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20-541/S-010

Statistical Review(s)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Medical Division: Oncology Drug Products (HFD-150)

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NDA NUMBER: NDA 20-541/ S-010

DRUG NAME: ARIMIDEX[®] (anastrozole) 1 mg Tablets

INDICATION: Adjuvant Treatment in Postmenopausal Women with
Breast Cancer

SPONSOR: AstraZeneca

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1 Executive Summary of Statistical Findings

1.1 Recommendations and Conclusions

In this reviewer's opinion the results of Study 1033IL/0029 (ATAC Trial) appears to demonstrate efficacy of arimidex (1 mg once daily) when compared to tamoxifen (20 mg once daily) treatment in the adjuvant treatment of postmenopausal women with breast cancer. The results presented are based on less than 3 years of median duration of treatment and median follow-up. The strength and consistency of efficacy and safety of arimidex compared to tamoxifen can only be determined with adequate treatment duration and follow-up.

1.2 Brief Overview of Clinical Studies

This application consists of report of results from Study 1033IL/0029 (ATAC Trial). Study 1033IL/0029 was a multicenter, double-blind, randomized, phase III comparative trial of arimidex (1 mg tablet) versus tamoxifen (20 mg tablet) versus arimidex 1 mg + tamoxifen 20 mg as an adjuvant therapy in postmenopausal patients with breast cancer. A total of 381 centers from 21 countries worldwide participated in this study. The trial treatment was planned to be administered everyday for 5 years or until disease recurrence, or discontinuation of trial therapy. The current standard of care in US is tamoxifen 20 mg once daily treatment for 5 years as adjuvant treatment.

First patient was entered in this study on July 12, 1996 and the last patient was entered on March 24, 2000. The data cut-off date for this application was June 29, 2001. Accrual to this trial is closed although the trial is still ongoing. A total of 9366 patients (3125, 3116 and 3125 patients received respectively, arimidex, tamoxifen, and arimidex plus tamoxifen treatment) have been entered in this trial. The median duration of treatment and follow-up are less than 3 years. Baseline characteristics were well balanced among the three treatment arms. Approximately 84% of the patients entered were hormone receptor positive patients.

The primary objectives of this trial were (1) to compare tamoxifen 20 mg once daily (od) with arimidex 1 mg (od), and (2) to compare tamoxifen (20 mg od) with the combination of arimidex (1 mg od) plus tamoxifen (20 mg od) as adjuvant treatment in postmenopausal women who were candidates to receive adjuvant hormonal treatment for invasive primary breast cancer. The primary efficacy endpoint was the time to disease recurrence (recurrence defined by sponsor as the earliest of loco-regional or distant recurrence, new primary (contralateral) breast cancer, or deaths (as first event)).

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In addition, some patients from this trial were also included in one or more separate protocols which were performed at specific centers. These sub-protocols were designed to address the following objectives: (1) pharmacokinetic interactions of anastrozole and tamoxifen when used in combination (protocol number 1033IA/0029), (2) endometrial status (protocol number 1033IC/0029), (3) bone mineral metabolism (protocol number 1033ID/0029), and (4) quality of life (protocol number 1033IE/0029).

The focus of this review was on the results of the main 1033IL/0029 study.

1.3 Statistical Issues and Findings

Statistical Issues:

- In the original protocol the primary endpoint was specified as time to disease recurrence. However, disease recurrence was not defined in the original protocol. Disease recurrence was defined to include loco-regional or distant recurrence whichever occurs first, deaths due to all causes and new primary (contralateral) breast cancer in the amendment 6 (April 2000), after all patients were recruited (date of last patient recruited: March 24, 2000).
- The primary endpoint, disease recurrence is a composite endpoint with differential prognosis. (Reference: I.C.H. E-9 Guidelines: Section 2.2.3, Composite Variables: "The method of combining the multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit.")
- In the original protocol a minimum of two years of follow-up was required. This statement was dropped from the protocol in the Amendment 5 dated January 12, 1999.
- Increase in sample size during the course of the study might have an impact on the detection of superior efficacy with short patient follow-up.
- The effect of active control treatment as of data cut-off date is sub-optimal as the current standard of practice is 5 years of adjuvant tamoxifen treatment.
- The claim on decreased incidence of new contralateral breast cancers with Arimidex 1 mg is based on one component of the composite primary endpoint.

Findings:

The primary efficacy endpoint was time to disease recurrence. Recurrence was defined by the sponsor to include earliest occurrence of loco-regional (including new primary ipsilateral breast cancer) or distant recurrence, new primary (contralateral) breast cancer, or death (as first event). The absolute recurrence rate per this definition was 10.2, 12.2 and 12.3 respectively, in the Arimidex,

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Tamoxifen and Arimidex + Tamoxifen arms. The results from the sponsor's and FDA analyses are presented in the following Tables A – C. The results analyses of subgroups (hormone receptor positive patients, US patients, patients who had received prior adjuvant chemotherapy, and patients in different age groups) are presented in Table D. Table E summarizes analyses of time to first fracture.

Table A: Analyses of Time to Disease Recurrence Comparing Arimidex 1 mg po (A) versus Tamoxifen 20 mg po (T)

Recurrence Events	Hazard Ratio*	2-sided 95% Confidence Interval	P-value
Local or Distant Recurrences, New Contralateral Breast Primaries, All Causes Deaths (<i>Sponsor Analysis</i>)	0.83	0.71-0.96	0.0144 ^a
Local or Distant Recurrences (including deaths due to breast cancer) (<i>FDA Analysis</i>)	0.85	0.71 – 1.02	0.0758 ^b
Distant Recurrences (including deaths due to breast cancer) (<i>FDA Analysis</i>)	0.88	0.71 – 1.08	0.2199 ^b

^a: Compared to 0.024 level, adjusting for multiple hypotheses testing; ^b: not adjusted for multiple comparisons and analyses. *: HR < 1 implies A better than T

Table B: Analyses of Time to Disease Recurrence Comparing Tamoxifen 20 mg po + Arimidex 1 mg po versus Tamoxifen 20 mg po

Recurrence Events	Hazard Ratio*	2-sided 95% Confidence Interval	P-value
Local or Distant Recurrences, New Contralateral Breast Primaries, All Causes Deaths (<i>Sponsor Analysis</i>)	1.02	0.89 – 1.18	0.7700 ^a
Local or Distant Recurrences (including deaths due to breast cancer) (<i>FDA Analysis</i>)	1.08	0.91 – 1.28	0.3756 ^b
Distant Recurrences (including deaths due to breast cancer) (<i>FDA Analysis</i>)	1.12	0.92 – 1.37	0.2567 ^b

^a: Compared to 0.024 level, adjusting for multiple hypotheses testing; ^b: not adjusted for multiple comparisons and analyses. *: HR > 1 implies A + T worse than T.

Table C: Analyses of Time to Disease Recurrence Comparing Tamoxifen 20 mg po + Arimidex 1 mg po versus Arimidex 1 mg po

Recurrence Events	Hazard Ratio*	2-sided 95% Confidence Interval	P-value ¹
Local or Distant Recurrences, New Contralateral Breast Primaries, All Causes Deaths (<i>Sponsor Analysis</i>)	1.23	1.06 – 1.42	0.0069
Local or Distant Recurrences (including deaths due to breast cancer) (<i>FDA Analysis</i>)	1.26	1.06 – 1.50	0.0086
Distant Recurrences (including deaths due to breast cancer) (<i>FDA Analysis</i>)	1.28	1.04 – 1.57	0.0200

¹: Not adjusted for multiple comparisons and analyses. *: HR > 1 implies A + T worse than A.

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Table D: Analyses of Time to Disease Recurrence* Comparing Arimidex 1 mg po versus Tamoxifen 20 mg po in Different Sub-Groups of Patients

SubGroups	Total Number of Patients	Hazard Ratio**	2-sided 95% Confidence Interval	P-value ¹
ER or PgR Positive Patients	5215	0.78	0.65 - 0.93	0.0063
US Patients	1476	0.90	0.65 - 1.24	0.5177
Patients who had prior adjuvant chemotherapy	1345	1.13	0.85 - 1.51	0.3879
< 60 years of Age	2208	0.78	0.60 - 1.02	0.0676
60 - 70 years of Age	2345	0.88	0.68 - 1.14	0.3432
> 70 years of Age	1688	0.84	0.65 - 1.07	0.1590

¹: Not adjusted for multiple comparisons and analyses. *: Recurrence includes Local or Distant Recurrences, New Contralateral Breast Primaries, All Causes Deaths ; **: HR < 1 implies A better than T

Table E: Time to First Fracture

Treatment comparison	Hazard Ratio	2-sided 95% C.I.	p-value ¹
A vs. T ²	1.557	1.263 - 1.919	< 0.0001
A + T vs. T	1.310	1.054 - 1.628	0.0148
A + T vs. A	0.842	0.693 - 1.023	0.0835

¹: Not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg, HR > 1 implies A is worse than T.

1. The timing of the final analyses was solely based on reaching the pre-specified total number of events (1056 events). Per sponsor's definition of recurrence and analysis (Table A) arimidex appears to be superior to tamoxifen. The current standard of care in this disease setting is tamoxifen 20 mg administered daily for 5 years. At the time of data cut-off date no patient had received 5 years of treatment. The sponsor's analysis could be therefore comparing to suboptimal active control. The meta-analysis (*The Lancet*, 351: 1451-1467, 1998) of tamoxifen trials based on 30,000 women with approximately 10 years of follow up have shown clearly that when 1 year, 2 years and about 5 years of adjuvant tamoxifen is compared to placebo, in both proportional recurrence reductions and proportional mortality reductions there is highly significant trend towards greater tamoxifen effect with longer treatment. In the trials of about 5 years of adjuvant tamoxifen the recurrence rate was reduced by about half during 0-4 years of follow-up and by about one-third during the next few years. The study under review here was designed with the intention of treating all patients for a period of 5 years as adjuvant treatment.
2. The median follow-up at the time of data cut-off date was 33.3 months with < 3 % of patients who had received 4 to 5 years of treatment and approximately 25% of patients who had withdrawn from the study before completing 5 years of treatment. The sample size was increased from a total of 6000 patients per

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original plan to 9500 patients, plausibly resulting in more events with a shorter follow-up. Conclusive evidence of strength of efficacy of arimidex 1 mg compared to tamoxifen 20 mg can only be assessed with adequate treatment and follow-up data.

3. The primary endpoint time to disease recurrence as defined by the sponsor is a composite endpoint with each component having a different prognosis. Loco-regional recurrences including DCIS, distant recurrences, new primary contralateral breast cancer including DCIS and all cause mortality as first event were considered as recurrences by the sponsor. There is no clear consensus on which of these components should be included as recurrence events (for example: local and distant recurrences only, or distant recurrences only, etc.).
4. Because the timing of the final analysis was based on reaching the pre-specified total number of events, depending on how the recurrence event is defined this goal might be reached or might not be reached. Further follow-up is therefore necessary to conclusively determine the efficacy of arimidex 1mg when compared to tamoxifen 20 mg. It is also to be noted that the required level of significance was not reached if other definitions were employed to define recurrence as demonstrated in Table A. However, using different definitions, the point estimates of hazard ratios were between 0.83-0.87.
5. There was no statistically significant difference between tamoxifen and tamoxifen + arimidex treatment arms with respect to time to disease recurrence (Table B).
6. The comparative results in the hormone receptor positive (ER or PgR positive) sub-group were similar to the overall population (Table D). The comparative results of other sub-groups are inconclusive and require further follow-up (Table D).
7. With respect to safety, arimidex appears to decrease the incidence of endometrial carcinoma compared to tamoxifen. There are significantly more fractures and hypercholesteraemia observed in the arimidex treatment arm compared to tamoxifen arm. The safety data presented in this application are premature and only longer follow-up data can confirm these early safety issues.

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2 Statistical Review and Evaluation of Evidence of Study 1033IL/0029 (ATAC Trial)

2.1 Introduction

The beneficial effect of estrogen antagonism in the treatment of early breast cancer in postmenopausal women has been clearly demonstrated for tamoxifen, which is currently considered to be the therapy of choice in this patient population. It is possible that estrogen deprivation through aromatase inhibition could also be advantageous in the early breast cancer setting. Arimidex or anastrozole is a highly selective, potent, and non-steroidal aromatase inhibitor. Arimidex has been approved for the treatment of advanced disease in postmenopausal women.

Study 1033IL/0029 was a multicenter, double-blind, randomized, phase III collaborative trial designed in conjunction with the Cancer Research Campaign, U.K., a parallel comparative trial of arimidex (1 mg tablet) versus tamoxifen (20 mg tablet) versus arimidex + tamoxifen as an adjuvant therapy in postmenopausal patients with breast cancer. The trial treatment is taken for 5 years or until disease recurrence, or discontinuation of trial therapy.

First patient was entered in this study on July 12, 1996 and the last patient was entered on March 24, 2000. The data cut-off date for this application was June 29, 2001.

Statistical evaluation of efficacy evidence of the study 1033IL/0029 is presented in section 2.10. In section 2.11 statistical review and evaluation of the special populations and subgroups are presented and in section 2.12 statistical review of safety evaluation are presented. An overall statistical evaluation of collective evidence and conclusions are presented in section 3 of this review.

2.2 Major Statistical Issues:

- In the original protocol the primary endpoint was specified as time to disease recurrence. However, disease recurrence was not defined in the original protocol. Disease recurrence was defined to include loco-regional or distant recurrence whichever occurs first, deaths due to all causes and new primary (contralateral) breast cancer in the amendment 6 (April 2000), after all patients were recruited (date of last patient recruited: March 24, 2000).
- The primary endpoint is a composite endpoint with differential prognosis. (Reference: I.C.H. E-9 Guidelines: Section 2.2.3, Composite Variables: "The method of combining the multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit.")

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- In the original protocol a minimum of two years of follow-up was required. This statement was dropped from the protocol in the Amendment 5 dated January 12, 1999.
- Increase in sample size during the course of the study might have an impact on the detection of superior efficacy with short patient follow-up.
- The effect of active control treatment as of data cut-off date is sub-optimal the current standard of practice is 5 years of adjuvant tamoxifen treatment.
- The decreased incidence of new contralateral breast cancers with Arimidex 1 mg is based on one component of the composite primary endpoint.

2.3 Data Analyzed and Sources

Data used for review is from the electronic submission received on 12/21/01. The network path is "\\CDSESUB1\N20541\N_000\2001-12-21\crt\datasets\1033il0029." Safety update data set submitted on July 3, 2002 with the following network path in the EDR has also been reviewed: "\\CDSESUB1\N20541\N_010\2002-07-03\crt\datasets\1033il0029."

2.4 Study Objectives

The primary objective of the study 1033IL/0029 was to compare tamoxifen (20 mg od) versus anastrozole (1 mg od) and to compare tamoxifen (20 mg od) versus the combination of anastrozole (1 mg od) + tamoxifen (20 mg od) as adjuvant treatment with respect to time to recurrence of breast cancer (defined as the earliest of loco-regional or distant recurrence, new primary [contralateral] breast cancer, or death [as first event]).

