1)
Body mass index (kg/m^2)			
n (%)	317 (93.2)	308 (93.9)	625 (93.6)
Mean (Range)	27(16 to 42)	27(16 to 44)	27(16 to 44
Ethnic origin			
Caucasian	313 (92.1)	297 (90.5)	610(91.3)
Afro-Caribbean	3 (0.9)	1 (0.3)	4(0.6)
Asian/Oriental	0	2 (0.6)	2 (0.3)
Hispanic	9 (2.6)	9 (2.7)	18(2.7)
Other*	15 (4.4)	19 (5.8)	34(5.1)

*Other includes patients of mixed origin.

8.1.9.1..2 Breast cancer history: Hormone Receptor and Disease Status at Diagnosis, Prior Adjuvant Therapy

Table 3 summarizes hormone receptor status characteristics, prior adjuvant therapy and disease status at entry, by treatment, and for all patients.
Hormone receptor status was similar between the 2 groups. In both groups, the sponsor reports approximately one-half of the patients had estrogen-receptor (ER) positive and/or progesterone-receptor (PR) positive breast cancer 154 (45.3%) anastrozole patients, versus 144 (43.9%) patients randomized to tamoxifen. The remaining patients were mostly of unknown ER or PR status; however

Reviewer's Comments: ER/PR studies were not obtained in the majority of patients. The distribution however appears balanced between the two treatment groups. It will be worthwhile to see an analysis of responses among patients with ER/PR Unknown and patient s with ER/PR positive results in both treatment groups.

TABLE 3 PATIENT CHARACTERISTICS

PATIENT CHARACTERISTICS	ANASTROZOLE N=340	TAMOXIFEN N=328 (%)	ALL PATIENTS N= 668 (%)
Hormone Receptor Status			
ER+/PR+	154 (45.3)	144 (43.9)	298 (44.6)
ERUnknown/PR Unknown	185 (54.4)	183 (55.8)	368 (
All other combinations	1 (0.3)	1 (0.3)	
Prior Adjuvant Therapy			
No previous adjuvant therapy	234 (68.8)	231 ((70.4)	465 (69.6)
Previous adjuvant therapy	105 (30.9)	97 (29.6)	202 (30.2)
Hormonal	31(9.1)	20(6.1)	51(7.6)
Cytotoxic	64(18.8)	62 (18.9)	126(18.9)
Hormonal and cytotoxic	10(2.9)	15 (4.6)	25(3.7)
Disease status at first diagnosis			
Advanced[a]	163 (47.9)	169 (51.5)	332 (49.7)
Early[b]	176 (51.8)	158 (48.2)	334 (50.0)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Total	340 (100.0)	328 (100.0)	668 (100.0)

Prior Adjuvant therapy status

The majority of patients in both groups had not been given previous adjuvant therapy. The proportions of patients who had been given either hormonal, cytotoxic, or hormonal and cytotoxic adjuvant therapy were similar between the 2 treatment groups. Forty-one (12.1%) patients who were randomized to anastrozole and 35 (10.7%) patients who were randomized to tamoxifen had been given previous hormonal therapy (either hormonal treatment only or both hormonal and cytotoxic treatment).

The estimated median duration of previous adjuvant hormonal treatment was shorter for patients who were randomized to anastrozole (105 weeks), compared with patients who were randomized to tamoxifen (141 weeks). However, the number of patients from whom these median values have been estimated are reported to be relatively small.

Reviewer's Comments: Patients with prior hormonal therapy may have been exposed to prior tamoxifen therapy i.e they could have been tamoxifen failures, some of whom could have been randomized to Tamoxifen. They could therefore have developed resistance to Tamoxifen. Even though an interval of 12 months after cessation of tamoxifen therapy was an inclusion entry criterion, some of these patients could still have persistent tamoxifen resistance and could therefore bias the results of those patients randomized to Tamoxifen therapy.

Table 4 Disease Characteristics

DISEASE CHARACTERISTICS	ANASTROZOLE N=340	TAMOXIFEN N=328 (%)	ALL PATIENTS N= 668 (%)
Disease status at first diagnosis			
Advanced	163 (47.9)	169 (51.5)	332 (49.7)
Early	176 (51.8)	158 (48.2)	334 (50.0)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Total	340 (100)	328 (100)	668 (100)
Disease measurability at entry			
Measurable disease	301(88.5)	286 (87.2)	587 (87.9)
No measurable disease	39 (11.5)	42 (12.8)	81 (12.1)
Sites of metastatic disease at entry			
Skin	183(53.8)	183 (55.8)	366 (54.8)
Lymph nodes	145 (42.6)	148 (45.1)	293 (43.9)
Bone	156 (45.9)	158 (48.2)	314 (47.0)
Lung	74 (21.8)	100 (30.5)	174 (26.0)
Liver	32 (9.4)	31 (9.5)	63 (9.4)
Abdominal	10 (2.9)	5 (1.5)	15 (2.2)
Other	1(0.3)	2 (0.6)	3 (0.4)
No evaluable disease	2 (0.6)	0	2 (0.3)

8.1.9.1.3 Breast cancer disease status at first diagnosis, site and extent of disease at entry:

Overall, most patients who entered the trial 587 (87.9%)) patients had measurable disease The sponsor claims that the proportion of patients who had who had measurable disease as well as advanced breast cancer disease at first diagnosis was similar between the 2 treatment groups. One-half of the total patient population had early-stage breast cancer at first diagnosis. The majority of patients in this trial had metastatic disease. Skin was the most frequent site of metastatic disease at entry in both treatment groups 366/668 (54.8%) patients. The proportion of patients with metastatic disease who had skin, lymph, and bone lesions at entry was similar between the 2 treatment groups. More patients who were randomized to tamoxifen had metastasis to the lung 100/328 (30.5%)] patients, compared with patients who were randomized to anastrozole 74/340 (21.8%) patients. For the other visceral sites, the proportion of patients who had disease at those sites was similar between the 2 treatment groups. Overall, 287 (43.0%) patients had soft tissue and/or lung disease only, while the majority of the patients 381 (57.0%) patients had other disease combinations. The extent of metastatic disease at entry was similar between the treatment groups. A similar proportion of patients in each treatment group had evidence of liver involvement.

Reviewer's Comments

Patients in the tamoxifen group had more advanced disease at first diagnosis and more sites of metastatic disease than in the anastozole group. The difference is most striking among patients with pulmonary metastases. If metastatic diseases are grouped into bony and soft tissue distributions, patients in the tamoxifen group appear to have more extensive disease in more critical soft tissue organs than in the anastrozole group.

8.1.9.1 4 Withdrawals

Table 5 Reasons for withdrawal from trial treatment by treatment given

	Number of patients			
Primary reason for withdrawal	Anastrozole 1 mg (n = 336) (%)		Tamoxifen 20 mg (n = 329) (%)	
Total number of patients who withdrew	235	(69.9)	241	(73.3)
Death	6	(1.8)	3	(0.9)
Adverse event	15	(4.5)	15	(4.6)
Protocol non-compliance	3	(0.9)	6	(1.8)
Disease progression (investigator's opinion)	193	(57.4)	197	(59.9)
Patient unwilling to continue	10	(3.0)	12	(3.6)
Patient lost to follow-up	2	(0.6)	1	(0.3)
Other reason	6	(1.8)	7	(2.1)

476 (71.6%) patients who started trial treatment withdrew from the trial
235 (69.9%) patients on **anastrozole** and 241 (73.3%) patients on **tamoxifen**
The majority of all patients (58.6%) withdrew because of disease progression.
13 patients withdrew from trial treatment for other reasons:

6(1.8%) patients who were given **anastrozole** withdrew, the reasons included:

- patient was unable to comply
- patient was unable to take medication due to bronchopneumonia
- a mix up in medication number occurred
- presence of peritoneal mass confirmed as peritoneal metastasis
- Patient first diagnosis of brain lesion, metastasis subsequently confirmed as benign
- lack of efficacy.

7(2.1%) patients who were given **tamoxifen** withdrew. The reasons included:

- surgery due to progression
- patient was given a non-trial medication
- the investigator stopped trial treatment and started chemotherapy because of continuation of functional impairment of right arm caused by lymphedema
- presence of secondary primary tumor requiring chemotherapy
- metastasis of secondary primary tumor
- patient lost to follow-up and not tracked by telephone
- general deterioration and therefore patient unable to take trial medication

Treatment given after withdrawal.

Table 6 indicates therapy given after withdrawal from trial treatment.

Table 6 Therapy given after withdrawal from trial treatment

	Number of patients (%)			
Therapy	Anastrozole 1 mg (n = 235)		Tamoxifen 20 mg (n = 241)	
Radiotherapy	73	(31.1)	77	(32.0)
Chemotherapy	106	(45.1)	105	(43.6)
Hormonal therapy	117	(49.8)	142	(58.9)
Other	52	(22.1)	49	(20.3)

The 476 patients who had withdrawn from the trial by the time of data cut-off were given radiotherapy, chemotherapy, hormonal therapy, or other therapy following the withdrawal of trial treatment. The proportion of patients who were given radiotherapy, chemotherapy, or other therapy following withdrawal from treatment was similar in both treatment groups. A greater proportion of patients who were given tamoxifen received subsequent hormonal therapy. Comparisons between the groups for the specific therapy received following withdrawal were difficult to make because of the low numbers of patients who were given some of the classes of drugs within each specific type of subsequent therapy. However, the proportion of patients who were given tamoxifen as subsequent therapy was higher within the group of patients who were given anastrozole during the trial 66/235 (28.1%) compared with the group of patients who were given tamoxifen during the trial 18/241 (7.5%) patients. Similarly, the proportion of patients who were given anastrozole as subsequent therapy was higher within the group of patients who were given tamoxifen during the trial (56/241 [23.2%] patients), compared with the group of patients who were given anastrozole during the trial 9/235 ([3.8%).

