(at 5% level of significance), a likelihood ratio test developed by Gail and Simon (1985) was used to test the nature of the interaction (quantitative or qualitative). If the interaction was deemed to be quantitative, the combined analysis was performed for that time to event end point. If the interaction was deemed to be qualitative, the combined analysis was not performed for that time to event end point and the reason was explored.

The comparison of the treatments was estimated using the hazard ratio of tamoxifen to anastrozole together with the lower 1-sided 95% confidence limit of the hazard ratio. If the lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen:anastrozole) was no less than 0.8, it would be concluded that anastrozole is non-inferior to tamoxifen.

The assumptions of the adjusted Cox regression model were assessed using plots of the log against log(time), in which parallel lines indicated proportional hazards. The assumptions of proportionality were also investigated with a time-dependent explanatory variable which is defined as treatment . If the p-value from Wald chi-squared statistic for this variable was less than 5%, this would be evidence of a departure from the adjusted model assumptions. In this case, the reason would be explored and reported.

2.7.4 Objective response

2.7.4.1 Objective response for all subjects

The best objective response of CR, PR, SD ≥ 24 weeks, SD < 24 weeks, or progression was summarized by randomized trial treatment for all subjects. Also the best objective response was summarized by extent of disease at entry.

Objective response rate was defined as proportion of responders (CR and PR). Treatment comparison in objective response rate was analyzed using a logistic regression model to assess whether anastrozole was non-inferior to tamoxifen. The SAS procedure was implemented. The logistic regression model was used in 2 ways: (a) adjusted analysis with treatment factor and the baseline prognostic covariates using "trial" as an additional covariate, and (b) unadjusted analysis with treatment factor only. The primary analysis was Method (a) and the other analysis was considered as supportive. In analysis (a), trial-by-treatment interaction was assessed and if there was evidence of significant trial-by-treatment interaction (at 5% level of significance), a likelihood ratio test developed by Gail and Simon (1985) was used to test the nature of the interaction (quantitative or qualitative). If the interaction was deemed to be quantitative, the combined analysis was performed for objective response rate. If the interaction was deemed to be qualitative, the combined analysis was not performed for objective response rate and the reason was explored.

The comparison of the treatments was estimated using the odds ratio of anastrozole to tamoxifen together with the lower 1-sided 95% confidence limit of the odds ratio. If the lower 1-sided 95% confidence limit for the difference in response rate (anastrozole - tamoxifen) was no less than −10%, we will conclude that anastrozole is non-inferior to tamoxifen.

As logistic regression was used, SAS output an estimated odds ratio) rather than a difference in response rates. An odds ratio greater than 1 indicated that the odds of responding on anastrozole were higher than the odds of responding on tamoxifen. An odds ratio less than 1 indicated that the odds of responding on anastrozole was less than the odds of responding on tamoxifen. An odds ratio equal to 1 indicated that the odds of responding were equal in both treatment groups.

Where the odds ratio (anastrozole /tamoxifen), is the observed number of responders in the tamoxifen group and is the observed number of non-responders in the tamoxifen group.

In order to determine the difference in response rates and the associated confidence limit, the values for the estimated odds ratio and the lower 1-sided 95% confidence limit of the odds ratio were the above equation. This provided the difference in response rates between anastrozole and tamoxifen, and the corresponding lower confidence limit assuming that the response rate on tamoxifen was fixed at the observed response rate in this treatment group.

2.7.4.2 Objective response for subjects with measurable disease

For individual subject with measurable disease, response for measurable disease was assigned for each site at each visit. No summary statistics were presented for site response at each visit. Only the best overall objective response in measurable disease was summarized by randomized trial treatment for subjects with measurable disease. No formal statistical analysis was performed to compare treatment groups.

2.7.5 Duration of response and duration of clinical benefit

Duration of response (see definitions in Section 2.6.5) and duration of clinical benefit (see definition in Section 2.6.6) were summarized by randomized trial treatment using Kaplan-Meier method, respectively. Kaplan-Meier plots and Kaplan-Meier estimates of median duration are presented for each treatment.

No formal statistical analysis was performed to compare treatment groups.