The secondary objectives of this trial were to compare tamoxifen and anastrozole and to compare tamoxifen and the combination of anastrozole plus tamoxifen as adjuvant treatment with respect to time to distant recurrence, survival, incidence of new breast primaries (ie, new primary [contralateral] breast cancers).

In addition, some patients from this trial were also included in one or more separate protocols which were performed at specific centers. These sub-protocols were designed to address the following objectives: (1) pharmacokinetic interactions of anastrozole and tamoxifen when used in combination (protocol number 1033IA/0029), (2) endometrial status (protocol number 1033IC/0029), (3) bone mineral metabolism (protocol number 1033ID/0029), and (4) quality of life (protocol number 1033IE/0029).

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2.5 Efficacy Endpoints

The primary efficacy endpoint was time to disease recurrence (recurrence-free survival). Time to disease recurrence was defined (per amendment 6) as the time between randomization and the earliest occurrence of loco-regional (including new primary ipsilateral breast cancer) or distant recurrence, new primary (contralateral) breast cancer, or death (as first event).

The secondary efficacy variables were time to distant recurrence, survival, and incidence of new primary (contralateral) breast cancer. Time to distant recurrence was defined as the time between randomization and the earliest occurrence of distant recurrence or death.

Reviewer's Comments:

1. In the original protocol the primary endpoint was specified as time to disease recurrence. However, disease recurrence was not defined in the original protocol. Disease recurrence was defined to include loco-regional or distant recurrence whichever occurs first, deaths due to all causes and new primary (contralateral) breast cancer in the amendment 6 (April 2000), after all patients were recruited (date of last patient recruited: March 24, 2000).
2. In the original protocol a minimum of two years of follow-up was required. This statement was dropped from the protocol in the Amendment 5 dated January 12, 1999.

2.6 Sample Size Considerations

Patients who met the eligibility criteria were randomized on 1:1:1 basis into three oral treatment schedules to receive one of the following: (1) active arimidex 1 mg once daily + tamoxifen placebo once daily; (2) active tamoxifen 20 mg once daily + arimidex placebo once daily; and (3) active arimidex 1 mg once daily in combination with active tamoxifen 20 mg once daily. The estimated sample size was a total of 9500 patients with the final analysis planned when a total of 1056 events would be observed.

This trial was designed to perform the following comparisons of disease recurrence rates:

- (1) Evidence of non-inferiority in terms of disease recurrence rates between patients randomized to arimidex and those randomized to tamoxifen. Evidence of non-inferiority was to be concluded if the upper limit of the 2-sided 90% confidence interval (CI) for the hazard ratio (anastrozole/tamoxifen) did not exceed 1.25. If the true hazard ratio was 1.0, the power to show non-inferiority was 91% (based on a 90% 2-sided CI), i.e., the trial had 91% power to demonstrate non-inferiority if the treatments were truly identical.

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(2) Evidence of a difference in disease recurrence rate between patients randomized to tamoxifen compared with those randomized to the combination of arimidex plus tamoxifen. A difference was defined as a hazard ratio (arimidex plus tamoxifen/tamoxifen) of less than 0.80 or greater than 1.25. This corresponds to a 20% reduction or a 25% increase in recurrence rates. The trial had 80% power to detect a 20% reduction or a 25% increase in the recurrence rate for the anastrozole plus tamoxifen arm relative to the tamoxifen arm using a 2-sided 5% significance level.

Reviewer's Comments:

1. The original estimated disease recurrence rates for patients diagnosed with either stage I or stage II disease while receiving tamoxifen were 3.6 and 11.3 events per year per 100 patients, respectively, in the period 0 to 4 years following surgery (Cancer Research Campaign, based upon Ref EBCTCG [1992]). Based upon this event rate, after 3 years of recruitment at a uniform rate of 2000 patients per year and a minimum of 2 years' follow-up, ie, 5 years after the start of recruitment, the expected number of events in stage I was estimated to be 11.8 per 100 patients, 32.3 per 100 patients in stage II patients, and 50% of each was then estimated to be 22.1 per 100 patients. Using these event rates and assuming an equal distribution of stage I and stage II patients, per original protocol 6000 patients (2000 per arm) were planned to be recruited which would result in 442 expected events per treatment arm after 5 years of treatment. This sample size was first increased to a total of 7500 patients (2500 patients in each arm) in the Amendment 4 (dated June 1, 1998). The reason for the increase in sample size per sponsor was that the assumption of uniform recruitment did not hold over the initial 12 months.
2. The protocol was amended again in January of 1999. With the amended protocol accrual of a total of 9500 patients was planned which would result in 352 expected events per treatment arm after 5 years of treatment. The reason for this increase in sample size per sponsor was that the event rate predictions were inconsistent with recent publication from the EBCTCG.
3. A statistical test was introduced in the Amendment 6 (dated April 28, 2000) to detect superiority of arimidex over tamoxifen. It is to be noted that in the original protocol this comparison was designed to test non-inferiority between the two treatment arms, and that the last patient of the trial was entered on March 23, 2000.
4. In response to the statistical analysis plan submitted by the sponsor in July and August of 2001 (Serial number # 428 and 440) the agency had conveyed to the sponsor that the cut-off criteria of hazard ratio of 1.25 ensures preservation of only 59% effect of tamoxifen by arimidex and that this cut-off is unlikely to be acceptable as the non-inferiority margin in the disease-free population under study. It was also pointed out that the estimate of the control effect from the review article included patients pre- and post-menopausal, all

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ER/PgR status (+, 0, or unknown), and differing duration of tamoxifen treatment. The sponsor was advised to make an effort to find a better estimate of control effect by including studies with post-menopausal patients only and only those studies in which 5 years of tamoxifen treatment was administered. The agency also recommended comparing arimidex versus arimedex + tamoxifen treatment arms to be included in the first step of simultaneous comparisons and subsequent steps of the Hochberg sequentially rejective procedure to be modified accordingly. The sponsor has not addressed these issues to date.

2.7 Stratification

The study was not stratified by any prognostic factors. However, there were a number of regional centers and the individual trial centers carried out randomization of patients through their local randomization center. The actual treatment given to individual patients was determined by a randomization scheme prepared by AstraZeneca Biometrics group. Separate randomization schemes were prepared for each participating center.

Reviewer's Comments:

ER/PgR status and nodal involvement are considered to be important prognostic factors in this disease setting and studies are generally stratified by these factors prior to randomization.

2.8 Interim Analysis

One interim analysis for efficacy was planned for this study. The primary analysis of time to disease recurrence was adjusted for the interim analysis using O'Brien Fleming type procedure. Accordingly, the nominal significance level was adjusted to 0.048 for the final analysis of time to disease recurrence.

Reviewer's Comments:

1. The multiplicity associated with the two treatment comparisons with tamoxifen in each of the efficacy analyses (tamoxifen vs. arimidex (non-inferiority), and tamoxifen vs. tamoxifen + arimidex (superiority)) was addressed using sequentially rejective variation of Bonferroni procedure proposed by Hochberg (1988). Thus the starting nominal significance level for each of the comparison was one-sided 2.4% level. In the statistical analysis plan submitted by the sponsor dated October 17, 2001, it was stated that if one of the two tests is significant at one-sided 2.4% level, then the smaller of the two p-values (obtained from the two comparisons) will be

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tested against one-sided 1.2% level ($\alpha/2$) and the final conclusions will be based on this test.

2. The overall significance level was not adjusted in the secondary efficacy analyses of time to distant recurrence, incidence of new primary breast cancer, time to disease recurrence in ER/PgR + patients and in other subgroup analyses. The sponsor has stated that at the interim analysis only time to disease recurrence was analyzed.

2.9 Efficacy Analysis Methods

The primary analysis for the primary efficacy variable, time to disease recurrence (recurrence-free survival) was planned to include all randomized patients and performed in the intention to treat (ITT) population using log-rank test (unadjusted Cox proportional hazards model). The secondary endpoints namely time to distant recurrence and overall survival, and analysis of a subgroup population of hormone receptor positive patients were also planned to be analyzed using log-rank test. The analysis of the incidence of new primary contralateral breast cancer was planned to be conducted using logistic regression. These analyses were also conducted in the per protocol (PP) population.

2.10 Sponsor's Results and Statistical Reviewer's Findings/Comments

This section will summarize the results of intention to treat analysis for study 1033IL/0029. In this study a total of 9366 female patients were randomized (from 381 centers and 21 countries worldwide) to arimidex (3125 patients), tamoxifen (3116 patients) and arimidex + tamoxifen (3125 patients).

2.10.1 Baseline Characteristics

The baseline demographic and breast cancer history characteristics including age, races, weight, ER/PgR status, and nodal involvement status were balanced between the three treatment groups as displayed in Table 1.

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Table 1: Baseline Characteristics of Study 1033IL/0029 (FDA Analysis)

Characteristic	Arimidex 1 mg N = 3125	Tamoxifen 20 mg N = 3116	Arimidex 1 mg + Tamoxifen 20 mg N = 3125
Age (years)			
Mean (SD)	64.1 (9.0)	64.1 (9.0)	64.3 (9.1)
Range	38.1 – 92.8	32.8 – 94.9	37.0 – 92.2
Age Distribution (n(%))			
< 45 years	23 (0.7)	12 (0.4)	16 (0.5)
≥ 45 to < 60 years	1081 (34.6)	1092 (35.0)	1079 (34.5)
≥ 60 to ≤ 70 years	1188 (38.0)	1157 (37.1)	1177 (37.7)
> 70 years	833 (26.7)	855 (27.4)	853 (27.3)
Weight (kg)			
Mean (SD)	70.8 (14.1)	71.1 (14.2)	71.3 (14.3)
Range	38 – 170	35 – 142	38 – 161
Race (n(%))			
Caucasian	3006 (96.6)	2997 (96.6)	2994 (96.2)
Black/Afro-Caribbean	37 (1.2)	44 (1.4)	47 (1.5)
Other	70 (2.2)	62 (2.0)	70 (2.3)
Hormone Receptor Status (n(%))			
Positive	2617 (83.7)	2598 (83.4)	2624 (84.0)
Negative	232 (7.4)	249 (8.0)	218 (7.0)
Unknown	276 (8.8)	269 (8.6)	283 (9.1)
Other Treatment Prior to Randomization (n(%))			
Mastectomy	1494 (47.8)	1474 (47.3)	1502 (48.1)
Breast Conservation	1630 (52.2)	1642 (52.7)	1623 (51.9)
Axillary surgery	2984 (95.5)	2983 (95.7)	2975 (95.2)
Radiotherapy	1978 (63.3)	1946 (62.5)	1936 (62.0)
Chemotherapy	698 (22.3)	647 (20.8)	651 (20.8)
Neoadjuvant Tamoxifen	50 (1.6)	51 (1.6)	53 (1.7)
HRT Prior to Randomization (n(%))	1114 (35.7)	1103 (35.4)	1103 (35.3)
Primary Tumor Size (n(%))			
T1 (≤ 2 cm)	1996 (63.9)	1959 (62.9)	2004 (64.1)
T2 (> 2 cm and ≤ 5 cm)	1018 (32.6)	1066 (34.2)	1027 (32.9)
T3 (> 5 cm)	85 (2.7)	69 (2.2)	73 (2.3)
Not recorded	26 (0.8)	22 (0.7)	21 (0.7)
Node Positive Patients (n(%))			
≤ 4 nodes	764 (24.0)	762 (24.0)	759 (23.9)
4 – 9 nodes	236 (7.4)	199 (6.3)	213 (6.7)
> 9 nodes	90 (2.8)	83 (2.6)	72 (2.3)

Reviewer's comments:

1. Approximately 83 – 84% of the patients in each of the treatment arms were hormone receptor positive.
2. Only 20 – 22 % of the patients had prior chemotherapy.

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2.10.2 Primary Efficacy Analyses: Recurrence-free Survival

The primary efficacy endpoint was the time to disease recurrence. Recurrence per sponsor was defined in their final analysis as the time between randomization and the earliest occurrence of loco-regional (including new primary ipsilateral breast cancer) or distant recurrence, new primary (contralateral) breast cancer, or death (as first event). The sponsor's primary endpoint analysis results are summarized in Tables 2 - 4 (Tables 16,17 and 19 Volume 1) and Figures 1-2.

Table 2: Duration of Follow-up for Time to Disease Recurrence (Sponsor's Analyses)

Duration of follow-up (months)	Arimidex 1 mg (N = 3125)	Tamoxifen 20 mg (N = 3116)	Arimidex 1 mg + Tamoxifen 20 mg (N = 3125)
Median	33.6	33.2	32.9
Range			

Table 3: Recurrence Status as of Data Cut-off According to First Confirmed Event (Sponsor's Analyses)

Recurrence status (first confirmed event)	Number (%) of patients		
	Arimidex 1 mg (N = 3125)	Tamoxifen 20 mg (N = 3116)	Arimidex 1 mg + Tamoxifen 20 mg (N = 3125)
Total number of events ¹	318 (10.2)	379 (12.2)	383 (12.3)
Loco-regional recurrence ²	67 (2.1)	83 (2.7)	81 (2.6)
Distant recurrence	157 (5.0)	181 (5.8)	202 (6.5)
Death related to breast cancer	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Death unrelated to breast cancer	78 (2.5)	81 (2.6)	70 (2.2)
New breast primary invasive	9 (0.3)	30 (1.0)	23 (0.7)
New breast primary DCIS	5 (0.2)	3 (< 0.1)	5 (0.2)

¹: Disease recurrence was defined as the earliest of loco-regional or distant recurrence, death, or new primary (contralateral) breast cancer; ²: includes new primary ipsilateral breast cancer and DCIS