8.1.9.4 Protocol violations and deviations

A protocol violation was defined as any infringement of the protocol selection criteria. A protocol deviation was defined as any departure from the protocol design or procedures after the patient had entered the trial. Categories are not mutually exclusive (ie, a patient may have violated or deviated from the protocol more than once and the violations or deviations may have occurred in different categories).

The secondary efficacy (per-protocol) analyses of time to progression, objective-response rate, and time to death (survival) excluded patients who had significant protocol violations or deviations.

Protocol violators and deviators:Total	87/668 (13.0%)
randomized to Anastrozole	50/340 (14.7%)
randomized to Tamoxifen	37/328 (11.3%)

Most frequent protocol deviation

Anastrozole	use of disallowed concurrent therapy 16/340 (4.7%) on anastrozole and 9/328 (2.7%) on tamoxifen.
Tamoxifen	missing more than 25% of the scheduled tumor assessments, 17/328 (5.2%) on tamoxifen and 15/340 (4.4% on anastrozole.

8.1.9.4.2 Patients included in the efficacy and safety analyses

All 668 randomized patients were included in the primary (ITT) analyses for all efficacy end points. After excluding the 87 (13.0%) patients who had significant protocol violations or deviations, or both, a total of 581 (87.0%) patients were included in the secondary analyses for the efficacy end points of time to progression, objective-response rate, and time to death (survival). The 665 patients who actually received trial treatment were included in the safety analyses.

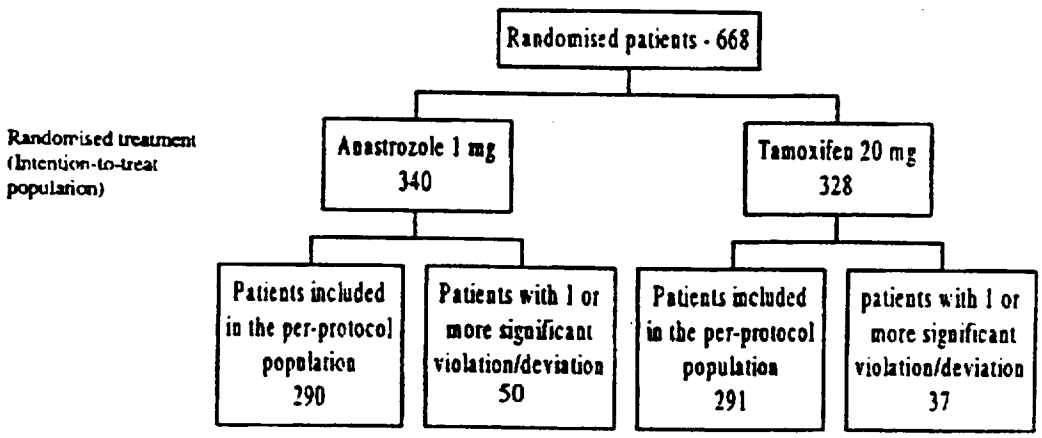

Figure 2

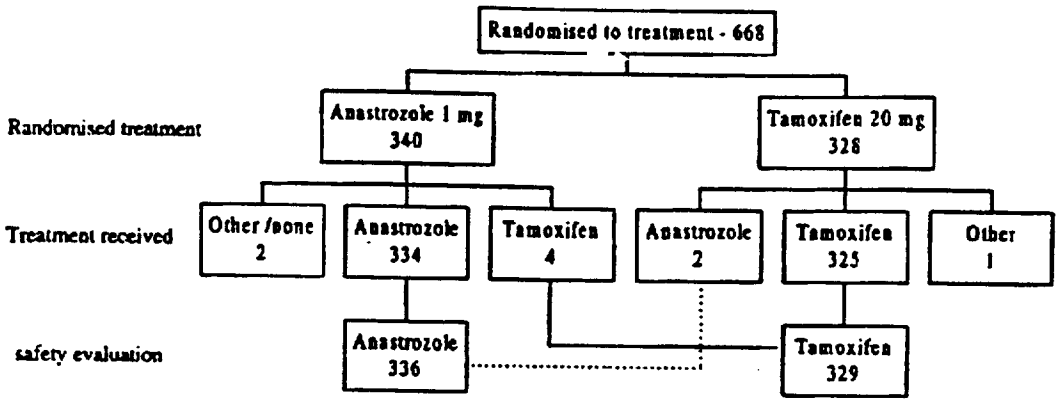

FIGURE 3

8.1.10. EFFICACY RESULTS

8.1.10.1 **Duration of follow-up and progression status**

The duration of follow-up for all patients who were known to be alive at the time of data cut-off is shown in Table 7.Median duration of follow-up was longer for the group of patients who were given tamoxifen. Overall, the estimated median duration of follow-up was 572 days for the 503 patients who were known to be alive at the time of data cut-off.

Table 7 Duration of follow-up and progression status of randomized patients at the time of data cut-off (10 March 199)

Duration of follow-up (days)	Anastrozole 1 mg (n = 249)	Tamoxifen 20 mg (n = 254)
Median	556	598
Range (Minimum/ Maximum)	0 / 1194	106/1260
Progression status	Anastrozole 1 mg (n = 340) (%)	Tamoxifen 20 mg (n = 328) (%)
Alive without progression[a]	91(26.8)	81 (24.7)
Progression during treatment	216 (63.5)	209 (63.7)
Progression after treatment withdrawal	15 (4.4)	18 (5.5)
Death before progression	18(5.3)	20 (6.1)

[a] Includes patients who were continuing treatment and patients withdrawn from treatment.

A total of 496 (74.3%) patients had disease progression (including death, from any cause, before progression). Patients who were randomized to anastrozole had a similar progression rate and estimated median time to progression (73.2% and 251 days, respectively), compared with patients who were randomised to tamoxifen (75.3% and 252 days, respectively). A formal statistical analysis on these data was not performed.

Results of the adjusted analysis showed that the tamoxifen:anastrozole comparison had a hazard ratio very close to 1, indicating that for this parameter the 2 treatments were almost identical. The lower 1-sided 95% confidence limit for the hazard ratio was 0.86, which was greater than the statistical criterion of 0.80 required to declare non-inferiority. Consistent results were obtained from the unadjusted analysis, which gave a hazard ratio of 1.01 and a lower 95% confidence limit of 0.87. The applicant concludes that anastrozole met the criteria for equivalence with tamoxifen for time to disease progression.

Per-protocol analysis

The per-protocol analysis of time to progression was performed in a total of 581 patients. 290 (49.9%) patients were randomized to anastrozole and 291 (50.1%) were randomized to tamoxifen. A total of 435 (74.9%) patients had disease progression. The results from the per-protocol analysis were consistent with those from the ITT analysis. Patients randomized to anastrozole appeared to have a similar progression rate and estimated median time to progression (75.2% and 251 days, respectively), compared with patients randomised to tamoxifen (74.6% and 252 days, respectively). The associated hazard ratios , tamoxifen:anastrozole were 0.97 and 0.98 for the adjusted and unadjusted analyses, respectively. Equivalence was also demonstrated with the lower 1-sided 95% confidence limit for the hazard ratio, which was greater than the statistical criterion of 0.8 for both the adjusted (0.83) and unadjusted analyses (0.84).

8.1.10.2: Objective Responses

Best objective response for all randomized patients

Table 8 summarizes the objective-responses for all randomized patients

The objective-response rate was defined as the proportion of patients showing best objective response of CR or PR. The best objective-response rate of complete or partial was very similar for patients randomized to anastrozole 32.9% (112/340) and patients randomized to tamoxifen 32.6% (107/328). The proportion of patients who had a best response of stable disease >24 weeks was also similar for patients who were randomized to anastrozole (23.2%) and patients who were randomized to tamoxifen (22.9%).

Table 8 Best objective response for all randomized patients

Objective response	Anastrozole 1 mg (n = 340)	Tamoxifen 20 mg (n = 328)
Responders	112 (32.9)	107 (32.6)
Complete response	19 (5.6)	16 (4.9)
Partial response	93 (27.4)	91 (27.7)
Non-responders	228 (67.1)	221 (67.4)
Stable disease ≥24 weeks	79 (23.2)	75 (22.9)
Stable disease <24 weeks	9 (2.6)	8 (2.4)
Progression	140 (41.2)	138 (42.1)

Of the 287 patients who had soft tissue and/or lung disease only, a best objective-response rate of CR or PR was higher for patients who were randomized to anastrozole

47.1% (73/155), compared with patients who were randomized to tamoxifen (41.7% (55/132). Of the 381 patients who had all other disease combinations, the best objective-response rate was lower for patients who were randomized to anastrozole 21.1% (39/185), compared with patients who were randomized to tamoxifen 26.5% (52/196).

8.1.10.3: Response Duration

Duration of response

Duration of response was assessed in 2 ways: from the date of randomization to the date of first determined progression or death from any cause, and from the date of first documentation of response to the date of first determined progression or death from any cause. Table 9 summarizes the duration of response for all randomized patients who had a best objective response of CR or PR. Overall, 219/668 (32.8%) patients were considered to be responders (patients who had a best objective response of CR or PR). The estimated median duration of response from the time of randomization and from the date of first documentation of response was longer for patients given tamoxifen than for patients given anastrozole. The sponsor agrees that these data should be interpreted with caution as they are based on relatively small numbers of patients grouped by response to trial treatment. Statistical analyses on these data have not been performed.

Table 9 Duration of objective response (CR or PR) for all randomized patients

Response data	Anastrozole 1 mg (n = 340)	Tamoxifen 20 mg (n = 328)
Number (%) of patients with objective response	112 (32.9)	107 (32.6)
Duration of response from randomization		
Median (days)	498	518
Range		
Duration of response from first response		
Median (days)	378	421
Range		

Reasons For Treatment Failure

Table 10 summarizes the reasons for treatment failure for all randomized patients up to the date of the last objective response assessment before the data cut-off date. Some patients had treatment failure resulting from objective progression before treatment was stopped. Of the 668 patients who were randomized to trial treatment, 455 (68.1%) patients had treatment failure resulting from disease progression 424 (63.5%) patients determined from the objective algorithm and 31 (4.6%) patients determined from the investigator's opinion). Seventy (10.5%) patients were withdrawn from the trial for reasons other than disease progression and 8 (1.2%) patients died before progression. A total of 533 (79.8%) patients had treatment failure. A slightly smaller proportion of patients who were randomized to anastrozole (78.5%) had treatment failure, compared with the proportion of patients who were randomized to tamoxifen (81.1%). Patients who were randomized to anastrozole also had a slightly longer estimated median time to

treatment failure (189 days), compared with the time for patients who were randomized to tamoxifen (182 days).
No formal statistical analysis was performed on these data.