2.7.6 Health economics

The health economic end points were summarized by trial treatment actually received. The number and percentage of subjects who received further breast cancer therapy including radiotherapy, chemotherapy, hormonal therapy, or other therapy were summarized. The length of these further breast cancer therapies were also be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum).

No formal statistical analysis was performed to compare treatment groups.

2.7.7 Analyses of demographic and other end points

2.7.7.1 Demographic and baseline characteristics

Subject characteristics (age, height, weight, body mass index, and ethnic origin), medical history, and physical examination at baseline were summarized by randomized trial treatment.

Breast cancer history at baseline, including previous adjuvant treatment (hormonal and/or cytotoxic) for breast cancer, estrogen and progesterone receptor status, extent of disease, extent of disease, measurable or no measurable disease was summarized by randomized trial treatment.

2.7.7.2 Duration of trial treatment

Duration of trial treatment was defined for each subject 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 subject who was not withdrawn from trial treatment. Duration of trial treatment was summarized by treatment received.

2.7.7.3 Duration of follow-up

Duration of follow-up was defined as the number of days from randomization date to the date of last contact for any subjects who are last known to be alive. Duration of follow-up was summarized by randomized trial treatment.

3 CONTROLLED TRIALS: DEMOGRAPHIC RESULTS

Overall, demographic characteristics were similar across treatment groups within each trial and across trials and, therefore, allowed valid conclusions to be established from the efficacy data. Subjects who participated in Trials 0030 and 0027 were representative of the designated population for the proposed indication of anastrozole.

3.1 Subject characteristics

A total of 1021 subjects, from 97 centers in the US and Canada (Trial 0030) and 83 centers in Europe, South America, Australia, and South Africa (Trial 0027), were randomized. Of these subjects, 511 were randomized to receive 1 mg of anastrozole once daily and 510 were randomized to receive 20 mg of tamoxifen once daily. A total of 1009 subjects began their randomized treatment. The details for the remaining 12 subjects who did not receive randomized treatment are provided in Section 4.1. All 1021 randomized subjects were included in the intent-to-treat efficacy analyses.

3.1.1 Age, sex, height, weight, body mass index, and ethnic origin

Summary tables: *Age, sex, height, weight, body mass index, and ethnic origin at entry; Tables T1.2 and T1.3 (Trial 0027) T12.2 and T12.3 (Trial 0030), and T23.2 and T23.3 (Combined)*

Table 2 summarizes demographic details for age, sex, height, weight, body mass index, and ethnic origin for all randomized subjects in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 2 Age, sex, height, weight, BMI, and ethnic origin of subjects in Trials 0030 and 0027, separately and combined

Demographic characteristic	Trial/Treatment group					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Age (y)						
Number of subjects	171	182	340	328	511	510
Mean	67	67	67	66	67	66
SD	11.8	11.2	11.0	10.6	11.2	10.8
Min	30	40	34	41	30	40
Max	88	92	91	92	91	92
≤65	74 (43.3)	76 (41.8)	160 (47.1)	160 (48.8)	234 (45.8)	236 (46.3)
>65	97(56.7)	106 (58.2)	180 (52.9)	168 (51.2)	277 (54.2)	274 (53.7)

Table 2 Age, sex, height, weight, BMI, and ethnic origin of subjects in Trials 0030 and 0027, separately and combined (continued)