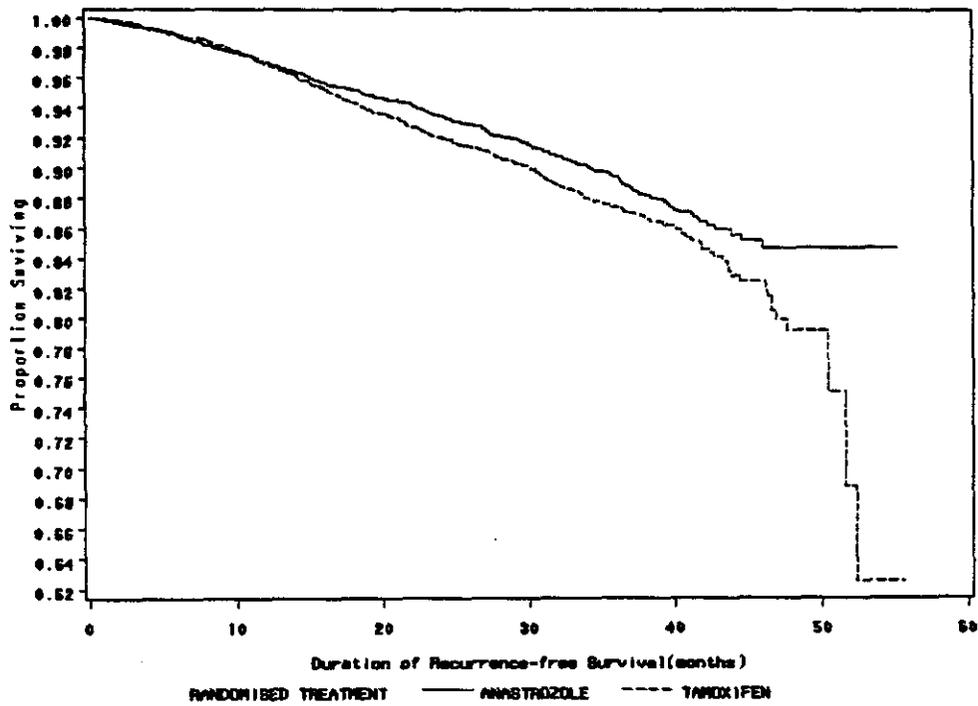
Table 4: Time to Disease Recurrence (Sponsor's Analyses)

Treatment comparison	Estimated HR	2-sided 95.2% C.I. ¹	p-value ²
A vs. T ³	0.83	0.71 - 0.96	0.0144
A + T vs. T	1.02	0.89 - 1.18	0.7700
A + T vs. A	1.23	1.06 - 1.42	0.0069 ⁴

¹: Adjusted for one interim analysis; ²: Cox proportional model without baseline co-variables; ³: A = Arimidex 1 mg, T = Tamoxifen 20 mg; ⁴: FDA Analysis, not adjusted for multiplicity; HR = hazard-ratio

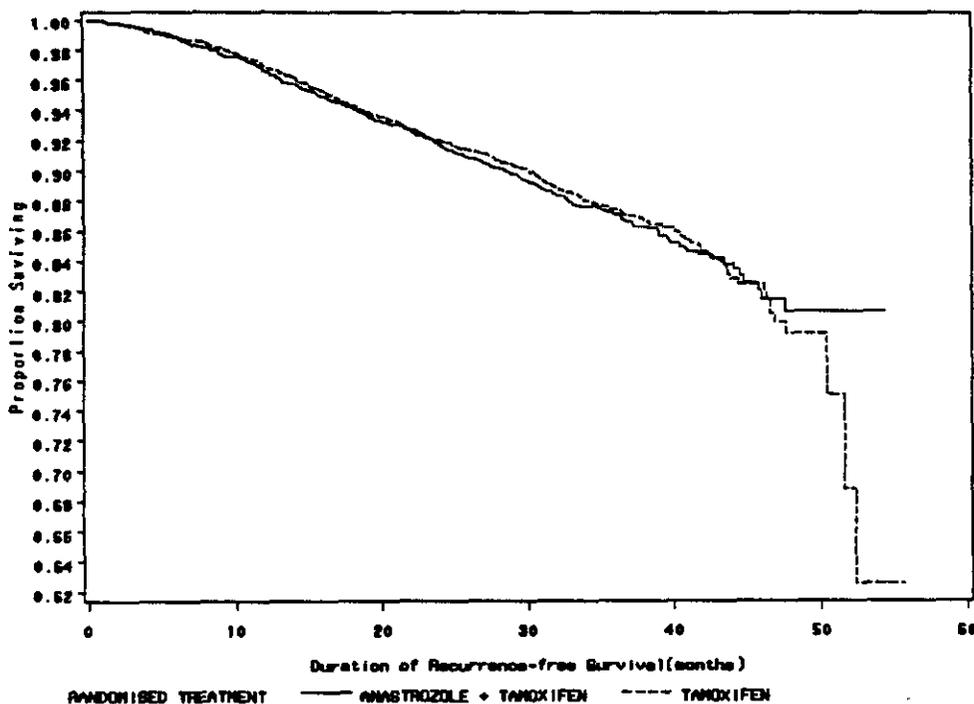
STATISTICAL REVIEW AND EVALUATION

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



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Figure 2: Kaplan-Meier Plot of Recurrence-free Survival of Tamoxifen versus Tamoxifen + Arimidex (Sponsor defined disease recurrence)



Reviewer's Comments:

1. The timing of the final analyses was based on reaching the pre-specified total number of events (1056 events). Per sponsor's definition of recurrence and analysis (Tables 3 and 4) arimidex appears to be superior to tamoxifen. Per sponsor's statistical analysis plan submitted on October 17, 2001, the comparisons were tested at 0.024 level of significance.
2. As of the data cut-off date (June 29, 2001) the duration of follow-up is less than 3 years (Table 2) and no patient has received the intended 5 years of treatment. The meta-analysis (The Lancet, 351: 1451-1467, 1998) of tamoxifen trials based on 30,000 women with approximately 10 years of follow up have shown clearly that when 1 year, 2 years and about 5 years of adjuvant tamoxifen is compared to placebo, in both proportional recurrence reductions and proportional mortality reductions there is highly significant trend towards greater tamoxifen effect with longer treatment. In the trials of about 5 years of adjuvant tamoxifen the recurrence rate was reduced by about half during 0-4 years of follow-up and by about one-third during the next few years. The study under review here was designed with the intention of

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treating all patients for a period of 5 years as adjuvant treatment of tamoxifen for 5 years is currently the standard of care in U.S. With the limited follow-up of this study, the effect of tamoxifen observed may be an underestimate of the control effect.

3. The timing of the final analysis of the time to disease recurrence was based on reaching the planned total number of events (1056 events) per protocol amendment. The definition of recurrence event is crucial in determining if the analyses were prematurely conducted or not. The sponsor's total number of events is based on the definition of recurrence as a composite of loco-regional recurrences, distant recurrences, deaths unrelated to breast cancer as first events, and new primary contralateral breast cancer (Table 3). All other new primary cancers have been censored at the time of incidence of cancer. Each of the components of this composite endpoint has different prognosis for overall survival. Furthermore, in the meta-analysis of tamoxifen trials referenced above deaths unrelated to breast cancer were censored at the time of death while considering time to disease recurrence. Given that approximately 27% of the patients were aged greater than 70 years, it is likely that a number of patients die due to causes other than the primary breast cancer under study. It is debatable if the new breast primaries should be treated differently, i.e., counted as recurrence while all new primaries at other sites are censored for disease recurrence. It is also debatable if non-invasive carcinoma in-situ (DCIS) in ipsilateral and contralateral breast cancers can be considered as disease recurrence. Currently there is no consensus on the definition of disease recurrence in this disease setting, i.e., post menopausal patients with early breast cancer who are disease free after surgery and radiotherapy and/or chemotherapy. Clearly if any of the components of the sponsor defined disease recurrence are censored and not counted as recurrence events then the current analysis will have to be considered as premature analysis.
4. In view of the differences in the definition of disease recurrence discussed above, following exploratory analyses were conducted by this reviewer. Three different definitions were used in these analyses. The break up of the recurrence status is listed in Table 5. The comparative results are presented in Tables 6-8 and Figures 3 -11 below. In all of these analyses the p-value comparing arimidex versus tamoxifen was > 0.024 and not statistically significant. However it should be noted that the point estimate of hazard ratios (effect size) were consistent using 3 different definitions and were between (1) 0.85-0.87 for comparisons between arimidex and tamoxifen, favoring arimidex (2) 1.08 – 1.09 for comparisons between arimidex + tamoxifen versus tamoxifen favoring tamoxifen, and (3) 1.25 – 1.26 for comparisons between arimidex + tamoxifen versus arimidex favoring arimidex. The lack of significance of the difference in efficacy could be due to fewer recurrence events per these definitions and lack of adequate follow-up.

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5. When an exploratory analysis was conducted using multivariate Cox-proportional hazards model, prior hormone replacement therapy, prior adjuvant chemotherapy, nodal status, hormone receptor status and age were observed as significant factors (results not presented in this review).

Table 5: Recurrence Status as of Data Cut-off According to First Confirmed Event (FDA Analyses)

Recurrence status (first confirmed event)	Number of patients		
	Arimidex 1 mg (N = 3125)	Tamoxifen 20 mg (N = 3116)	Arimidex 1 mg + Tamoxifen 20 mg (N = 3125)
Loco-regional recurrence ^{1,2,3}	63	76	76
Loco-regional with noninvasive DCIS ¹	2	2	1
Loco-regional recurrence with sub-optimal therapy ¹ (per efficacy medical reviewer)	2	5	4
Distant recurrence ^{1,2,3}	157	181	202
Death related to breast cancer ^{1,2,3}	4	1	0
Death unrelated to breast cancer	76	81	72
New breast primary invasive	9	30	23
New breast primary DCIS	5	3	5
Patients who received other treatment likely to impact on recurrence* (per efficacy medical reviewer)	34	35	28

¹: Included as events in Definition 1; ²: Included as events in Definition 2; ³: Included as events in Definition 3; *: These patients were recorded as events or censored per sponsor for the definition 1 and definition 2 analyses.

Table 6: Time to Disease Recurrence - FDA Analyses Definition 1: Events Censored Included - Deaths Unrelated* to Breast Cancer and All New Contralateral Breast Primary Cancer

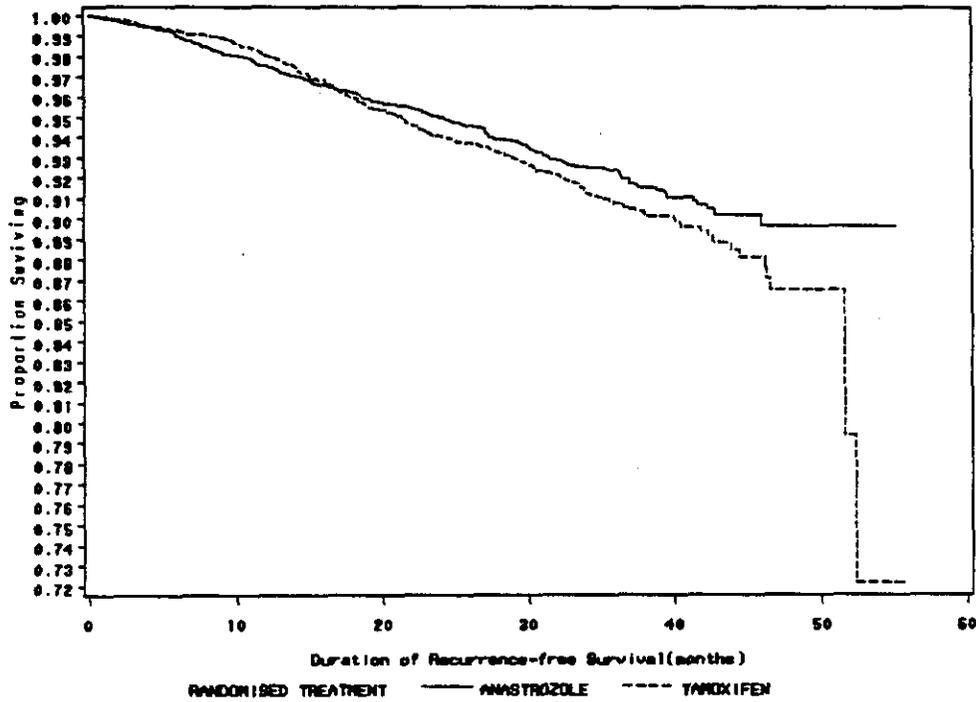
Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	0.852	0.714 – 1.017	0.0758
A + T vs. T	1.079	0.912 – 1.275	0.3756
A + T vs. A	1.264	1.061 – 1.504	0.0086

¹: 4/80 deaths in A and 1/82 in T were due to breast cancer and were counted as recurrence events (see Appendix 1).

²: Cox proportional model without baseline co-variates and not adjusted for multiple comparisons and analyses; ³: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio

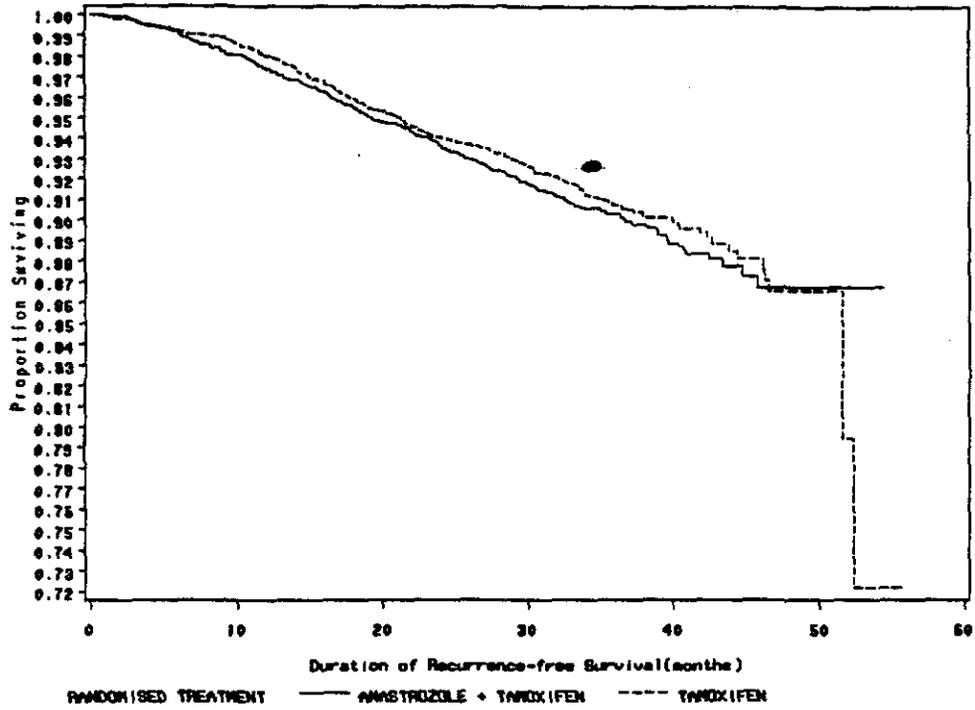
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Figure 3: Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen (FDA definition 1 of disease recurrence)



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Figure 4: Kaplan-Meier Plot of Recurrence-free Survival of Tamoxifen versus Tamoxifen + Arimidex (FDA definition 1 of disease recurrence)



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Figure 5: Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen + Arimidex (FDA definition 1 of disease recurrence)