Table 10 Reasons for treatment failure for all randomized patients

Primary reason for treatment failure	Anastrozole 1 mg (n = 340)		Tamoxifen 20 mg (n = 328)	
Disease progression (objective)	216	(63.5)	208	(63.4)
Treatment stopped because of disease-progression (investigator's opinion)	15	(4.4)	16	(4.9)
Adverse event	13	(3.8)	15	(4.6)
Unwilling to continue	5	(1.5)	10	(3.0)
Death without evidence of progression	5	(1.5)	3	(0.9)
Patient lost to follow-up	2	(0.6)	1	(0.3)
Protocol non-compliance	3	(0.9)	6	(1.8)
Never started randomized treatment	2	(0.6)	1	(0.3)
Other reason	6	(1.8)	6	(1.8)
Total number of patients with treatment failure	267	(78.5)	266	(81.1)

Clinical Benefit
Tables 11 summarizes the proportions of patients who experienced clinical benefit, defined as patients who had CR, PR, or SD for >24 weeks,. The proportions of patients who had a clinical benefit were similar for patients who were randomized to anastrozole 191/340 (56.2%) and patients who were randomized to tamoxifen 182/328 (55.5%).

Table 11 Patients who had clinical benefit

	Number of patients (%)			
Objective response	Anastrozole 1 mg (n = 340)		Tamoxifen 20 mg (n = 328)	
Clinical benefit				
Complete response	19	(5.6)	16	(4.9)
Partial response	93	(27.4)	91	(27.7)
Stable disease ≥24 weeks	79	(23.2)	75	(22.9)
No clinical benefit				
Stable disease <24 weeks	9	(2.6)	8	(2.4)
Progression	140	(41.2)	138	(42.1)

Reviewer's Comment: This reviewer does not believe that adding patients with stable disease to the clinical benefit response criteria is truly meaningful, even though the sponsor quotes literature reference to support that contention.

Duration of clinical Benefit
Table 12 summarizes the duration of clinical benefit in patients with CR,PR, or SD>24 weeks, from the date of randomization to the date of first determined progression or death from any cause. A total of 373 (55.8%) patients demonstrated clinical benefit. The

estimated duration of clinical benefit was longer for patients who were given anastrozole than for patients who were given tamoxifen. These data should be interpreted with caution since they are based on a relatively small number of patients grouped by response to trial treatment. Statistical analyses of these data were not planned in the protocol and were not performed

Table 12 Duration of clinical benefit from the date of randomization to the date of first determined progression or death from any cause

	Anastrozole 1 mg (n = 340)	Tamoxifen 20 mg (n = 328)
Number (%) of patients with CR, PR or SD ≥24	191 (56.2)	182 (55.5)
Duration of clinical benefit, Median (days)	462	448
Range		

Time to death (Survival status):

Table 13 shows the survival status of the patients at the time of last assessment before data cut-off for the ITT population.

The sponsor's updated data reveal no significant difference in death rates among patients who were randomized to receive Arimidex128/340 (37.6%), compared with patients who were randomized to receive tamoxifen 119 (36.3%) at the first time of data cut-off (March 10, 1999).

Table 13 Survival Status at March 10, 1999 cut-off date

	Randomized treatment		
Survival status	Anastrozole 1 mg (n = 340)	Tamoxifen 20 mg (n = 328)	(n = 668)
Alive[a]	249(73.2	254 (77.4)	503 (75.30
Dead	91 (26.8)	74 (22.6)	

[a] Data for these patients were censored at the last known observation

The death rate was slightly higher in patients who were randomized to receive anastrozole 91 (26.8%) patients, compared with patients who were randomized to receive tamoxifen 74 (22.6%) patients at the time of first data cut off date on March 10, 1999. The Kaplan-Meier estimate of the probability of surviving for more than 2 years was 67.9% for patients who were randomized to anastrozole and 73.3% for patients who were randomized to tamoxifen. These estimated values take into account the censored patients who had not been followed-up for 2 years at the time of data cut-off. However, the majority of the deaths 141/165 (85.5%) occurred after trial treatment was stopped , and were related to breast cancer. A statistical analysis of survival was not performed because only 165 (24.7%) patients in this trial had died at the time of data cut-off. The Kaplan-Meier plot for survival time is presented in Figure 4. There was a slight separation

between the 2 survival curves. The sponsor explains that the time to death data were relatively immature at the time of data cut-off.

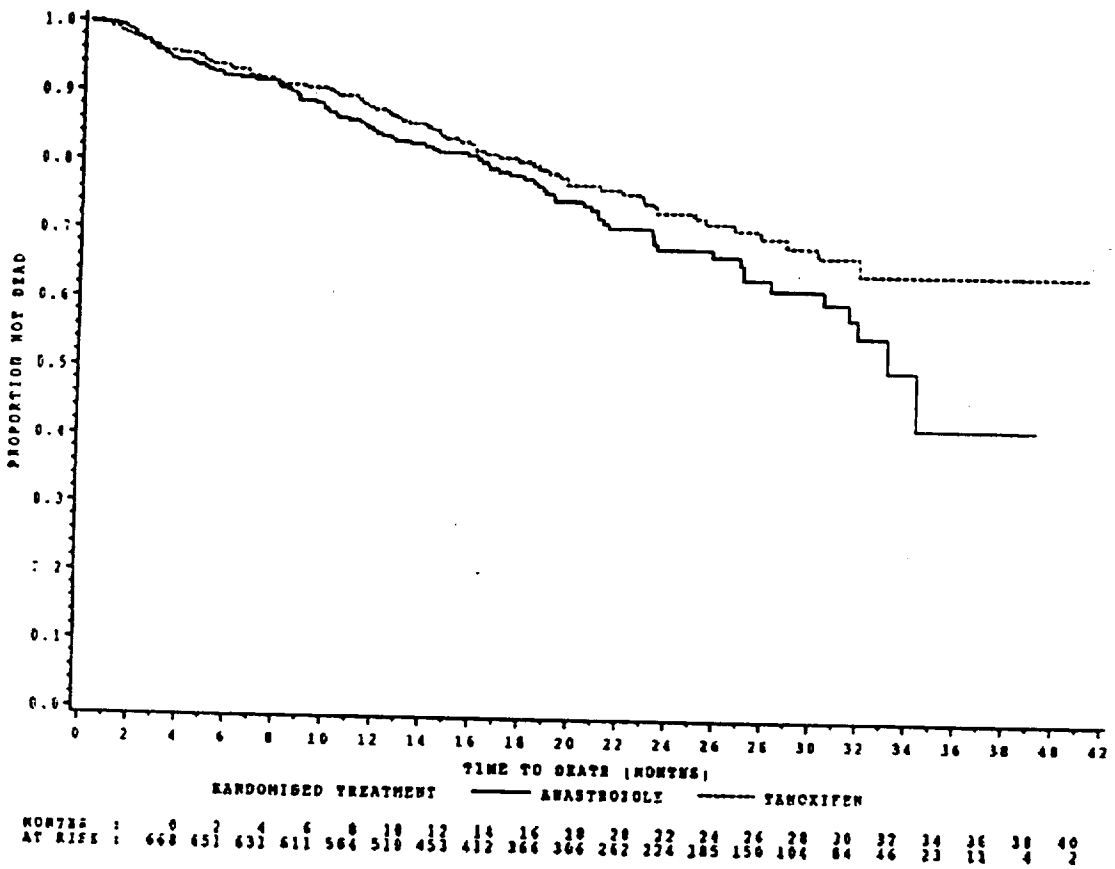

Figure 4

APPEARS THIS WAY
ON ORIGINAL

Table 13B shows the survival status of the patients at the time of last assessment before data cut-off for the ITT population

Table 13B Survival Status at February 23, 2000 cut-off date

	Randomized treatment		All patients
Survival status	**Anastrozole 1 mg (n = 340)**	**Tamoxifen 20 mg (n = 328)**	**(n = 668)**
Alive[a]	212 (62.4)	209 (63.7)	421 (63.0)
Dead	128 (37.6)	119 (36.3%)	247 (37.0)

However, the death rates were similar (37.6% vs. 36.3%) between the two groups at the second time of data cut-off (February 23, 2000). With the minimum follow-up of 8 months at the time of the original submission, the curves for Arimidex and tamoxifen were similar up to this 8-month time point; however, there was a degree of divergence beyond this point. With the minimum 20-month follow-up data now available, the curves remain closed out to 20 months. The sponsor believes that the previous appearance of the Kaplan-Meier curves was likely to have been the result of chance events involving a small number of patients.