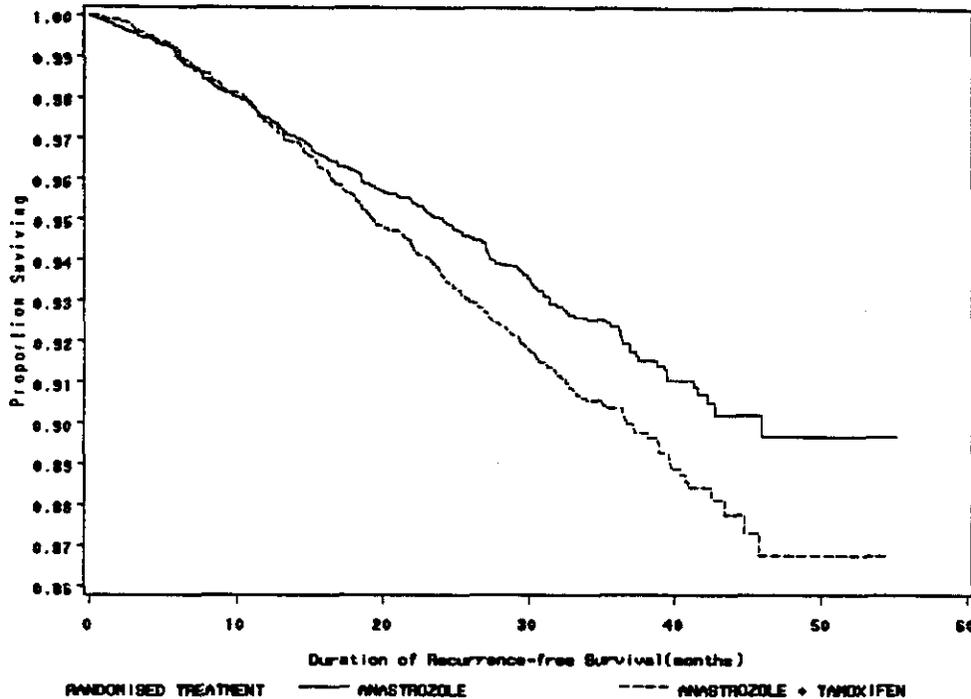


Table 7: Time to Disease Recurrence - FDA Analyses Definition 2: Events Censored Included - Deaths Unrelated^a to Breast Cancer, All New Contralateral Breast Primary Cancer and Loco-regional Recurrence Where the Treatment was Sub-optimal^b or the Event was Non-invasive DCIS^c

Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	0.857	0.717 - 1.024	0.0895
A + T vs. T	1.080	0.912 - 1.279	0.3716
A + T vs. A	1.258	1.055 - 1.500	0.0105

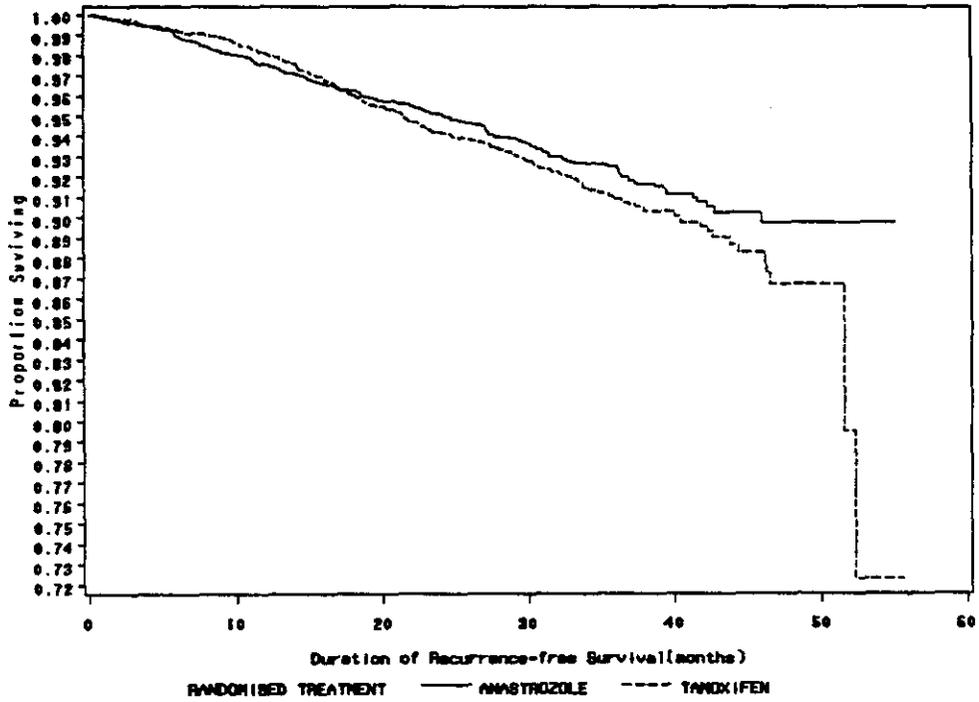
^a: 4/80 deaths in A and 1/82 in T were due to breast cancer and were counted as recurrence events;

^b: 2/67 in A, 5/83 in T and 4/81 in A+T had sub-optimal therapy (breast conservation surgery with no radiotherapy); c: 2/67 in A, 2/83 in T and 1/81 in A+T had DCIS with no invasion (see Appendix 1).

¹: Cox proportional model without baseline co-variables and not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio.

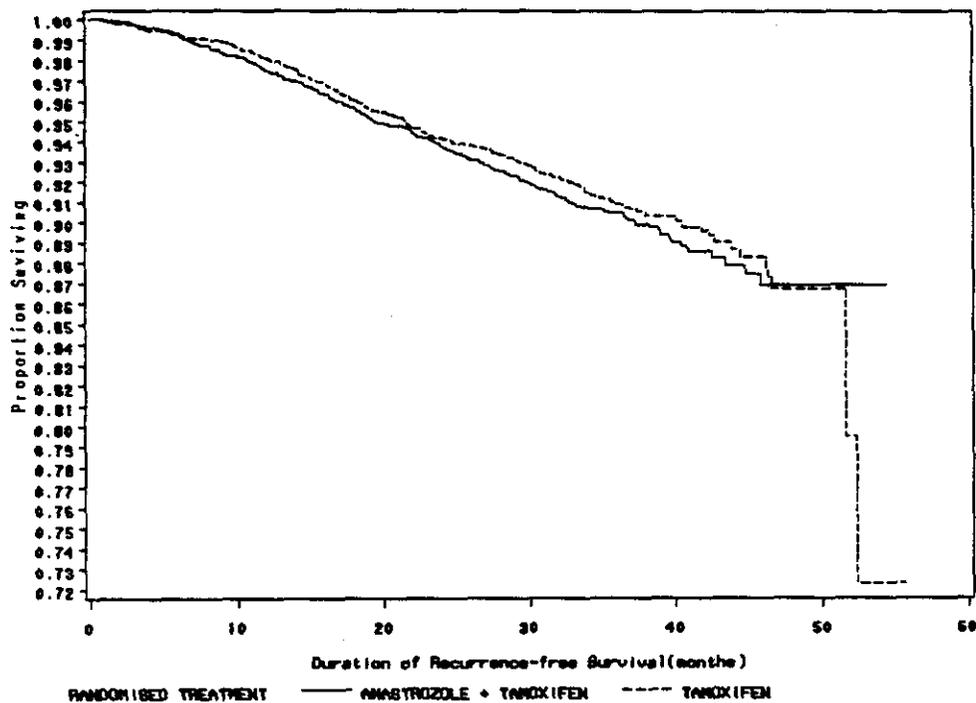
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Figure 6: Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen (FDA definition 2 of disease recurrence)



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Figure 7: Kaplan-Meier Plot of Recurrence-free Survival of Tamoxifen versus Tamoxifen + Arimidex (FDA definition 2 of disease recurrence)



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Figure 8: Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen + Arimidex (FDA definition 2 of disease recurrence)

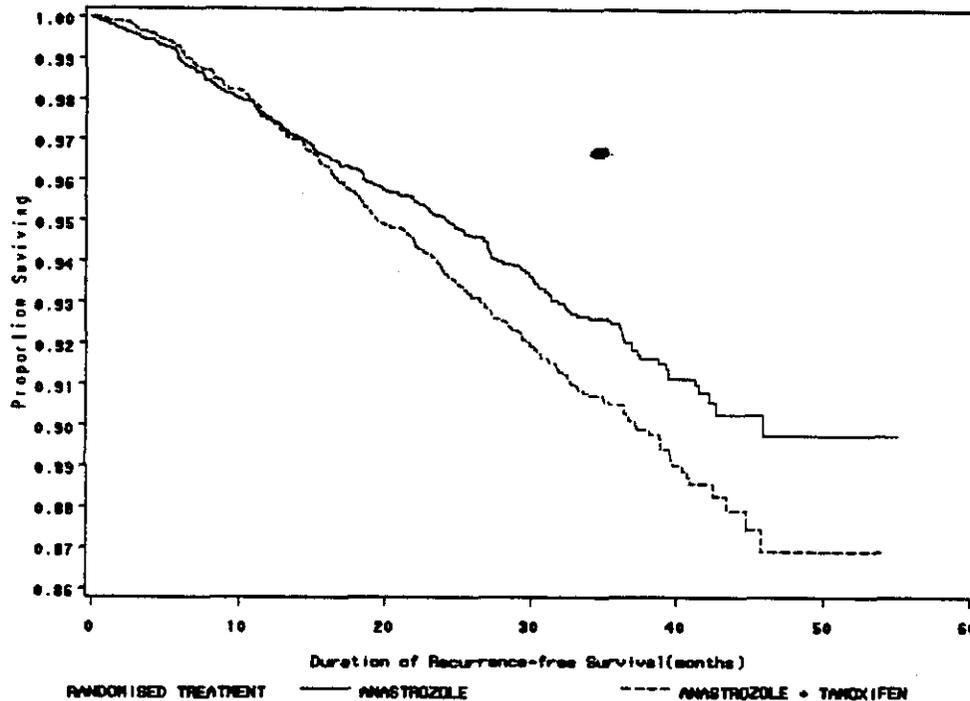


Table 8: Time to Disease recurrence - FDA Analyses Definition 3: Events Censored Included - Deaths Unrelated^a to Breast Cancer, All New Contralateral Breast Primary Cancer, Loco-regional Recurrence Where the Treatment was Sub-optimal^b or the Event was Non-invasive DCIS^c and Patients Who Received Other Treatment That is Likely to Affect^d Disease Recurrence

Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	0.866	0.724 – 1.036	0.1166
A + T vs. T	1.089	0.919 – 1.291	0.3254
A + T vs. A	1.254	1.052 – 1.496	0.0117

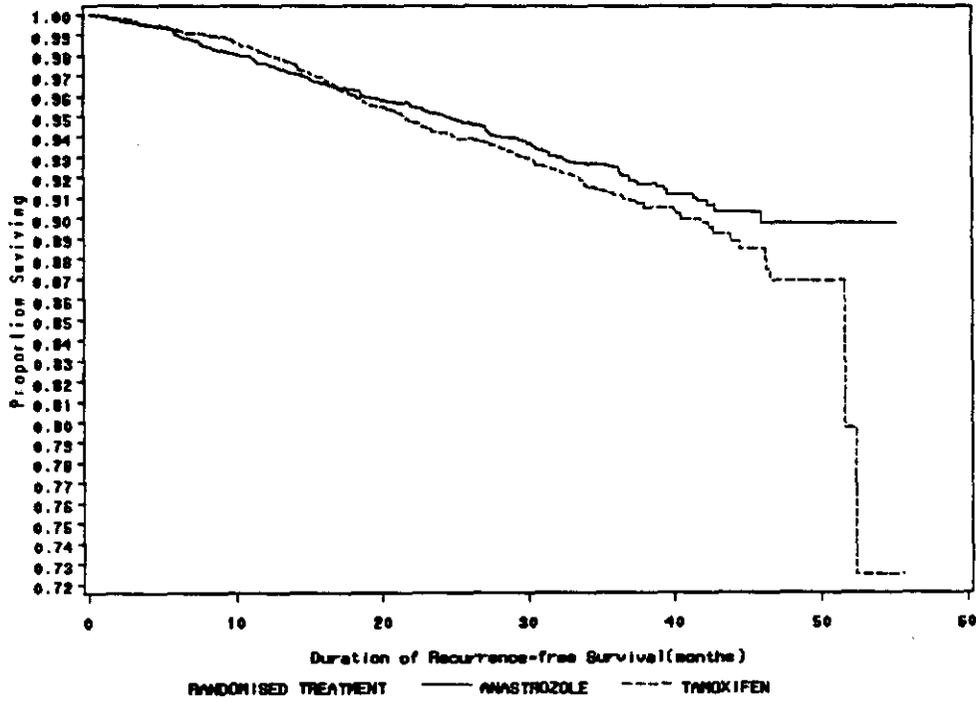
^a: 4/80 deaths in A and 1/ 82in T were due to breast cancer and were counted as recurrence events;

^b: 2/67 in A, 5/83 in T and 4/81 in A+T had sub-optimal therapy (breast conservation surgery with no radiotherapy); c: 2/67 in A, 2/83 in T and 1/81 in A=T had DCIS with no invasion; ^d: 34 patients in A, 35 patients in T and 28 patients in A+T received hormones, serms or chemotherapy during while on study (see Appendix 1).

¹: Cox proportional model without baseline co-variates and not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio.

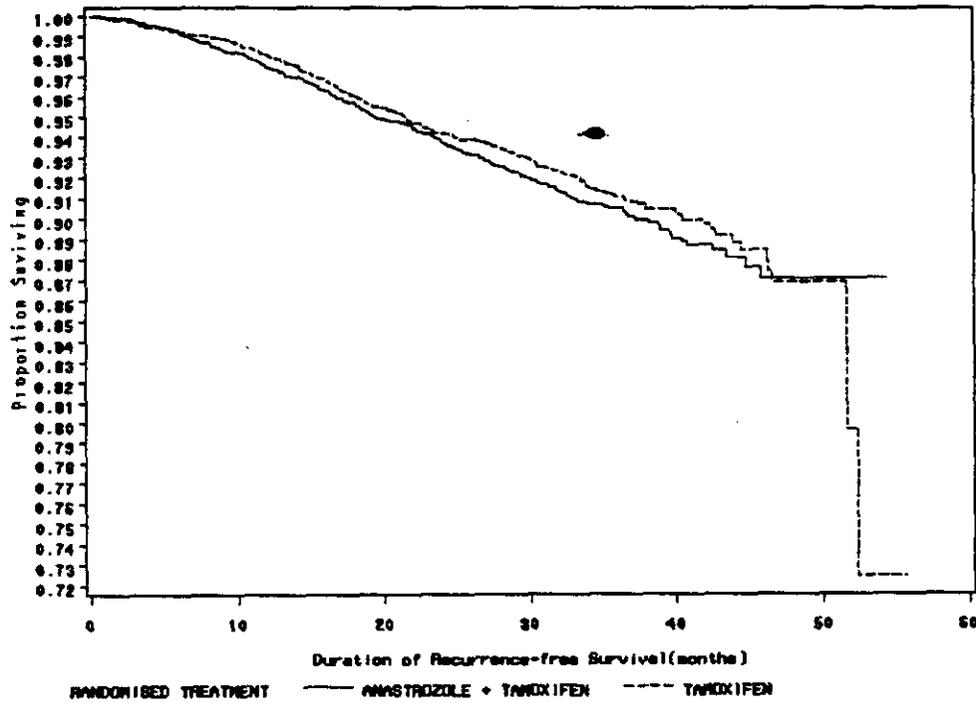
STATISTICAL REVIEW AND EVALUATION

Figure 9: Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen (FDA definition 3 of disease recurrence)



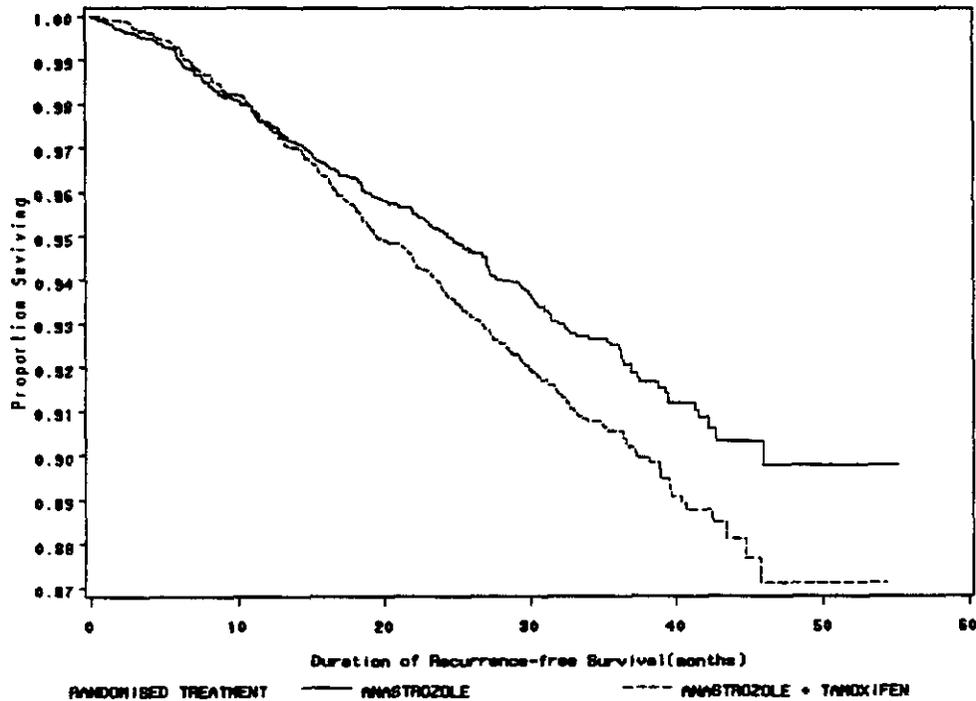
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Figure 10: Kaplan-Meier Plot of Recurrence-free Survival of Tamoxifen versus Tamoxifen + Arimidex (FDA definition 3 of disease recurrence)



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Figure 11: Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen + Arimidex (FDA definition 3 of disease recurrence)



2.10.3 Secondary Efficacy Analyses

The secondary efficacy endpoints for the study included time to first distant recurrence, time to disease recurrence in hormone receptor positive patients and overall survival. For the time to event analyses, "Time" defined in the protocol was the time period from the date of randomization to the first date of event or censoring date.

Analysis of Time to Distant Recurrence:

The results of the analysis of time to distant recurrence using Cox proportional hazards model without baseline co-variables and the Kaplan-Meier plots are presented in Table 9 and Figures 12-14.

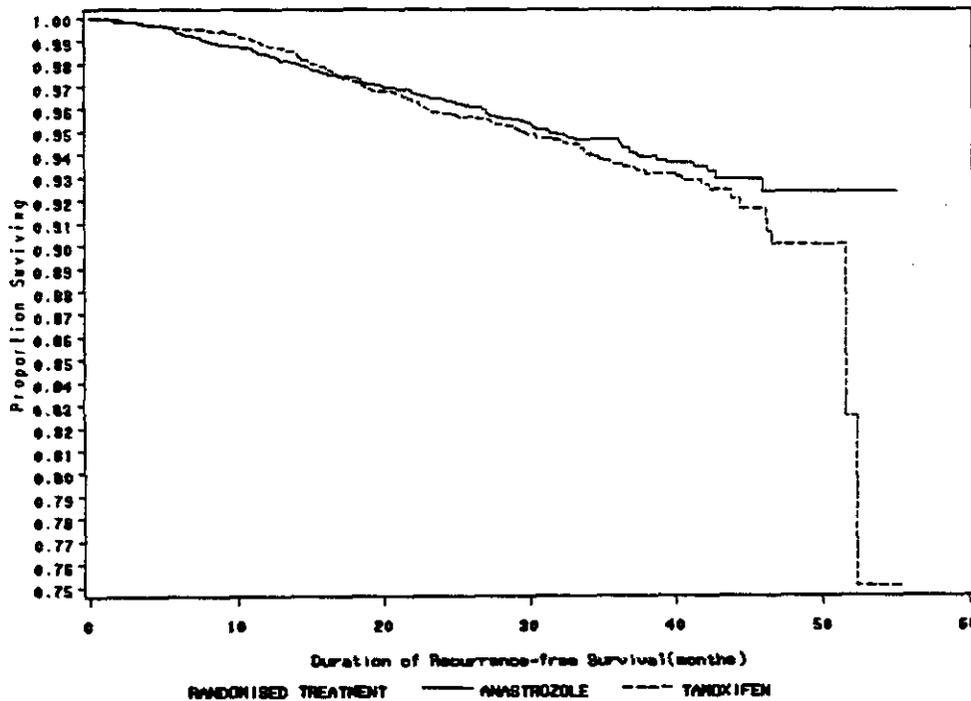
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Table 9: Time to Distant Disease Recurrence - FDA Analyses*

Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	0.876	0.708 – 1.083	0.2199
A + T vs. T	1.123	0.919 – 1.372	0.2567
A + T vs. A	1.279	1.039 – 1.573	0.0200

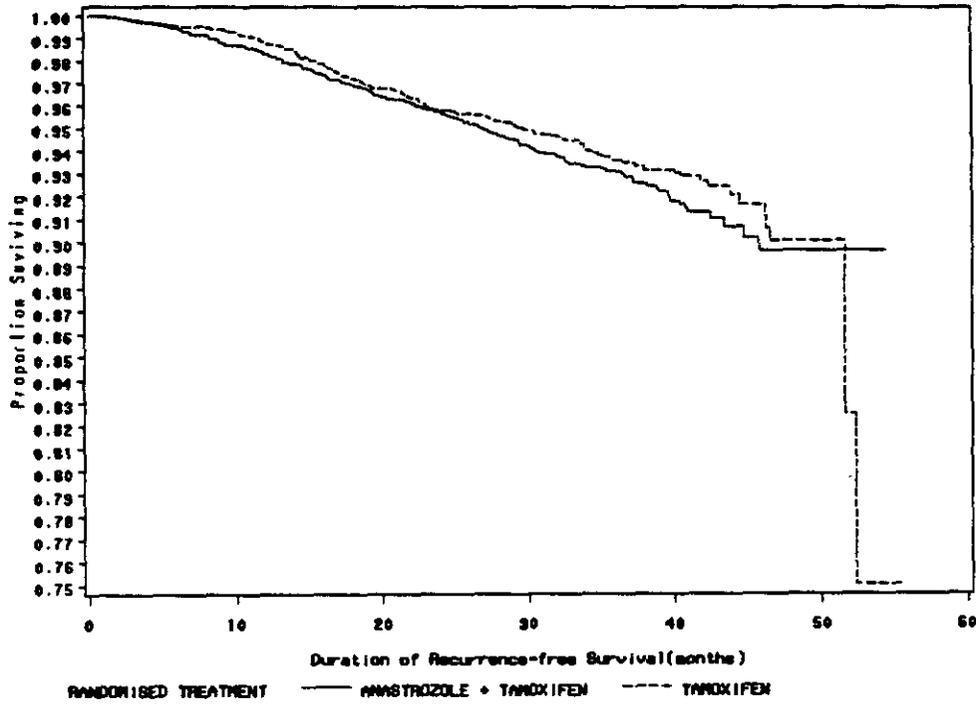
* 4/80 deaths in A and 1/82 in T were due to breast cancer and were counted as recurrence events.
¹: Cox proportional model without baseline co-variables and not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio.

Figure 12: Kaplan-Meier Plot of Distant Recurrence-free Survival of Arimidex versus Tamoxifen (FDA Analysis)



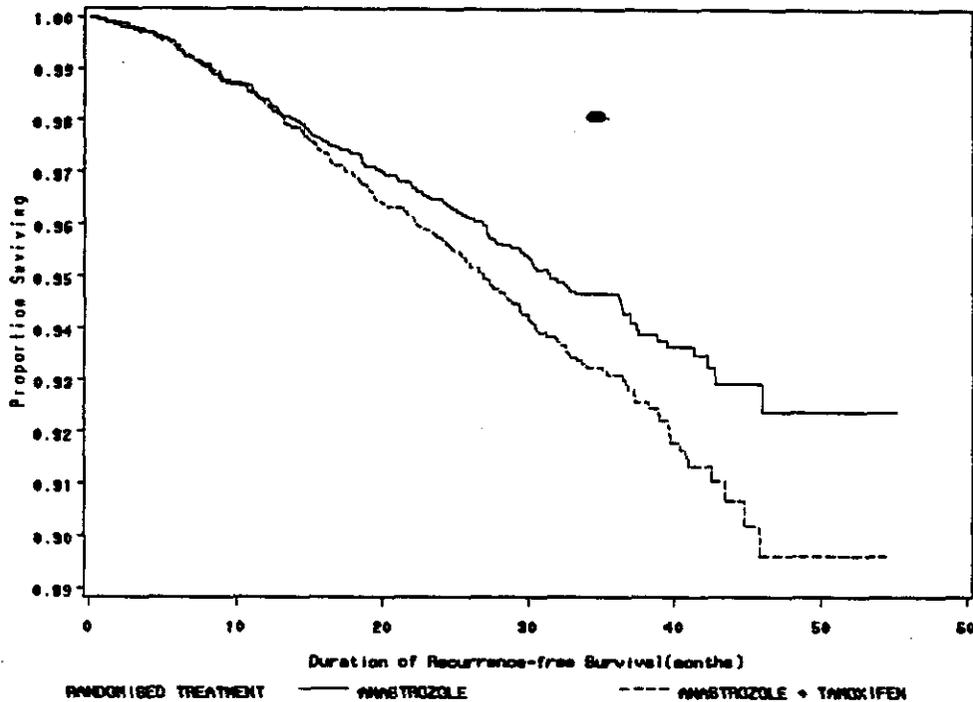
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Figure 13: Kaplan-Meier Plot of Distant Recurrence-free Survival of Tamoxifen versus Tamoxifen + Arimidex (FDA Analysis)



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Figure 14: Kaplan-Meier Plot of Distant Recurrence-free Survival of Arimidex versus Tamoxifen + Arimidex (FDA Analysis)



Reviewer's Comment:

There is no statistically significant difference between (1) arimidex and tamoxifen, and (2) tamoxifen and tamoxifen + arimidex in time to distant disease recurrence. However there appears to be a difference between arimidex and tamoxifen + arimidex in time to disease recurrence favoring arimidex.

Analysis of Time to Disease Recurrence in hormone receptor (ER/PgR) Positive Patients:

The results of the analysis of time to disease recurrence (per sponsor definition of recurrence) in the subgroup of hormone receptor positive patients using Cox proportional hazards model without baseline co-variables and the Kaplan-Meier plots are presented in Table 10 and Figures 15-17.

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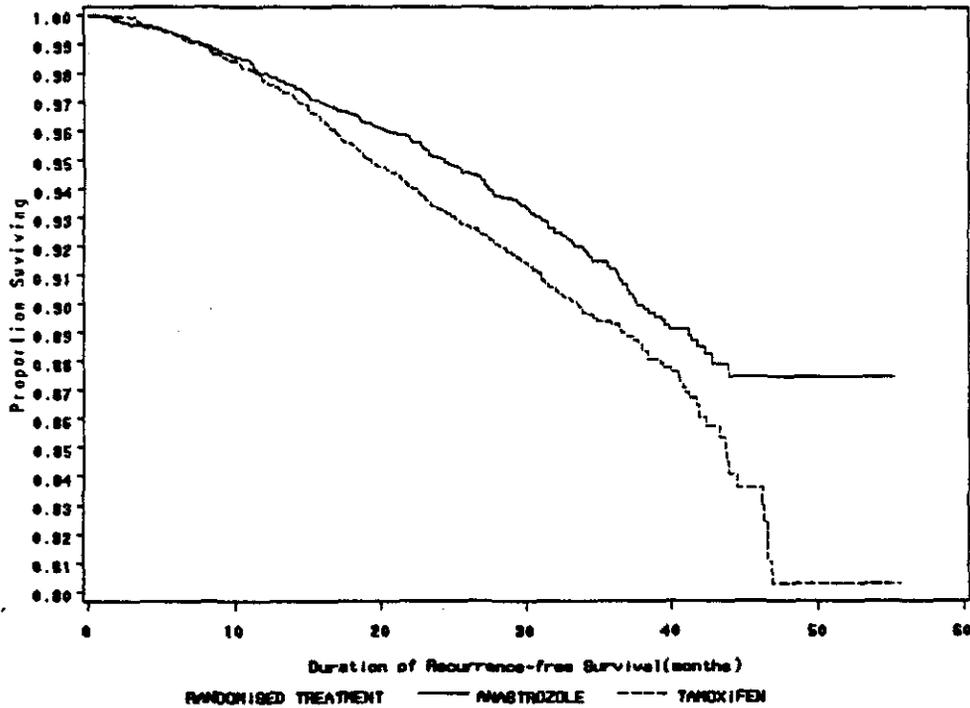
Table 10: Time to Disease Recurrence in ER/PgR Positive Patients - FDA Analyses*

Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	0.780	0.652 – 0.932	0.0063
A + T vs. T	1.025	0.867 – 1.212	0.7706
A + T vs. A	1.313	1.100 – 1.568	0.0026

* using sponsor definition of disease recurrence.