8.1.11 Age and Ethnicity Analysis

The applicant conducted age and ethnicity analysis. There was no difference in efficacy between Arimidex and Tamoxifen based on age. There were too few non-caucasians in the study for any meaningful ethnicity analysis to be performed. Patients ≥65 years of age had better overall efficacy results on both Arimidex and Tamoxifen than patients ≤65 years of age. *See Statistician's report for details.*

8.1.12 Applicant's Evaluation of efficacy results

The median duration of follow-up was 572 days, with 74.3% of patients having progressed at the time of data cut-off. These results are adequate for obtaining clinically reliable data for the 2 primary efficacy end points of time to progression and objective-response rate. Intention-to-treat analyses of both primary endpoints found that anastrozole met the pre-specified criteria for non-inferiority, compared with tamoxifen. For time to progression, the adjusted analysis (designated as the primary analysis) yielded a hazard ratio tamoxifen:anastrozole, of 0.99 and a lower 95% confidence limit of 0.86 (greater than the 0.8 confidence limit required for non-inferiority). The unadjusted analysis also demonstrated non-inferiority with a hazard ratio of 1.01 and a lower 95% confidence limit of 0.87. Similar progression rates and median times to progression were found for anastrozole (73.2% and 251 days) and tamoxifen (75.3% and 252 days) at the time of data cut-off. The per-protocol analyses for time to progression yielded hazard ratios of 0.97 and 0.98
for the adjusted and unadjusted analyses, with lower 95% confidence limits of 0.83 and 0.84. The consistent results of all analyses affirmed the robustness of the data and showed

anastrozole to be equivalent to tamoxifen for time to progression. Time to progression for patients in both treatment groups was broadly similar to what has been found in other first-line trials of tamoxifen in the treatment of post-menopausal women with advanced disease

For the objective-response rate, the adjusted analysis yielded an estimated difference in response rates of -1.01% (slightly in favor of tamoxifen), with a lower 95% confidence limit of -6.74% (greater than the -10% confidence limit required for non-inferiority). The unadjusted analysis for objective-response rate yielded an estimated difference in response rates of 0.32% (slightly in favor of anastrozole), with a lower 95% confidence limit of -5.37%. Thus, anastrozole was seen to be equivalent to tamoxifen in the proportion of patients who achieved a best objective response of CR or PR. The per-protocol analysis yielded estimated differences in response rates of -2.73% and -1.26% for the adjusted and unadjusted analyses, respectively, both favoring tamoxifen, but both meeting criteria for non-inferiority for anastrozole (lower 95% confidence limits of -8.86% and -7.34%, respectively). The consistent results for all analyses showed anastrozole to be equivalent to tamoxifen for objective response rate. The number of responders (ie, had a best objective response of complete or partial response) was 112 (32.9%) patients who were randomized to anastrozole and 107 (32.6%) patients who were randomized to tamoxifen. The adjusted analysis of time to treatment failure yielded a hazard ratio of 1.03 with lower 95% confidence limit of 0.89, while the unadjusted analysis yielded a hazard ratio of 1.04 with lower 95% confidence limit of 0.90. Anastrozole was thus shown to be equivalent to tamoxifen in time to treatment failure. The duration of clinical benefit was seen to be longer in patients who were randomized to anastrozole compared with those that were randomized to tamoxifen. This is in contrast to the duration of response results where an advantage for tamoxifen was observed. These results must be interpreted cautiously because they represent small numbers of patients grouped by response to therapy. No statistical analyses of these data were planned in the protocol, and none was done. Two-year survival was 67.9% for patients given anastrozole and 73.3% for patients given tamoxifen, while the death rate was 26.8% for anastrozole and 22.6% for tamoxifen. Because only 24.7% of the patients in the trial had died at the time of data cut-off, there were too few patients to allow meaningful statistical analysis. Significant protocol violations occurred for 1.5% (10/668) of the patients and significant protocol deviations for 12.1% (81/668) of the patients. The most common deviation was missing more than 25% of the tumor assessments (4.8% of patients). The intention-to-treat analysis and per-protocol analysis for the 2 secondary efficacy end points, for which the data were mature enough to undergo analysis, were similar, indicating that those patients who were excluded from the per-protocol analysis had little effect on the outcome. Response rates of 19% to 49% have previously been reported in first-line trials of tamoxifen in advanced disease; The overall response rates in this trial for both anastrozole and tamoxifen were in the middle of this range. Response was assessed by an algorithm which strictly applied the protocol definition of response.

As would be expected in evaluating the response rate in patients with different sites of disease at entry, the objective-response rate (complete and partial response) in patients with soft tissue and/or lung disease only was found to be much higher in both treatment groups than that in patients with all other disease combinations This finding supports

published data on endocrine treatment for advanced breast cancer in relation to response of disease site. In this study, there were similar numbers of patients with soft tissue disease only (except for lung metastases where more patients with lung metastases were randomized to tamoxifen), and all other disease combinations in both treatment groups. The proportion of patients who did not respond but received clinical benefit, that is had stable disease for 24 weeks or more, was similar in both treatment. In trials using less rigorous response criteria, it is likely that many of the patients who received clinical benefit would have been classified as responders. Previous studies of endocrine therapy for advanced breast cancer have shown that curves of time to progression and survival for patients who had stable disease for 6 months or more did not differ significantly from those for patients who had a partial response Following progression, a similar proportion of patients in both treatment groups went on to receive chemotherapy and radiotherapy, but the number of patients receiving hormonal therapy was greater in the tamoxifen group.

In this trial, equivalence of anastrozole and tamoxifen was demonstrated for both primary end-points of time to progression and objective response rate. These findings suggest that anastrozole was at least as efficacious as tamoxifen for the treatment of postmenopausal women with advanced breast cancer.

8.1.13 SAFETY RESULTS

All 665 treated patients were included in the safety evaluation according to actual treatment received. All adverse events that occurred during treatment or within 14 days after stopping treatment for any reason (2 week follow-up period) were recorded.

Exposure: Duration of Trial treatment

Of the 665 treated patients, 336 were randomized to treatment with anastrozole and 329 to tamoxifen. Table 14 summarizes the extent of exposure to trial treatment and the duration of treatment (defined as the number of days from the date of first dose until the date of last dose the last date of contact was assigned to any patient who was not withdrawn from trial treatment) by treatment group.

The distribution of duration of treatment was similar between the 2 treatment groups, with the exception of the period >48 to ≤96 weeks where the proportion of patients who were given anastrozole was greater than the proportion of patients who were given tamoxifen. The median duration of treatment was similar for patients who were given anastrozole, compared with patients who were given tamoxifen.

Table 14 **Extent of exposure to trial treatment and duration of treatment**

Parameter	Duration of treatment >0 ≤12 weeks	>12 ≤24 weeks	>24 ≤48 weeks	>48 ≤96 weeks	>96 weeks	Median (days)	Range
Anastrozole 1 mg (n = 336)	52 (15.5%)	67 (19.9%)	73 (21.7%)	107 (31.8%)	37 (11.0%)	263	-
Tamoxifen 20 mg (n = 329)	49 (14.9%)	69 (21.0%)	82 (24.9%)	82 (24.9%)	47 (14.3%)	253	

Table 15: Adverse events reported for more than 5% of patients in either treatment group during treatment, by body system

Body system and adverse event	Number (%) of patients Anastrozole 1 mg (n = 336)		Tamoxifen 20 mg (n = 329)	
Body as a whole	122	(36.3)	118	(35.9)
Asthenia	29	(8.6)	16	(4.9)
Pain	27	(8.0)	25	(7.6)
Back pain	19	(5.7)	25	(7.6)
Headache	18	(5.4)	13	(4.0)
Flu syndrome	20	(6.0)	19	(5.8)
Cardiovascular system	100	(29.8)	117	(35.6)
Vasodilatation	66	(19.6)	62	(18.8)
Hypertension	18	(5.4)	27	(8.2)
Digestive system	95	(28.3)	105	(31.9)
Nausea	42	(12.5)	44	(13.4)
Constipation	21	(6.3)	28	(8.5)
Anorexia	7	(2.1)	17	(5.2)
Metabolic and nutritional system	37	(11.0)	37	(11.2)
Peripheral oedema	21	(6.3)	18	(5.5)
Musculoskeletal system	57	(17.0)	54	(16.4)
Bone pain	21	(6.3)	20	(6.1)
Nervous system	72	(21.4)	66	(20.1)
Depression	14	(4.2)	18	(5.5)
Respiratory system	72	(21.4)	81	(24.6)
Cough increased	19	(5.7)	23	(7.0)
Pharyngitis	15	(4.5)	30	(9.1)
Dyspnoea	18	(5.4)	18	(5.5)
Bronchitis	6	(1.8)	17	(5.2)

DEATHS

Most patients 69 (20.5%) who were given anastrozole and 60 (18.2%) patients who were given tamoxifen died from causes related to breast cancer either during treatment (including the 14-day follow-up period) or after treatment had been withdrawn. A greater

proportion of patients who were given anastrozole (27.1%), compared with patients who were given tamoxifen (22.5%), had died by the time of data cut-off. Some of this difference is the result of a greater number of non-breast cancer related deaths that occurred more than 14 days after the withdrawal of trial therapy for the group of patients who were given anastrozole 15 (4.5%) patients, compared with patients who were given tamoxifen 7 (2.1%) patients. No patterns were seen in the cause of death for patients who died of non-breast cancer causes after treatment had been stopped.

Table 16 Adverse events leading to withdrawal from treatment

Body system and adverse event	Number (%) of patients Anastrozole 1 mg (n = 336)		Tamoxifen 20 mg (n = 329)	
Total number of patients who had adverse events that led to withdrawal	15	(4.5)	19	(5.8)
Abdominal pain	1	(0.3)	1	(0.3)
Cardiovascular system	3	(0.9)	8	(2.4)
Cerebrovascular accident	1	(0.3)	3	(0.9)
Embolus	1	(0.3)	1	(0.3)
Heart failure	1	(0.3)	0	
Vascular disorder	1	(0.3)	0	
Pulmonary embolus	0		2	(0.6)
Atrial fibrillation	0		1	(0.3)
Cerebral haemorrhage	0		1	(0.3)
Congestive heart failure	0		1	(0.3)
Retinal vein thrombosis	0		1	(0.3)
Digestive system	6	(1.8)	1	(0.3)
Diarrhea	2	(0.6)	0	
Nausea	2	(0.6)	1	(0.3)
Constipation	1	(0.3)	0	
GI neoplasia	1	(0.3)	0	
Haemic and lymphatic system	1	(0.3)	0	
Lymphoma like reaction	1	(0.3)	0	
Metabolic and nutritional system	2	(0.6)	2	(0.6)
Special senses	2	(0.6)	0	
Amblyopia	2	(0.6)	0	
Musculoskeletal system	0		1	(0.3)
Pathological fracture	0		1	(0.3)
Respiratory system	0		3	(0.9)
Dyspnoea	0		2	(0.6)
Pneumonia	0		1	(0.3)
Urogenital system	0		3	(0.9)

* A patient may have had more than 1 adverse event leading to withdrawal

The incidence of serious adverse events, serious adverse events leading to withdrawal, and serious drug-related adverse events was slightly lower in the group of patients who were given anastrozole, compared with the group of patients who were given tamoxifen. The incidence of serious adverse events leading to death was slightly greater in the group of patients who were given anastrozole than in the group of patients who were given tamoxifen. However, none of these events was considered to be related to trial treatment Serious adverse events that were reported for at least 1% of patients in either treatment group are presented in Table 17.