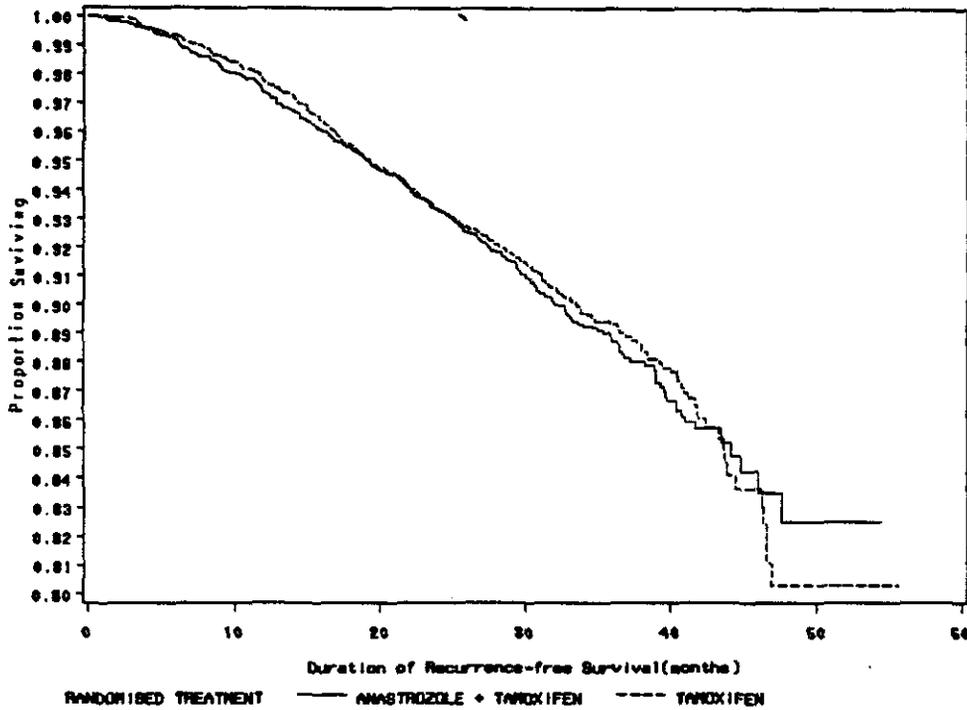
¹: Cox proportional model without baseline co-variables and not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio.

Figure 15: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in ER/PgR Positive Patients of Arimidex versus Tamoxifen (FDA Analysis)



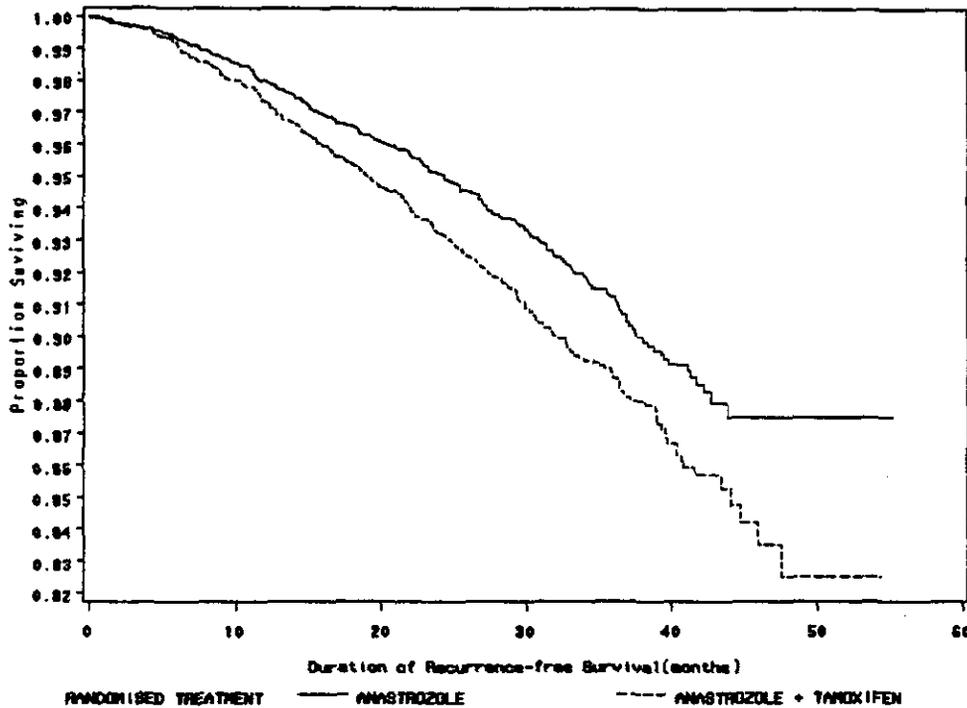
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Figure 16: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in ER/PgR Positive Patients of Tamoxifen versus Tamoxifen + Arimidex (FDA Analysis)



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Figure 17: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in ER/PgR Positive Patients of Arimidex versus Tamoxifen + Arimidex (FDA Analysis)



Reviewer's Comment:

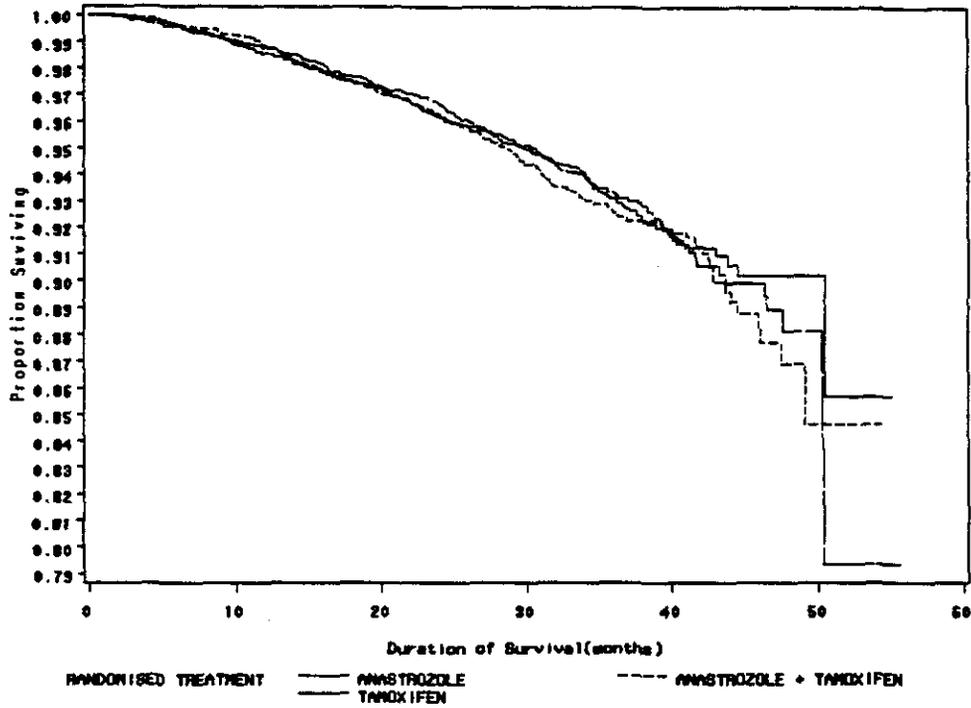
The results in the hormone receptor positive sub-population are similar to the overall ITT population.

Analysis of Overall Survival:

The overall survival data was not mature at the time of data cut-off date. No formal comparative analyses have been conducted. Figure 18 gives the Kaplan-Meier Plot of overall survival in the three treatment arms.

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Figure 18: Kaplan-Meier Plot of Overall Survival (FDA Analysis)



Reviewer's Comment:

At the time of data cut-off date 200 deaths in arimidex arm, 203 deaths in tamoxifen arm and 214 deaths in the tamoxifen + arimidex arm were observed.

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2.11 Statistical Review of Special Population and Subgroups

2.11.1 Results in Female Population

This is a study in female patients only and therefore no separate analysis was conducted in this population.

2.11.2 Results in the Subgroup of US Population

The results of the analysis of the primary endpoint, time to disease recurrence (using sponsor's definition of recurrence) in the subgroup of US population, using Cox proportional hazards model without baseline co-variates and the Kaplan-Meier plots are presented in Table 11 and Figures 19-21. There were a total of 741 patients in the arimidex arm, 735 patients in the tamoxifen arm and 746 patients in the tamoxifen + arimidex arm entered in US centers. Per sponsor definition of recurrence, there were 71/741 patients in arimidex arm, 77/735 patients in the tamoxifen arm and 67/746 patients in the tamoxifen + arimidex arm who had disease recurrence.

Table 11: Time to Disease Recurrence in US Patients - FDA Analyses*

Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	0.899	0.651 - 1.241	0.5177
A + T vs. T	0.867	0.625 - 1.203	0.3920
A + T vs. A	0.963	0.690 - 1.345	0.8270

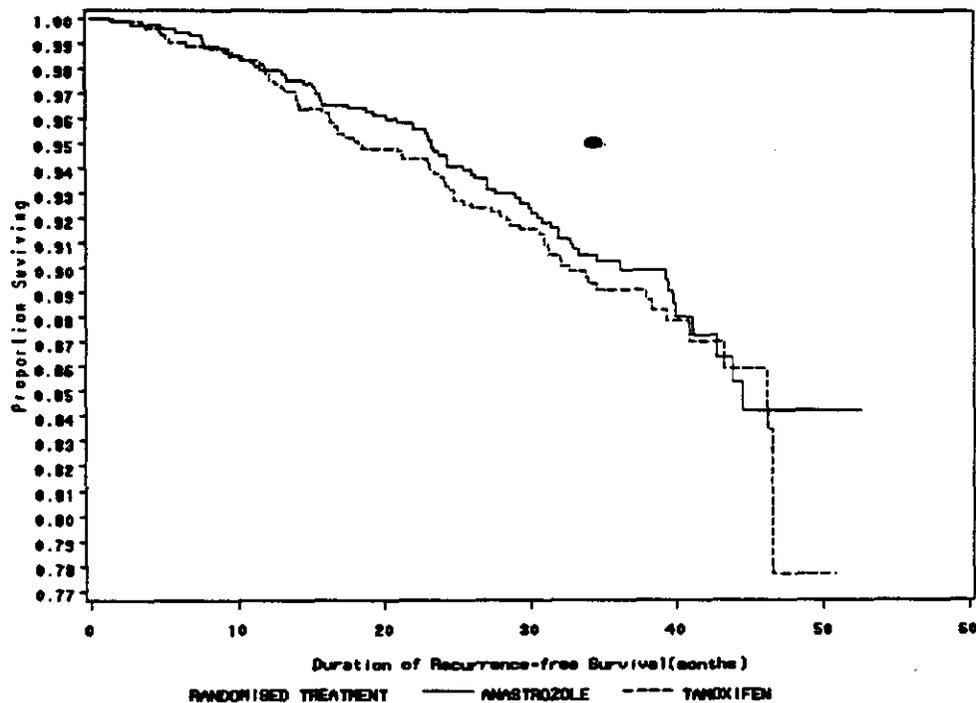
*: using sponsor definition of disease recurrence.

¹: Cox proportional model without baseline co-variates and not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio.

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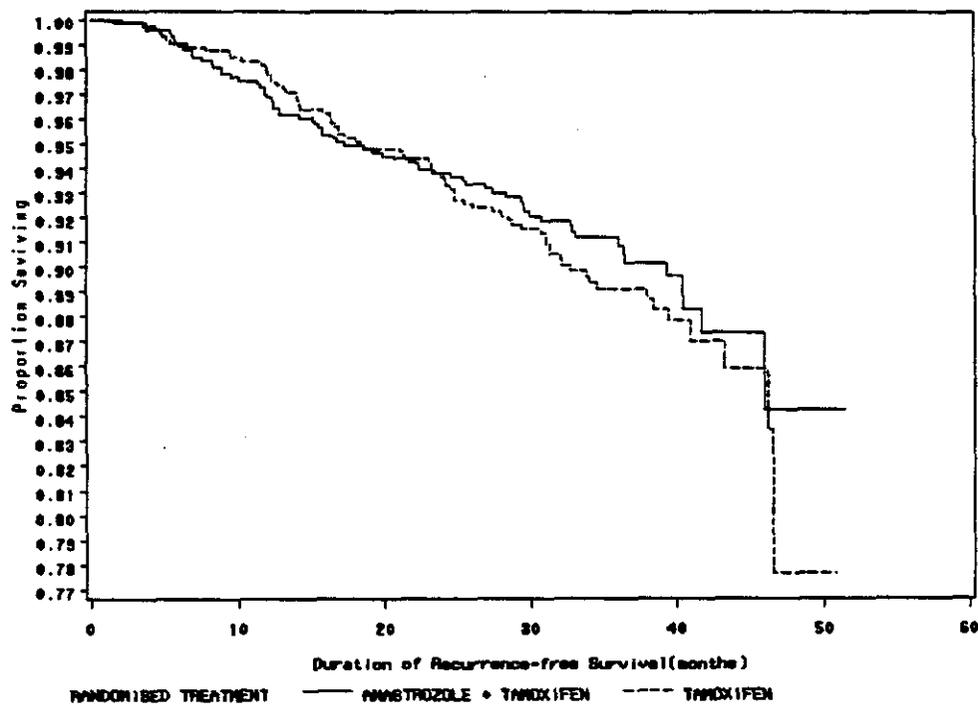
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Figure 19: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in US Patients of Arimidex versus Tamoxifen (FDA Analysis)



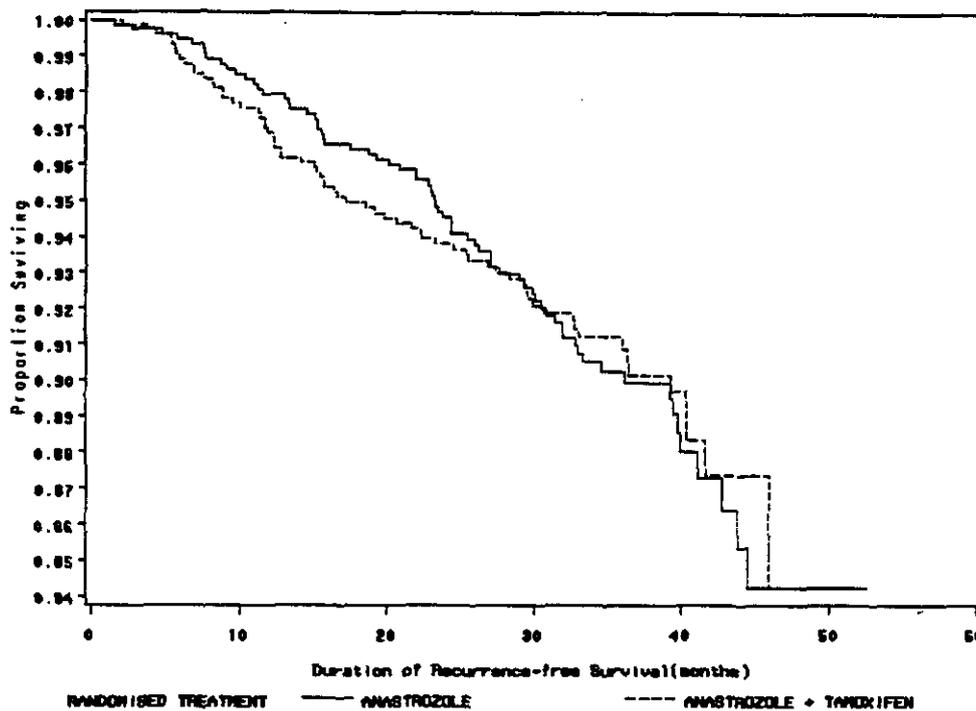
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Figure 20: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in US Patients of Tamoxifen versus Tamoxifen + Arimidex (FDA Analysis)



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Figure 21: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in US Positive Patients of Arimidex versus Tamoxifen + Arimidex (FDA Analysis)



Reviewer's Comments:

1. Approximately 24% of the overall study population were US patients.
2. It is to be noted that in this sub-population the trend in the time to disease recurrence is different compared to the overall population, specifically in the tamoxifen + arimidex combination arm. Only in this subgroup of patients the combination treatment appears to be better than either of the two single agents. However it is a subgroup of patients and adequate follow-up and further trials are necessary to confirm these results. It was not possible to identify if any specific country contributed predominantly to the efficacy of arimidex.