Table 17 Serious adverse events reported for at least 1% of patients in either treatment group during treatment, by body system

Body system and adverse event [a]	Number (%) of patients			
	Anastrozole 1 mg (n = 336)		Tamoxifen 20 mg (n = 329)	
Cardiovascular system[b]	11	(3.3)	21	(6.4)
Cerebrovascular accident	3	(0.9)	4	(1.2)
Digestive system[b]	11	(3.3)	7	(2.1)
Nausea	4	(1.2)	2	(0.6)
Musculoskeletal system[b]	5	(1.5)	9	(2.7)
Pathological fracture	3	(0.9)	6	(1.8)
Nervous system[b]	7	(2.1)	4	(1.2)
Convulsion	4	(1.2)	0	
Respiratory system[b]	8	(2.4)	12	(3.6)
Dyspnoea	1	(0.3)	4	(1.2)

[a] A patient may have had more than 1 serious adverse event.
[b] Values given for each body system include all adverse events reported.

The number of serious adverse events in the cardiovascular system reported by patients who were given tamoxifen was almost double that seen in the group of patients who were given anastrozole. Patients who were given tamoxifen also reported a slightly greater proportion of serious adverse events in the musculoskeletal and respiratory systems compared with patients who were given anastrozole. Serious events in the digestive and nervous systems were more frequently reported by patients who were given anastrozole group, compared with patients who were given tamoxifen. Four patients who received anastrozole had a serious adverse event of convulsions. A possible contributory cause to the convulsions was present in 3 of these patients: 1 patient had intracerebral bleeding, 1 patient had brain metastases, and 1 patient had the event following an operation. Of the individual serious adverse events, pathological fracture, cerebrovascular accident, and nausea were the most commonly reported. The largest differences between the treatment groups were for the events of convulsion (4 incidences reported by patients who were given anastrozole, compared with none in patients who were given tamoxifen), pathological fracture (3 incidences and 6 incidences in patients who were given

anastrozole and tamoxifen, respectively), and dyspnea (1 incidence and 4 incidences, respectively).

Reviewer's Comments: There appears to be more serious thromboembolic and pulmonary complications with Tamoxifen and more serious GI complications with Anastrozole.

CLINICAL LABORATORY DATA

TABLE 18: Summary of Laboratory abnormalities in Hematology and Biochemistry

	ANASTROZOLE N = 336		TAMOXIFEN N = 329		TOTAL N = 665	
	N	%	N	%	N	%
AT LEAST ONE ZENECA DEFINED LABORATORY ABNORMALITY	57	17.0	69	21.0	126	18.9
ALKALINE PHOSPHATASE	19	5.7	11	3.3	30	4.5
ALT	3	0.9	6	1.8	9	1.4
AST	7	2.1	4	1.2	11	1.7
CALCIUM	1	0.3	1	0.3	2	0.3
CHOLESTEROL	5	1.5	5	1.5	10	1.5
CREATININE	1	0.3	1	0.3	2	0.3
GAMMA GLUTAMYL TRANSFERASE	11	3.3	16	4.9	27	4.1
HAEMOGLOBIN	7	2.1	21	6.4	28	4.2
PLATELETS	3	0.9	0	0.0	3	0.5
POTASSIUM	9	2.7	14	4.3	23	3.5
SODIUM	2	0.6	1	0.3	3	0.5
TOTAL BILIRUBIN	4	1.2	1	0.3	5	0.8
WHITE CELL COUNT	9	2.7	7	2.1	16	2.4

Laboratory abnormalities were observed for all 3 hematology variables assessed. A smaller proportion of patients who were given anastrozole, compared with patients who were given tamoxifen, had abnormal hemoglobin levels during treatment. All of these abnormalities were the result of a low hemoglobin value. Investigations into the possible causes of the difference in occurrence of low hemoglobin values between the 2 treatment groups showed that the incidence of bone marrow disease and elevated bilirubin levels was similar across the groups. The only abnormal platelet counts (all lower than normal) were observed in patients who were given anastrozole. Similar proportions of patients in each group had abnormal WBC counts.

BIOCHEMICAL ABNORMALITIES

Mean cholesterol levels decreased slightly over the first 84 weeks in patients who were given tamoxifen but remained stable in patients who were given anastrozole. In both treatment groups mean triglyceride and apolipoprotein A levels were seen to increase with time while mean levels for HDL, lipoprotein A, and GGT decreased with time. Mean LDL levels remained stable with time in the group of patients who were given anastrozole and decreased slightly in the group of patients who were given tamoxifen. No significant changes or trends were seen in bilirubin or albumin levels in either

treatment group. However, for the group of patients who were given anastrozole, the mean levels were seen to gradually increase over the first 96 weeks before falling to pre-treatment levels while in the group of patients who were given tamoxifen the reverse was seen with levels initially decreasing until Week 84 and then increasing to pre-treatment levels.

Table 19 **Mean values for Lipid biochemistry variables before and during treatment**

Variable	Number of weeks									
	Baseline	12	24	48	72	84	96	108	120	132
Total cholesterol (mmol/l)										
Anastrozole 1 mg										
n	308	262	187	133	52	39	24	17	8	7
Mean	5.9	6.1	6.0	6.0	6.0	6.2	6.4	6.0	5.8	6.0
Tamoxifen 20 mg										
n	307	253	193	121	50	36	29	23	18	6
Mean	6.0	5.7	5.6	5.6	5.5	5.2	5.5	5.7	6.1	5.7
Triglycerides (mmol/l)										
Anastrozole 1 mg										
n	308	262	187	133	52	39	24	17	8	7
Mean	1.87	1.90	1.99	1.98	2.01	2.08	1.82	1.80	2.09	1.72
Tamoxifen 20 mg										
n	306	253	193	121	50	36	29	23	18	6
Mean	1.91	2.06	2.06	2.02	1.79	1.96	1.94	1.95	1.75	2.49
Apolipoprotein A (mg/dl)										
Anastrozole1 mg	306	260	186	133	51	39	24	17	8	7
n	144	148	152	154	157	158	168	162	162	154
Mean										
Tamoxifen 20 mg	304	252	190	121	50	36	29	23	18	6
n	144	160	162	166	171	170	174	183	191	187
Mean										

Table 19A: HDL Cholesterol Biochemistry Profile

		NOMINAL TRIAL TIME								
		ENTRY	WEEK 12	WEEK 24	WEEK 36	WEEK 48	WEEK 60	WEEK 72	WEEK 84	WEEK 96
ANASTROZOLE N = 336	N	306	263	186	169	132	80	52	38	23
	MEAN	2.4	2.8	1.4	1.4	1.5	1.4	1.4	1.4	1.6
	SD	17.65	23.53	0.40	0.42	0.46	0.42	0.41	0.43	0.41
	MIN	0.4	0.6	0.5	0.6	0.6	0.6	0.6	0.6	0.9
	MAX	310.0	383.0	2.8	3.0	2.8	2.4	2.4	2.6	2.4
TAMOXIFEN N = 329	N	304	250	180	158	121	69	50	36	29
	MEAN	2.7	1.4	1.4	1.4	1.5	1.4	1.5	1.5	1.5
	SD	28.48	0.40	0.38	0.42	0.39	0.39	0.41	0.40	0.51
	MIN	0.3	0.2	0.6	0.6	0.6	0.6	0.9	0.9	0.8
	MAX	353.0	3.0	2.6	3.4	3.2	2.6	3.2	2.2	3.4

Table 19B: LDL Cholesterol Biochemistry Profile

		NOMINAL TRIAL TIME								
		ENTRY	WEEK 12	WEEK 24	WEEK 36	WEEK 48	WEEK 60	WEEK 72	WEEK 84	WEEK 96
ANASTROZOLE N = 336	N	304	262	185	169	132	80	52	38	23
	MEAN	3.7	3.8	3.7	3.7	3.6	3.7	3.7	3.9	4.1
	SD	1.12	1.10	1.00	1.04	1.01	0.96	0.90	0.90	0.90
	MIN	1.2	0.4	0.9	1.6	1.5	1.6	2.1	2.1	2.6
	MAX	10.0	9.9	6.5	6.6	7.3	7.5	5.9	5.6	5.9
TAMOXIFEN N = 329	N	302	250	180	158	121	69	50	36	29
	MEAN	3.8	3.4	3.3	3.3	3.2	3.3	3.2	2.9	3.1
	SD	1.09	1.01	1.17	1.20	1.29	1.44	0.97	0.69	0.77
	MIN	1.3	0.9	0.8	1.2	1.3	1.5	1.5	1.8	2.0
	MAX	7.5	9.3	13.5	12.6	13.3	12.9	5.7	4.5	4.6

Nineteen patients who were given anastrozole had abnormal alkaline phosphatase levels. Thirteen of these patients (68.4%) had bony disease, 4 (21.1%) patients had liver disease, with 2 (10.5%) patients being included in both of these groups. The abnormal result was reported within 1 month (before or after) of disease progression in 13 (68.4%) patients; 12 (63.2%) of these patients had bony disease and 2 (10.5%) had liver disease.

For patients who were given tamoxifen, 11 patients reported abnormal alkaline phosphatase levels. Nine of these patients (81.8%) had bony disease and 1 (9.1%) had both liver and bony disease. The abnormal result was reported within 1 month of progression in 6 (54.5%) patients all of whom had bony disease with 1 patient also having liver disease. One patient did not have disease progression; this patient did not have bony disease.

Abnormal total bilirubin levels were observed in 4 patients who were given anastrozole, 2 of whom had liver metastases. In the tamoxifen group, only 1 patient had a abnormal total bilirubin; this patient had liver metastases and the event occurred within 1 month of disease progression.

Table 20: Serum Alkaline Phosphatase Biochemistry Profile

		NOMINAL TRIAL TIME								
		ENTRY	WEEK 12	WEEK 24	WEEK 36	WEEK 48	WEEK 60	WEEK 72	WEEK 84	WEEK 96
ANASTROZOLE N = 336	N	316	265	188	171	134	79	52	39	24
	MEAN	268	263	221	214	218	227	246	239	229
	SD	204.2	263.8	102.6	83.0	87.7	87.7	149.8	160.9	175.5
	MIN	4	47	44	57	52	74	88	85	83
	MAX	1705	3245	835	725	750	720	1090	956	985
TAMOXIFEN N = 329	N	307	253	192	159	121	69	51	37	29
	MEAN	265	200	179	175	164	157	161	170	144
	SD	213.4	110.7	116.8	125.9	75.1	85.5	75.0	67.3	42.5
	MIN	51	45	45	46	49	36	46	64	49
	MAX	2842	877	1300	1326	600	672	515	411	256

A smaller proportion of patients (9 [2.7%] patients) who were given anastrozole had abnormal potassium values at any time during treatment compared with patients who were given tamoxifen (14 [4.3%] patients). The majority of these abnormal values were as a result of an increase in potassium levels. There were few abnormal values for creatinine, sodium, and calcium in the 2 treatment groups.

8.1.14 Age and Ethnicity Analysis of Safety

The applicant conducted age and ethnicity analysis. There was no difference in safety parameters between Arimidex and Tamoxifen based on age. There were too few non-caucasians in the study for any meaningful ethnicity analysis to be performed.

8.1.15 Applicant's Evaluation of safety results

In general, the numbers of adverse events, serious adverse events, events leading to withdrawal, and events leading to death were similar between the 2 treatment groups. In the pre-specified categories of pharmacologically expected adverse events, the occurrence of tumor flare and weight gain were the same in both treatment groups. A lower proportion of patients who were given anastrozole, compared with those who were given tamoxifen, reported depression, thromboembolic disease, hot flushes, lethargy, and vaginal bleeding. The reviewer however believes the data provided do not support the sponsor's claim that there was a lower proportion of gastrointestinal disturbances among patients who were given anastrozole, than patints who were given tamoxifen. A higher proportion of patients who received anastrozole reported vaginal dryness. This might be

due to anastrozole's ability to lower serum estradiol levels to the limit of detection, whereas tamoxifen has some estrogen-agonist activity.

A slightly smaller percentage of patients who were given anastrozole reported respiratory adverse events compared with patients who were given tamoxifen. Specifically, the reported incidence of cough, pharyngitis, and bronchitis was lower in the group of patients who were given anastrozole, compared with the group of patients who were given tamoxifen. There were no notable differences in leukocyte levels between the treatment groups throughout the study that may have suggested a reason behind the differences in the observed incidences of respiratory adverse events. No patient withdrew from the study as a result of experiencing a respiratory event. A greater number of patients who were given anastrozole experienced asthenia compared with those who were given tamoxifen.

Over one-third of the patients in the trial had drug-related adverse events. The most commonly reported drug-related adverse events were vasodilatation, nausea, leukorrhoea, and alopecia with the proportion of patients who experienced these events being similar in both treatment groups. More patients in the tamoxifen group had leukorrhoea, while the incidence of alopecia was higher in patients treated with anastrozole. Vaginal bleeding and vaginal discharge (leukorrhoea) were more common in patients who received tamoxifen, and vaginal dryness was more common in patients who received anastrozole. This is consistent with the known pharmacological profile of anastrozole, which would not be expected to have oestrogenic effects or oestrogenic effects on the endometrium.

Overall, 165 patients died during the trial with a greater proportion of deaths being reported in patients who were given anastrozole (91/165, 55.2%) than those who were given tamoxifen (74/165, 44.8%). The majority of the deaths 129/165, (78.2%) were related to breast cancer, including 11 patients (7 who were given anastrozole and 4 who were given tamoxifen) who died during treatment.
Seven patients who were given anastrozole, compared with 6 patients who were given tamoxifen, died as a result of adverse events experienced during treatment. The most frequently reported adverse events resulting in death (4 patients in each group) were associated with the cardiovascular system. None of the adverse events that led to death was considered to be related to trial treatment.

Fifteen (4.5%) patients who were given anastrozole, compared with 19 (5.8%) patients who were given tamoxifen, experienced adverse events which led to withdrawal A smaller proportion of patients who were given anastrozole compared with those who were given tamoxifen was withdrawn following cardiovascular-related events (0.9% and 2.4%, respectively) while the proportion of patients withdrawn because of gastrointestinal (digestive) events was greater in the patients who were given anastrozole (1.8% and 0.3%, respectively). There were 3 patients given anastrozole who experienced a serious drug-related adverse event that led to withdrawal (headache, blurred vision, and nausea). There were 7 such patients given tamoxifen (retinal vein thrombosis, hypercalcaemia,

depression, atrial fibrillation/cerebrovascular accident/pulmonary embolism, dyspnea/pulmonary embolism, and cerebrovascular accident).

The overall incidence of serious adverse events was similar between the treatment groups (14.9% for anastrozole and 17.3% for tamoxifen). The largest difference between the 2 treatment groups in serious adverse events was reported for cardiovascular-related events (3.3% of patients who were given anastrozole, 6.4% of patients who were given tamoxifen).

Despite concerns about the effect of anastrozole on bone mineral density, fractures were more common in patients who received tamoxifen (6 patients) than anastrozole (3 patients). An increase in joint symptoms (arthritis, arthrosis and arthralgia) was seen in patients who were given anastrozole, but a causal relationship and physiological mechanism remains uncertain.

Abnormalities in hematology and clinical chemistry assessments were reported in patients in both treatment groups. The most frequent abnormalities of clinical chemistry were raised levels of alkaline phosphatase, gamma glutamyltransferase, the transaminases, and potassium, which all appeared to be related to the disease process. Of particular note was the finding that of the 30 patients who had a abnormalities in alkaline phosphatase levels, 22 had bony disease. In the 20 incidences when the abnormal alkaline phosphatase level was within 1 month of the date of progression, 18 of the patients had bony disease. Low hemoglobin concentrations were noted in patients in both treatment groups, as were leukopenia or leukocytosis, and occasionally thrombocytopenia. These were considered to be probably related to the disease process or an inter-current illness. Due to the small number of these abnormalities, it was not possible to define any trends within each group and, in general, the incidence of abnormalities was similar in both treatment groups.
Overall, there were no discernible trends in changes in hematological or biochemical parameters in either of the treatment groups. As expected in a large group of patients with advanced breast cancer, it was not uncommon to see isolated laboratory results above or below the reference range or as persistent features within individual patients. Many of these abnormal results were present at entry to the trial and were related to disease state, and changes throughout the trial followed patterns consistent with disease progression.

As expected, there was a large number of recorded adverse events, many of which were related to disease and disease progression. The majority of the more common adverse events were seen in similar numbers in both treatment groups. Although both serious and non-serious cases of thromboembolic events were seen more frequently in the patients who were given tamoxifen, serious adverse events of nausea and diarrhea were seen more frequently in patients who were given anastrozole. There were more serious drug-related adverse events in patients who were given tamoxifen than in patients who were given anastrozole, and, overall, more patients who were given tamoxifen had serious adverse events which led to withdrawal from the trial compared with the group of patients who were given anastrozole. Overall, both anastrozole and tamoxifen were well tolerated.

8.1.16 Applicant's Overall Conclusions of Trial 1033IL/0027

The trial was designed to evaluate the efficacy and tolerability of anastrozole compared with tamoxifen as a first-line therapy in the treatment of advanced breast cancer in post-menopausal women. Anastrozole satisfied the pre-defined criteria for equivalence to tamoxifen for the 2 primary endpoints of time to disease progression and objective-response rate in both the intention-to-treat and per-protocol analyses. Supporting results were observed from the secondary end points. The data had not matured enough at the time of database lock to carry out an analysis of survival. Therefore, one may conclude that anastrozole is at least as effective as tamoxifen in the first-line treatment of advanced breast cancer in postmenopausal women.

In general, both treatments were well tolerated by the patients with similar rates of adverse events, serious adverse events, adverse events leading to withdrawal, and adverse events leading to death being reported for both treatment groups. As expected in a group of patients with advanced breast cancer, there was a large number of recorded adverse events, many of which were related to the disease and disease progression. The majority of the more commonly reported adverse events were seen in similar numbers in both treatment groups. Among the pre-specified adverse event categories, depression, thromboembolism, gastrointestinal disturbances, and lethargy were less common in patients who were given anastrozole compared with tamoxifen. Patients treated with tamoxifen reported more serious and non-serious cases of thromboembolic events, experienced more serious drug-related adverse events, and a greater proportion of these events led to withdrawal when compared with the anastrozole group.

These data support the use of anastrozole as first-line therapy in post-menopausal women with advanced breast cancer.

Protocol 0030

8.2. Protocol 1033IL/0030

8.2.1.1 RATIONALE

Same as for Protocol 0027

8.2.1.2 OBJECTIVES

The objective of this trial was to compare the efficacy and safety of anastrozole (1mg daily) with tamoxifen (20mg daily) as first line therapy for advanced breast cancer in post menopausal women.