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2.11.3 Results in the Subgroup of Patients Who Received Prior Adjuvant Chemotherapy

The results of the analysis of the primary endpoint, time to disease recurrence (using sponsor's definition of recurrence) in the subgroup of patients who had received adjuvant chemotherapy prior to the entry into the current study under review, using Cox proportional hazards model without baseline co-variables and the Kaplan-Meier plots are presented in Table 12 and Figures 22-24. There were a total of 698 patients in the arimidex arm, 647 patients in the tamoxifen arm and 651 patients in the tamoxifen + arimidex arm who had prior adjuvant chemotherapy. Per sponsor definition of recurrence, in this subgroup of patients there were 104/698 patients in arimidex arm, 87/647 patients in the tamoxifen arm and 104/651 patients in the tamoxifen + arimidex arm who had disease recurrence.

Table 12: Time to Disease Recurrence in Patients Treated with Prior Adjuvant Chemotherapy - FDA Analyses*

Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	1.134	0.852 - 1.509	0.3879
A + T vs. T	1.237	0.930 - 1.646	0.1445
A + T vs. A	1.093	0.833 - 1.434	0.5212

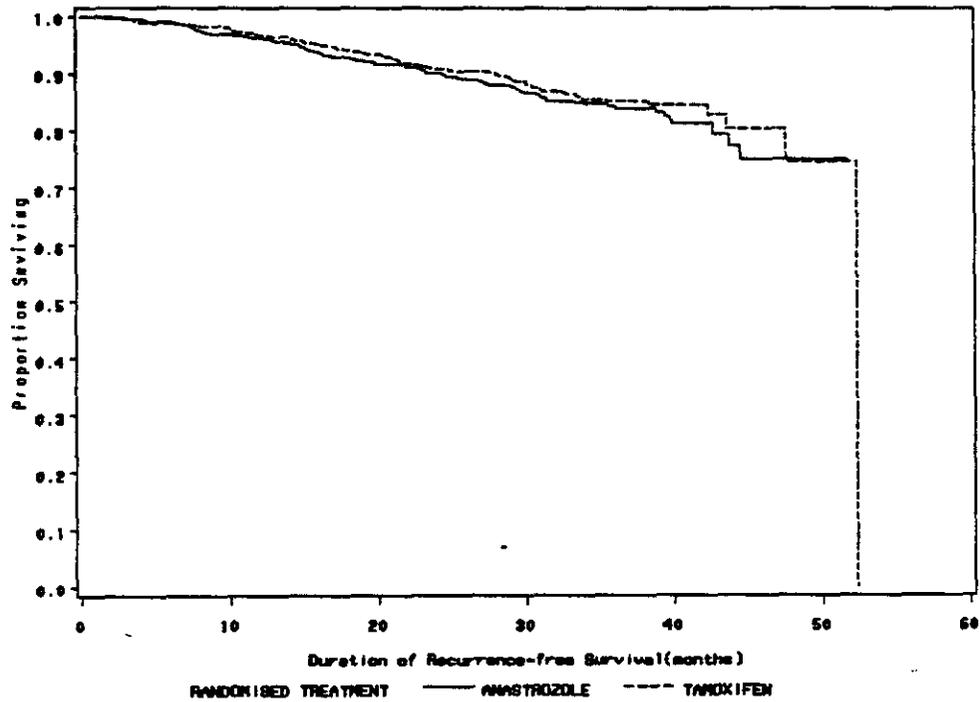
* using sponsor definition of disease recurrence.

¹: Cox proportional model without baseline co-variables and not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio.

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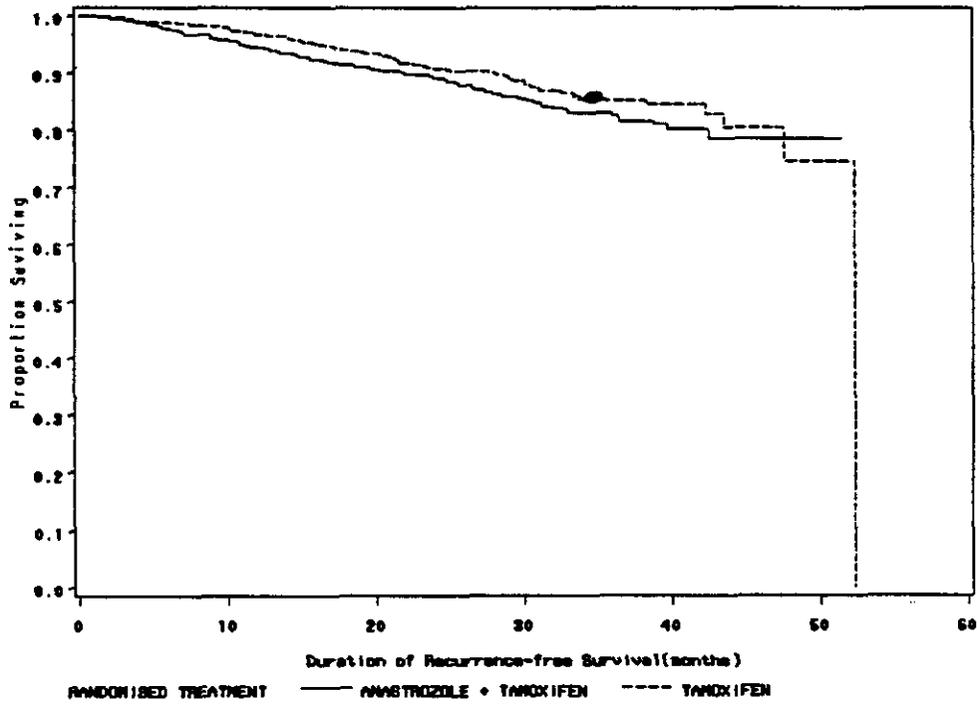
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Figure 22: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in Patients Treated With Prior Adjuvant Chemotherapy of Arimidex versus Tamoxifen (FDA Analysis)



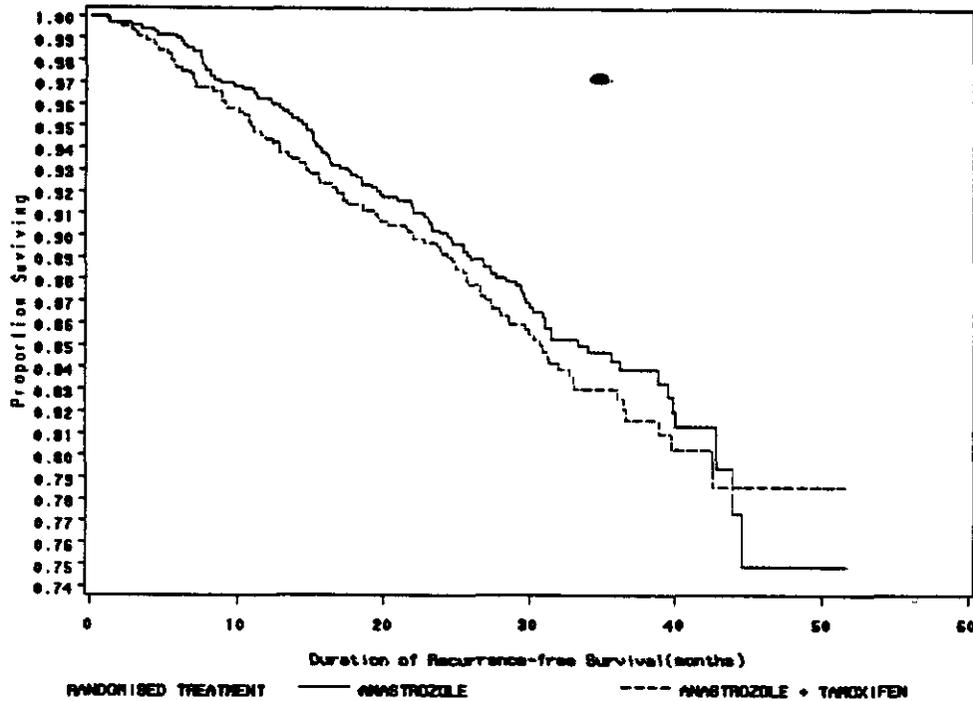
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Figure 23: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in Patients Treated With Prior Adjuvant Chemotherapy of Tamoxifen versus Tamoxifen + Arimidex (FDA Analysis)



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Figure 24: Kaplan-Meier Plot of Recurrence-free Survival (Sponsor definition) in Patients Treated With Prior Adjuvant Chemotherapy of Arimidex versus Tamoxifen + Arimidex (FDA Analysis)



Reviewer's Comments:

It is to be noted that in this sub-population the trend in the time to disease recurrence is in the opposite direction compared to the overall population, specifically in the arimidex arm compared to tamoxifen arm. Furthermore, it appears both tamoxifen and arimidex are better than the combination tamoxifen + arimidex treatment arm. However this is a subgroup of patients and adequate follow-up and further trials are necessary to confirm these results.

2.11.4 Results in Different Age Group of Patients

The results of the analysis of time to disease recurrence (per sponsor definition of recurrence) comparing arimidex with tamoxifen in the three age groups: < 60

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years, 60 – 70 years and > 70 years of patients using Cox proportional hazards model without baseline co-variables are presented in Table 13.

Table 13: Analyses of Time to Disease Recurrence* Comparing Arimidex versus Tamoxifen in Different Age Groups of Patients

SubGroups	Total Number of Patients	Hazard Ratio**	2-sided 95% Confidence Interval	P-value ¹
< 60 years of Age	2208	0.78	0.60 – 1.02	0.0676
60 – 70 years of Age	2345	0.88	0.68 – 1.14	0.3432
> 70 years of Age	1688	0.84	0.65 – 1.07	0.1590

¹: not adjusted for multiple comparisons and analyses. *: Sponsor's definition of Recurrence; **: HR < 1 implies A better than T

Reviewer's Comment:

Due to small numbers in each of the subgroups conclusive interpretation of results can not be made. However arimidex appears to demonstrate similar efficacy in all the three age groups.

2.11.5 Results from Additional Sub-protocols

In addition to the main trial some patients from this trial were also included in one or more separate protocols which were performed at specific centers. Three of these sub-protocols were designed to address the following objectives: (1) endometrial status (protocol number 1033IC/0029), (2) bone mineral metabolism (protocol number 1033ID/0029), and (3) quality of life (protocol number 1033IE/0029). An in depth review of these sub-protocols was not conducted.

Reviewer Comments:

1. The endometrial carcinoma sub-protocol was designed to enter 500 patients. However only 285 patients were entered by the close of the main trial and this protocol was closed prematurely and the results are not interpretable.
2. The primary objective of the bone mineral metabolism sub-protocol was to assess and quantify the changes in bone mineral density (BMD) of patients receiving arimidex or arimidex + tamoxifen compared to tamoxifen alone for the duration of trial therapy. The results submitted from this protocol included data up to 1-year visit only. A total of 308 patients were enrolled into this sub-protocol. The primary endpoint was the change in BMD from baseline. Per sponsor's analysis changes in BMD from baseline to 12 months

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showed a statistically significant difference between arimidex and tamoxifen treatment groups, with lower values at 1 year in the arimidex arm, i.e. favoring tamoxifen arm.

3. In the quality of life (QOL) protocol, data were collected using the Functional Assessment of Cancer Therapy – Breast (FACT-B) and Endocrine sub-scale (ES) questionnaire from a total of 1105 patients. The primary endpoint was the Trial Outcome index (TOI) of the FACT-B. Per sponsor's analyses there appears to be no significant difference between arimidex and tamoxifen arms with respect to TOI.

2.12 Safety Analyses

All treated patients were included in the safety evaluation according to treatment first received. The safety information reviewed by this reviewer consists of adverse events including new primary cancers.

The following table (Table 14) lists the pre-specified adverse events observed in each of the treatment arms. The highlighted categories are those where the adverse event rate was higher in the arimidex arm compared to tamoxifen arm. Table 15 includes further exploratory comparative analyses of these events. A time to first fracture (any fracture) was conducted and the results are presented in Table 16 and Figures 25-27. Table 17 lists incidence of all new primaries (other than breast cancer) in each of the treatment arms (cancers where the incidence was higher in arimidex arm compared to tamoxifen arm are highlighted). The sponsor has reported under clinical laboratory data (Volume 1, Section 5.11, Table 62) that there were 186/3092 patients in arimidex arm, 68/3094 patients in the tamoxifen arm, and 58/3097 patients in the tamoxifen + arimidex arm who had hypercholesteraemia. This data could not be verified by the reviewer as the raw laboratory data was not submitted with the NDA by the sponsor.

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Table 14: Incidence of Pre-specified Adverse Events Occurring in Any Treatment Group (Updated Data, FDA Analyses)

Category	Number of patients		
	Arimidex 1 mg (N = 3092)	Tamoxifen 20 mg (N = 3093)	Arimidex 1 mg + Tamoxifen 20 mg (N = 3098)
Hot flushes	1082	1246	1261
Mood disturbances	521	511	507
Fatigue/asthenia	513	491	468
Nausea and vomiting	348	342	379
Vaginal discharge	94	378	368
Vaginal bleeding	147	270	265
Cataracts	128	140	126
Musculoskeletal disorders	940	737	766
All Fractures	224	145	186
Fractures of spine, hip or wrist/Colles	89	62	68
All venous thromboembolic events	73	120	146
Deep venous thromboembolic events	40	60	80
Ischaemic cardiovascular disease	92	74	84
Ischaemic cerebrovascular events	40	74	63
Endometrial cancer	3	15	10

Table 15: Pre-specified Adverse Events Occurring in Any Treatment Group (Updated Data, FDA Comparative Analyses)

Category	A vs. T			A + T vs. T		
	Odds Ratio	95% CI	P- value*	Odds Ratio	95% CI	P- value*
Hot flushes	0.80	0.73 – 0.87	<0.0001	0.98	0.91 – 1.07	0.6633
Mood disturbances	1.02	0.90 – 1.16	0.7042	1.01	0.89 – 1.15	0.8566
Fatigue/asthenia	1.05	0.93 – 1.20	0.4040	1.06	0.93 – 1.21	0.3639
Nausea and vomiting	1.02	0.88 – 1.19	0.7936	0.89	0.77 – 1.04	0.1250
Vaginal discharge	0.23	0.18 – 0.28	<0.0001	1.03	0.89 – 1.20	0.6592
Vaginal bleeding	0.52	0.42 – 0.64	<0.0001	1.02	0.86 – 1.22	0.7973
Cataracts	0.91	0.71 – 1.17	0.4461	1.12	0.87 – 1.43	0.3634
Musculoskeletal disorders	1.41	1.28 – 1.55	<0.0001	0.95	0.86 – 1.06	0.3440
All Fractures	1.59	1.28 – 1.97	<0.0001	0.77	0.62 – 0.96	0.0181
Fractures of spine, hip or wrist/Colles	1.45	1.04 – 2.04	0.0244	0.91	0.64 – 1.31	0.5990
All venous thromboembolic events	0.60	0.44 – 0.81	0.0005	0.82	0.64 – 1.05	0.0990
Deep venous thromboembolic events	0.66	0.43 – 1.00	0.0428	0.75	0.52 – 1.06	0.0863
Ischaemic cardiovascular disease	1.25	0.91 – 1.72	0.1515	0.88	0.63 – 1.22	0.4218
Ischaemic cerebrovascular events	0.53	0.35 – 0.80	0.0012	1.18	0.83 – 1.68	0.3335
Endometrial cancer	0.20	0.04 – 0.70	0.0043	1.50	0.63 – 3.70	0.3230

* Not adjusted for multiple comparisons and analyses.