The primary objectives of this trial were to compare anastrozole with tamoxifen, based on the following measures:

- time to progression
- objective-response rate
- safety

The secondary objectives of this trial were to compare the 2 treatment groups based on the following measures:

- time to treatment failure
- time to death (survival)
- duration of response
- duration of clinical benefit
- analgesic use
- World Health Organization (WHO) performance score
- bone pain
- health economics

8.2.1.3 Trial Design

A randomized, double-blind, double-dummy, multicenter trial conducted in institutions in North America. Patients were randomized in a 1:1 ratio to oral treatment with anastrozole (1 mg once daily) plus tamoxifen placebo, or tamoxifen (20 mg once daily) plus anastrozole placebo. Placebos were added to protect the double-blind because the anastrozole and tamoxifen tablets were not similar in appearance.

Patients were given their randomized treatment until there was sufficient objective evidence of disease progression to stop treatment. For patients who were withdrawn from trial treatment for reasons other than disease progression, tumor assessments continued to be performed until disease progression was observed. Patients who were withdrawn from trial treatment for any reason were followed at 6-month intervals for survival until death.

All adverse events were documented and details of concurrent medications were recorded 14 days after cessation of trial treatment. Patients who were withdrawn from trial treatment because of an adverse event had tumor assessments every 3 months until disease progression, whenever possible.

Because this trial was analyzed on an intention-to-treat basis, all randomized patients were monitored until objective disease progression or death occurred, irrespective of actual trial treatment given.

8.2.2 Protocol amendments

There were three protocol amendments in these trials

- 8 July 1996: allowed for concomitant treatment with bisphosphonates in those countries where this medication had been registered for the treatment of bone metastases related to breast cancer.
- 15 December 1997: allowed for an increase in patient enrolment from 426 to 660.
- 30 March 1998: allowed for statistical modifications and clarification in statistical methods, as well as amendments to add age as an independent covariate.

8.2.3 Protocol

8.2.3.1 Trial Population:

A total of 353 patients from 97 centers were entered in the trial. Patients were recruited from 26 February 1996 to 9 July 1998. Data collected up to cut off date of 10 March 1999 constituted the substance of this submission. The database was locked 1 month after this data cut-off date with unblinding of the treatment groups only occurring after this lock had been performed. The estimation of sample size was based on the primary efficacy end points of time to
progression and objective-response rate. The trial was powered to demonstrate non inferiority, as defined by the confidence intervals, for each of these end points.
For time to progression, the lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen:anastrozole) had to be no less than 0.8 to assume non-inferiority. For response rate, the lower 1-sided 95% confidence limit for the difference in response rates (anastrozole – tamoxifen) had to be no less than –10% to assume non-inferiority.

The minimum follow-up time was 8 months.

8.2.3.2 Inclusion / Exclusion Criteria

Inclusion Criteria

Women with

1) histologic diagnosis of locally advanced or metastatic breast cancer suitable candidates for hormonal therapy as first-line therapy for advanced disease (patients may have been given adjuvant chemotherapy or hormonal therapy, but patients who had been given tamoxifen as adjuvant therapy must have had an interval of at least 12 months between stopping tamoxifen treatment and entering this trial)
2) post-menopausal status, defined as:
   (i) women aged 50 years or over who have not menstruated during the preceding 12 months or who have follicle stimulating hormone (FSH) levels within the post-menopausal range;

(ii) women under the age of 50 years who have FSH levels within the post-menopausal range
iii) having had bilateral oophorectomy

(3) hormone receptor status (estrogen receptor and/or progesterone receptor) positive or unknown

(4) measurable or evaluable disease

(5) informed consent for participation (documented preferably in writing although witnessed verbal consent was acceptable)

(6) WHO performance status score of 0,1, or 2

Exclusion criteria

Same as for protocol 0027, but includes women receiving gonadotropin-releasing hormone (GnRH) analogs

8.2.3.3 Withdrawal criteria

Same as for protocol 0027.

8.2.3.4 Assignment to treatment

Patient eligibility was established by trial site personnel before randomization to treatment. Randomization to trial treatment with anastrozole or tamoxifen. was assigned according to predetermined computer-generated randomization schemes prepared separately for each center by Zeneca personnel.

Within each level, a patient was assigned to the next sequential patient number at a given center and trial treatment was dispensed for that patient number.

Once a patient number was assigned, that number was not used again and a patient was not randomized more than once.

8.2.4 Study Therapy

8.2.4.1 Formulation

Same as for protocol 0027

8.2.4.2 Dosage Schedule

Patients were given a 12-week supply at Visits 1, 4 and 7 and at every visit thereafter until withdrawal from trial treatment.

8.2.4.3 Treatment-blinding technique

Same as for protocol 0027.

8.2.5 Concomitant treatment

Same as for protocol 0027

8.2.6 Efficacy assessments

8.2.6.1 Primary end points

Same as for protocol 0027

8.2.6.2 Secondary end points

Same as for protocol 0027

8.2.6.3 Methods of disease assessment

The schedule for timing of events and disease assessments is as indicated in Table 1

8.2.6.3.1 Time to progression

Same as for protocol 0027

8.2.6.3.2 Objective response

(a) Objective tumor assessments

Same as for protocol 0027.

(i) Measurement of local and regional disease

Same as for protocol 0027

(ii) Assessment of bone metastases

Same as for protocol 0027.

(iii) Assessment of pulmonary metastases

Same as for protocol 0027 except A chest radiograph was repeated every 24 weeks until disease progression and at withdrawal from trial treatment for any reason if no pulmonary metastasis was seen was seen, on chest radiograph before trial treatment began.

(iv) Assessment of liver and abdominal metastases

Same as for protocol 0027.

(v) Assessment of brain metastases

Same as for protocol 0027.

(b) Assignment of objective response

Same as for protocol 0027.

(i) Assignment of visit response in measurable disease

Same as for protocol 0027.

(ii) Assignment of visit response in non-measurable disease

Same as for protocol 0027.

(iii) Assignment of overall visit response

For each patient, the algorithm assigned an overall objective response for each visit, taking into account the visit response in both measurable and non-measurable disease. The categories of response (CR, PR, SD, PROG, and not evaluable) are defined in same manner as in protocol 0027. Assignment of objective response was similarly as in protocol 0027.

Time to treatment failure

Same as for protocol 0027..

Duration of response
Same as for protocol 0027.

Duration of clinical benefit
Same as for protocol 0027.
Time to death (survival)
Same as for protocol 0027.

Populations analyzed
The methods for analyses of study population were the same as for protocol 0027.

Statistical analysis
The equivalence of the 2 treatments, in terms of the primary and secondary end points, was assessed using non-inferiority criteria similarly to protocol 0027.
(a) Primary efficacy end points
Same as for protocol 0027.
(i) Time to progression
Same as for protocol 0027..
(ii) Objective-response rate
Same as for protocol 0027.

(b) Secondary end points
Same as for protocol 0027.
(i) Time to treatment failure
Same as for protocol 0027..
(ii) Duration of response and duration of clinical benefit
Same as for protocol 0027.
(iii) Time to death (survival)
Same as for protocol 0027.

8.2.7 Safety assessments

8.2.7.1 Adverse events
Methods of assessment
(a) All adverse events
Same as for protocol 0027.
(b) Serious adverse events
Same as for protocol 0027.

8.2.7.2 **Clinical laboratory assessments**
Methods of assessment
Same as for protocol 0027.

Other assessments

Same as for protocol 0027.

8.2 8 Statistical considerations

Interim analyses and Multiple testing

These analyses were carried out in protocol 0027 but not in protocol 0030

8.2.1.1.4 Results

8.2.1.1.4.1. **Patient Disposition,**

Comparability

Table 21 summarizes demographic details for all patients at entry.
A total of 353patients were randomized to trial treatment 171(48.4%) patients were randomized to anastrozole and 182 (51.6) were randomized to tamoxifen The mean age for all patients who were randomized to anastrozole was 67 years (range (30 to 88 years), and 67 years (range 30 to 92 years)for tamoxifen.. The age distribution was similar between the 2 treatment groups; however, slightly more patients in each treatment group were aged 65 years or more. The distribution of body mass index was similar between the 2 treatment groups. The majority (88.4%) of patients were Caucasian.

Table 21
Demographic characteristics

	Anastrozole 1 mg	**Tamoxifen 20 mg**	
Age (years)	**(n = 171) (%)**	**(n = 182) (%)**	**(n = 353) (%)**
Mean(Range)	67(	67(	67(
<65	74 (43.3)	76 (41.8)	150 (42.5)
>65	97 (56.7)	106 (58.2)	203 (57.5)
Body mass index (kg/m^2)			
n (%)	317 (93.2)	308 (93.9)	625 (93.6)
Mean (Range)	27(	27(	27(
Ethnic origin			
Caucasian	152 (88.9)	160 (87.9)	312 (88.4)
Afro-Caribbean	8 (4.7)	11 (6.0)	19(5.4)
Asian/Oriental	1 (0.6)	1 (0.5)	2 (0.6)
Hispanic	5 (2.9)	8 (4.4)	13(3.7)
Other	5 (2.9)	2 (1.1)	7(2.0)

Table 23 **Disease Characteristics**

DISEASE CHARACTERISTICS	ANASTROZOLE N=171	TAMOXIFEN N=182 (%)	ALL PATIENTS N= 353 (%)
Disease status at first diagnosis			
Advanced[a]	52 (30.4)	60 (33.0)	112 (31.7))
Early[b]	118 (69.0)	122 (67.0))	240 (68.0)
Unknown	1 (0.6)	0	1 (0.3)
Total	171(100.0)	182 (100.0)	353(100.0)
Disease measurability at entry			
Measurable disease[a]	117 (68.4)	140 (76.9)	257 (72.8)
No measurable disease[b]	54 (31.6)	42 (23.1)	96 (27.2
Sites of metastatic disease at entry			
Skin[c]	52(30.4)	50(27.5)	102 (28.9)
Lymph nodes	63 (36.8)	64 (35.2	127 (36.0)
Bone	112 (65.5)	98 (53.8)	210 (59.5)
Lung	76 (44.4)	68 (37.4)	144 (40.8)
Liver	13 (7.6)	30 (16.5)	43 (12.2)
Abdominal(excluding liver)	7 (4.1)	8 (4.4)	15 (4.2)
Other	0	1 (0.5)	1 (0.3)
No evaluable disease	2 (1.2)	2 (1.1)	4 (1.1)

a Patients with advanced disease at first diagnosis entered trial soon after diagnosis
bPatients with early disease at first diagnosis entered trial at disease recurrence

8.2.9.1.3 Breast cancer disease status at first diagnosis, site and extent of disease at entry:

Overall, most patients who entered the trial 257 (72.8%)) patients had measurable disease . In this study, unlike study 0027, fewer patients who were randomized to anastrozole had measurable disease, compared to patients who were randomized to tamoxifen. The majority of the patients in this study had *early* breast cancer at first diagnosis. The proportion with advanced breast cancer was however similar between the two treatment groups. The majority of patients in this trial had metastatic disease. *Bone* was the most frequent site of metastatic disease at entry in both treatment groups 210/353 (59.5) patients. More patients randomized to anastrozole had bony metastsis than patients randomized to tamoxifen. More patients who were randomized to tamoxifen however had metastasis to the liver 30 (16.5%)] patients, compared with patients who were randomized to anastrozole 13 (7.6%).

The extent of metastatic disease at entry was similar between the treatment groups.

8.2.9.1. Breast cancer history: Hormone Receptor and Disease Status at Diagnosis, Prior Adjuvant Therapy

Table 22 summarizes hormone receptor status characteristics, prior adjuvant therapy and disease status at entry, by treatment, and for all patients.
Hormone receptor status was similar between the 2 groups. In both groups, the sponsor reports the majority of patients had estrogen-receptor (ER) positive and/or progesterone-receptor (PR) positive breast cancer; 151 (88.3%) anastrozole patients, versus 162 (89.0) patients randomized to tamoxifen. The remaining patients were mostly of unknown ER or PR status; however

Reviewer's Comments: Unlike protocol 0027 ER/PR studies were obtained in the majority of patients. More patients in protocol 0030 had been exposed to prior adjuvant therapy, especially hormonal therapy than in protocol 0027.These factors could provide differences in results between the two studies.

TABLE 22 PATIENT CHARACTERISTICS

PATIENT CHARACTERISTICS	ANASTROZOLE N= 171) (%)	TAMOXIFEN N=182 (%)	ALL PATIENTS N= 353 (%)
Hormone Receptor Status			
ER+/PR+	151 (88.3)	162 (89.0)	313 (88.7)
ERUnknown/PR Unknown	19(11.1)	20 (11.0)	39 (11.0)
All other combinations	20 (11.7)	20 (11.0)	40 (11.3)
Prior Adjuvant Therapy			
No previous adjuvant therapy	102 (59.6)	111 (61.0)	213 (60.3)
Previous adjuvant therapy	68 (39.8)	70 (38.5)	138 (39.1)
Hormonal	21 (12.3)	20(11.0)	41 (11.6)
Cytotoxic	32 (18.7)	37 (20.3)	69 19.5)
Hormonal and cytotoxic	15 (8.8)	13 (7.1)	28(7.9)

Prior Adjuvant therapy status
The majority of patients in both groups had not been given previous adjuvant therapy. The proportions of patients who had been given either hormonal, cytotoxic, or hormonal and cytotoxic adjuvant therapy were similar between the 2 treatment groups. Thirty-six (21.1%) patients who were randomized to anastrozole and thirty three (18.1%) patients who were randomized to tamoxifen had been given previous hormonal therapy (either hormonal treatment only or both hormonal and cytotoxic treatment).

The estimated median duration of previous adjuvant hormonal treatment was *longer* for patients who were randomized to anastrozole (257 weeks), compared with patients who were randomized to tamoxifen (104 weeks).

8.2.9.1 4 Withdrawals

Table 24 Reasons for withdrawal from trial treatment by treatment given

Primary reason for withdrawal	Number of patients			
	Anastrozole 1 mg (n = 170) (%)		**Tamoxifen 20 mg (n = 182) (%)**	
Total number of patients who withdrew	122	(71.8)	142	(78.0)
Death	6	(3.5)	2	(1.1)
Adverse event	8	(4.7)	7	(3.8)
Protocol non-compliance	5	(2.9)	3	(1.6)
Disease progression (investigator's opinion)	94	(55.3)	122	(67.0)
Informed consent withdrawn	2	(1.2)	5	(2.7)
Miscellaneous other reasons	7	(4.1)	3	(1.6)
Other reason	6	(1.8)	7	(2.1)

264 (75%) patients who started trial treatment withdrew from the trial, 122 (71.8%) patients were on anastrozole and 142 (78.0%) patients were on tamoxifen.
The majority of all patients (61.4%) withdrew because of disease progression.
10 patients withdrew from trial treatment for other reasons. 7(4.1%) patients who were given anastrozole and 3(1.6%) patients who were given tamoxifen withdrew for other reasons.

8.2.9.4 Protocol violations and deviations

A protocol violation was defined as any infringement of the protocol selection criteria.
A protocol deviation was defined as any departure from the protocol design or procedures after the patient had entered the trial. Categories are not mutually exclusive (ie, a patient may have violated or deviated from the protocol more than once and the violations or deviations may have occurred in different categories).
The secondary efficacy (per-protocol) analyses of time to progression, objective-response rate, and time to death (survival) excluded patients who had significant protocol violations or deviations.

Protocol violators and deviators:Total	62 (17.5%)
randomized to Anastrozole	30
randomized to Tamoxifen	32

Most frequent protocol deviation in both Anastrozol and Tamoxifen groups were:
use of disallowed concurrent therapy especially glucocorticoids
"significant interruption of trial therapy" in the opinion of the investigator

8.2.9.4.2 Patients included in the efficacy and safety analyses

All 353 randomized patients were included in the primary (ITT) analyses for all efficacy and demographic end points. After excluding the 62 (17.5%) patients who had significant protocol violations or deviations, or both, a total of 283 (80.2%) patients were included in the secondary analyses for the 3 efficacy end points of time to progression, objective-response rate, and time to death (survival). The 352 patients who actually received trial treatment were included in the safety by treatments received.

8.2.10 EFFICACY RESULTS

Table 25 presents trial treatment information for all patients by randomized treatment (ITT population) and treatment actually given.

8.2.10.1 Best objective response for all randomized patients

(a) Intention-to-treat analysis: Objective assessments

Time to progression

The primary analysis for time to progression was the intent-to treat analysis, which was performed for all 353 randomized patients. This analysis compared the treatment groups on the basis of randomized treatment, regardless of whether this treatment was actually given. The secondary analysis was the per-protocol analysis, which was performed excluding patients with significant protocol violations and deviations.

Intent-to-treat analysis

Table 25 summarizes the progression status and duration of follow up of all randomized patients by treatment as of 10 March 1999, the data cutoff date.

Table 25

Duration of follow-up and progression status of randomized patients at the time of data cut-off (10 March 1999)

	Anastrozole 1 mg (n = 171)	**Tamoxifen 20 mg (n = 182)**
Duration of follow-up (days)		
Median	533	538
Range (Minimum/ Maximum)	1 / 931	35/1097
Progression status	**Anastrozole 1 mg (n = 171) (%)**	**Tamoxifen 20 mg (n = 182) (%)**
Alive without progression[a]	57 (33.3)	44 (24.2)
Progression during treatment	100 (58.5)	121 (66.5)
Progression after treatment withdrawal	2 (1.4)	3 (1.6)
Death before progression	12 (7.0)	14 (7.7)

[a] Includes patients who were continuing treatment and patients withdrawn from treatment.

A total of 252 (71.4%) patients had disease progression (including death before progression from any cause). Patients who were randomized to anastrozole appeared to have a lower rate of progression and a longer estimated median time to progression (66.7% and 338 days, respectively) than did patients who were randomized to tamoxifen (75.8% and 170 days, respectively). Statistical testing of these data was not performed. Median duration of follow-up was *similar* for both treatment groups. Overall, the estimated median duration of follow-up was 538days for the 253 patients who were known to be alive at the time of data cut-off.

Objective assessments

Intention-to-treat analysis

A total of 252 (71.4%) patients had disease progression (including death, from any cause, before progression). Patients who were randomized to anastrozole had a *lower* progression rate and longer estimated median time to progression (66.7% and 338 days, respectively), compared with patients who were randomised to tamoxifen (75.8% and 170days, respectively). A formal statistical analysis on these data was not performed.

Time to progression.

Results of the adjusted analysis showed that the tamoxifen:anastrozole comparison had a hazard ratio very close to 1, indicating that for this parameter the 2 treatments were almost identical. The lower 1-sided 95% confidence limit for the hazard ratio was 0.86, which was greater than the statistical criterion of 0.80 required to declare non-inferiority. Consistent results were obtained from the unadjusted analysis, which gave a hazard ratio of 1.01 and a lower 95% confidence limit of 0.87. The applicant concludes that anastrozole met the criteria for equivalence with tamoxifen for time to disease progression.

Per-protocol analysis

The per-protocol analysis of time to progression was performed for 283 patients, 133 patients who were randomized to anastrozole and 150 who were randomized to tamoxifen. The results from the per-protocol analysis are consistent with those from the intent-to-treat analysis. Patients who were randomized to anastrozole appeared to have a lower rate of progression and a longer estimated median time to progression (63.9% and 407 days, respectively) than did patients who were randomized to tamoxifen (75.3% and 170 days, respectively). The associated hazard ratios were 1.53 and 1.51 for the adjusted and unadjusted analyses, respectively. Non-inferiority was also demonstrated with the lower 1-sided 95% confidence limit for the hazard ratio, which was greater than the statistical criterion of 0.8 for both the adjusted (1.21 confidence limit) and unadjusted analyses (1.19 confidence limit).

Objective response

The primary analysis for objective-response rate was the intent-to-treat analysis, which was performed for all 353 randomized patients. This analysis compared the treatment groups on the basis of randomized treatment, regardless of whether this treatment was actually given. The secondary analysis was the per-protocol analysis, which was performed excluding patients with significant protocol violations and deviations.