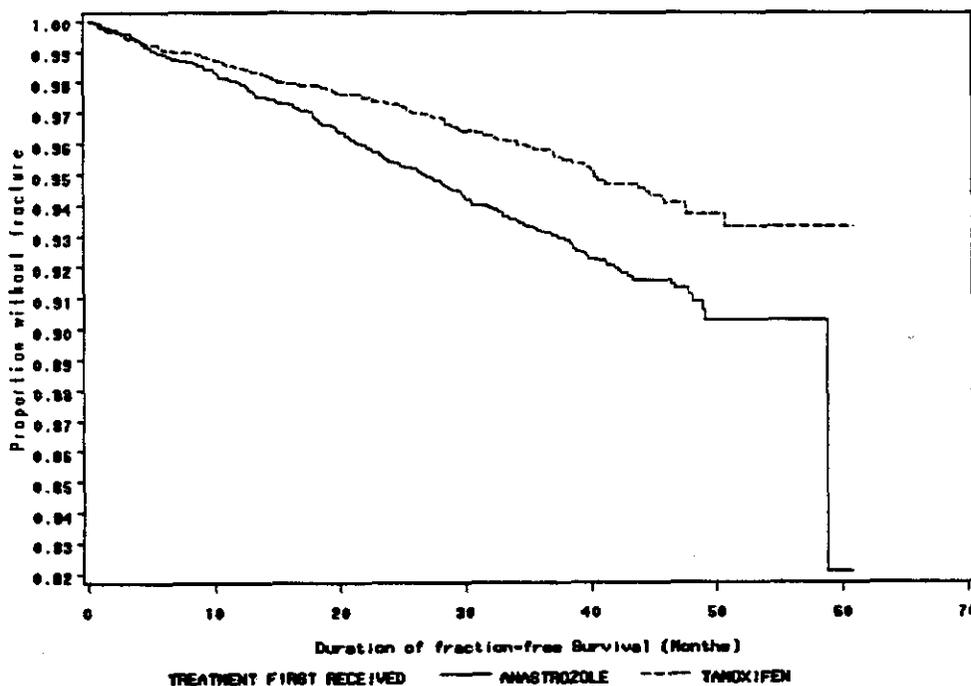
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Table 16: Time to first fracture - FDA Analyses

Treatment comparison	Estimated HR	2-sided 95% C.I.	p-value ¹
A vs. T ²	1.557	1.263 – 1.919	< 0.0001
A + T vs. T	1.310	1.054 – 1.628	0.0148
A + T vs. A	0.842	0.693 – 1.023	0.0835

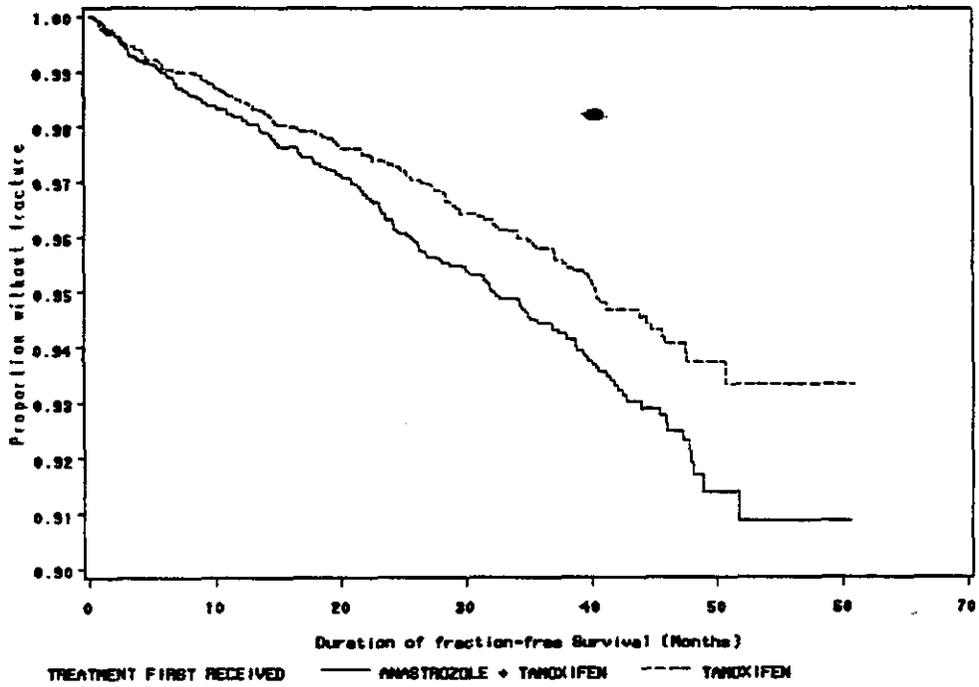
¹: Cox proportional model without baseline co-variables and not adjusted for multiple comparisons and analyses; ²: A = Arimidex 1 mg, T = Tamoxifen 20 mg. HR = hazard-ratio

Figure 25: Kaplan-Meier Plot of Time to First Fracture of Arimidex versus Tamoxifen (FDA Analysis)



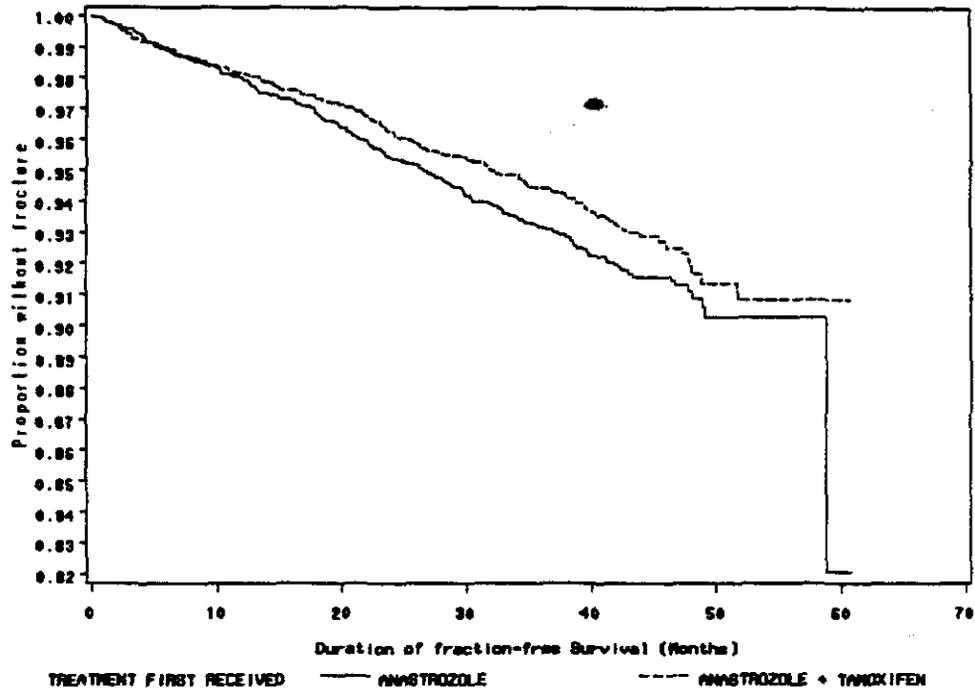
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Figure 26: Kaplan-Meier Plot of Time to First Fracture of Tamoxifen versus Tamoxifen + Arimidex (FDA Analysis)



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Figure 27: Kaplan-Meier Plot of Time to First Fracture of Arimidex versus Tamoxifen + Arimidex (FDA Analysis)



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**Table 17: Incidence of New Primary Cancers Other Than Breast Cancer
Occurring in Any Treatment Group (Updated Data - FDA Analyses)**

New Primary Cancer	Number of patients		
	Arimidex 1 mg (N = 3092)	Tamoxifen 20 mg (N = 3093)	Arimidex 1 mg + Tamoxifen 20 mg (N = 3098)
Skin	47	41	40
Colorectal	23	20	11
Lung	9	9	10
Ovary	6	10	8
Endometrial	2	15	12
Cervix	0	3	3
Head and Neck	5	2	3
Gastric/esophagus	4	3	10
CNS	2	2	5
Hepatic/Colongial	2	1	3
Renal	4	1	2
Bladder	3	3	2
Leukemia/Lymphoma	7	8	3
Other	11	17	10
Unknown	0	0	3
Total	124	135	128

Reviewer's Comments:

There appears to be significantly higher incidence of fractures, musculoskeletal events, and hypercholesteraemia in arimidex arm compared to tamoxifen arm and significantly fewer incidence of endometrial carcinoma in the arimidex arm compared to tamoxifen arm. This study is still on going with less than 3 years of median follow-up and further monitoring of these adverse events are necessary.

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2.13 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Study 1033IL/0029 was a randomized, double-blind, multicenter, parallel-group, Phase III study conducted in a total of 9366 postmenopausal women with breast cancer. The primary objective of this study was to assess the efficacy of arimidex 1 mg compared to tamoxifen 20 mg, and assess efficacy of the combination of arimidex 1 mg and tamoxifen 20 mg compared to tamoxifen 20 mg alone as adjuvant treatment in early breast cancer patients. The primary efficacy endpoint was the time to disease recurrence. The sponsor claims that this study has demonstrated that arimidex 1 mg provides significant clinical benefit over tamoxifen 20 mg in terms of both efficacy and safety. Furthermore, the sponsor claims that results of the analysis of the primary endpoint time to disease recurrence indicate a 17% reduction in the risk of disease recurrence in favor of arimidex 1 mg in comparison with tamoxifen 20 mg.

1. The primary endpoint time to disease recurrence as defined by the sponsor is a composite endpoint with each component having a different prognosis. Loco-regional recurrences including DCIS, distant recurrences, new primary contralateral breast cancer including DCIS and all cause mortality as first event were considered as recurrences by the sponsor. There is no clear consensus on which of these components should be included as recurrence events.
2. The current standard of care in this disease setting is tamoxifen 20 mg administered daily for 5 years. At the time of data cut-off date no patient had received 5 years of treatment. The sponsor's analysis could be therefore comparing to suboptimal active control. The meta-analysis (*The Lancet*, 351: 1451-1467, 1998) of tamoxifen trials based on 30,000 women with approximately 10 years of follow up have shown clearly that when 1 year, 2 years and about 5 years of adjuvant tamoxifen is compared to placebo, in both proportional recurrence reductions and proportional mortality reductions there is highly significant trend towards greater tamoxifen effect with longer treatment. In the trials of about 5 years of adjuvant tamoxifen the recurrence rate was reduced by about half during 0-4 years of follow-up and by about one-third during the next few years. The study under review here was designed with the intention of treating all patients for a period of 5 years as adjuvant treatment.
3. The median follow-up at the time of data cut-off date was 33.3 months with < 3 % of patients who had received 4 to 5 years of treatment and approximately 25% of patients who had withdrawn from the study before completing 5 years of treatment. The sample size was increased from a total of 6000 patients per original plan to 9500 patients, plausibly resulting in more events with a shorter follow-up. Conclusive evidence of strength of efficacy of arimidex 1

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mg compared to tamoxifen 20 mg can only be assessed with adequate treatment and follow-up data.

4. The timing of the final analysis was solely based on reaching the prespecified total number of events. Depending on how the recurrence event is defined this goal might be or not be reached. Further follow-up is therefore necessary to conclusively determine the efficacy of arimidex 1mg when compared to tamoxifen 20 mg. It is also to be noted that the required level of significance was not reached if other definitions were employed to define recurrence as demonstrated in Tables 6-8.
5. With respect to safety, arimidex appears to decrease the incidence of endometrial carcinoma compared to tamoxifen. There are significantly more fractures and hypercholesteraemia observed in the arimidex treatment arm compared to tamoxifen arm. The safety data presented in this application are premature and only longer follow-up data can confirm these early safety issues.

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3 Statistical Evaluation of Collective Evidence

In this reviewer's opinion the results of Study 1033IL/0029 (ATAC Trial) appears to demonstrate efficacy of arimidex 1 mg when compared to less than 5 years of tamoxifen 20 mg treatment in the adjuvant treatment of postmenopausal women with breast cancer with less than 3 years of follow-up. The strength and consistency of efficacy and safety of arimidex compared to tamoxifen can only be determined with adequate treatment duration and follow-up.

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/S/

Rajeshwari Sridhara, Ph.D.
Mathematical Statistician
Date:

Concur: Dr. Chen
Team Leader

Dr. Mahjoob
Deputy Division Director, DBI

Cc:
HFD-150/ Ms. Baird
HFD-150/ Dr. Cortazar
HFD-150/ Dr. Farrell
HFD-150/ Dr. Williams
HFD-150/ Dr. Pazdur
HFD-710/ Dr. Sridhara
HFD-710/ Dr. Chen
HFD-710/ Dr. Mahjoob
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello

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4 APPENDICES

4.1 APPENDIX 1 – Patient ID's who were censored for disease recurrence (per efficacy medical reviewer's evaluation)

Table 18: List of Patients with Loco-regional Breast Cancer Recurrence with non-invasive DCIS or sub-optimal therapy (breast conserving therapy without radiation)

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

Table 19: List of Patients Who Died Due to Breast Cancer as First Event

Arimidex	Tamoxifen
0001/0063, 0012.0002, 0018/0101, 0413.0013	0435/0077

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Table 20: List of Patients Who Received Not-allowed Therapy That Were Administered During the Trial Prior to Recurrence Known to Have Effect on Primary Endpoint (Medical Reviewer's table from CRFs) (Reference: Table 6 of efficacy medical review)

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

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