Demographic characteristic	Trial/Treatment group					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Sex (number [%] of subjects)						
Female	171 (100.0)	182 (100.0)	340 (100.0)	328 (100.0)	511 (100.0)	510 (100.0)
Male	0	0	0	0	0	0
Height (cm)						
Number of subjects	165	173	320	310	485	483
Mean	160	160	159	159	160	160
SD	7.8	7.2	7.1	7.2	7.3	7.2
Min	133	142	139	125	133	125
Max	180	183	174	180	180	183
Weight (kg)						
Number of subjects	168	178	333	318	501	496
Mean	73	71	68	68	69	69
SD	15.2	17.6	13.2	12.9	14.1	14.8
Min	43	36	40	42	40	36
Max	121	140	121	111	121	140
BMI (kg/m^2)						
Number of subjects	163	172	317	308	480	480
Mean	28	28	27	27	27	27
SD	6.1	6.6	4.9	5.0	5.4	5.6
Min	16	14	16	16	16	14
Max	48	53	42	44	48	53
Ethnic origin (number [%] of subjects)						
Caucasian	152 (88.9)	160 (87.9)	313 (92.1)	297 (90.5)	465 (91.0)	457 (89.6)
Black	8 (4.7)	11 (6.0)	3 (0.9)	1 (0.3)	11 (2.2)	12 (2.4)
Asian/Oriental	1 (0.6)	1 (0.5)	0 (0.0)	2 (0.6)	1 (0.2)	3 (0.6)
Hispanic	5 (2.9)	8 (4.4)	9 (2.6)	9 (2.7)	14 (2.7)	17 (3.3)
Other[a]	5 (2.9)	2 (1.1)	15 (4.4)	19 (5.8)	20 (3.9)	21 (4.1)

[a] Other includes subjects of mixed origin.
n Number of randomized subjects.
BMI Body mass index; calculated by dividing weight in kilograms by the square of height in meters.

The mean age for all subjects who were randomized to anastrozole was 67 years (range 30 through 91 years). The mean age for subjects who were randomized to tamoxifen was 66 years (range 40 through 92 years). The age distribution (≤65 years or >65 years) was similar between the 2 treatment groups. The distributions of height, weight, and body mass index were similar between the 2 treatment groups. Ethnic origin distribution was similar between treatment groups. The majority (90.3%) of all subjects were Caucasian. This is consistent with the ethnic origin of the majority of breast cancer subjects in North America and Europe being Caucasian.

3.1.2 Breast cancer history

Summary tables:

Previous adjuvant therapy; Tables T1.5.1 and T1.5.2 (Trial 0027) T12.5.1 and T12.5.2 (Trial 0030), and T23.5.1 and T23.5.2 (Combined)
Hormone-receptor status; Tables T1.6.1 and T1.6.2 (Trial 0027), T12.6.1 and T12.6.2 (Trial 0030), and T23.6.1 and T23.6.2 (Combined)
Breast cancer disease status at first diagnosis; Tables T1.4 (Trial 0027), T12.4 (Trial 0030), and T23.4 (Combined)

Table 3 summarizes hormonal receptor status at entry and Table 4 summarizes previous adjuvant therapy for all randomized subjects in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 3 Hormonal receptor status at entry for all randomized subjects in Trials 0030 and 0027, separately and combined

Receptor status	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
ER+ and/or PR+	151 (88.3)	162 (89.0)	154 (45.3)	144 (43.9)	305 (59.7)	306 (60.0)
ER+, PR+	109 (63.7)	121 (66.5)	80 (23.5)	85 (25.9)	189 (37.0)	206 (40.4)
ER+, PR–	32 (18.7)	31 (17.0)	30 (8.8)	27 (8.2)	62 (12.1)	58 (11.4)
ER–, PR+	6 (3.5)	5 (2.7)	8 (2.4)	1 (0.3)	14 (2.7)	6 (1.2)
ER+, PR unknown	4 (2.3)	4 (2.2)	36 (10.6)	30 (9.1)	40 (7.8)	34 (6.7)
ER unknown, PR+	0	1 (0.5)	0	1 (0.3)	0	2 (0.4)
All other combinations	20 (11.7)	20 (11.0)	186 (54.7)	184 (56.1)	206 (40.3)	204 (40.0)
ER–, PR unknown	0	0	0	0	0	0
ER unknown, PR–	0	0	0	0	0	0
ER unknown, PR unknown	19 (11.1)	20 (11.0)	185 (54.4)	183 (55.8)	204 (39.9)	203 (39.8)
ER–, PR–	1 (0.6)	0	1 (0.3)	1 (0.3)	2 (0.4)	1 (0.2)

ER Estrogen receptor.
PR Progesterone receptor.

Hormone receptor status was similar between the 2 treatment groups. Overall, 611 (59.8%) subjects had estrogen-receptor (ER) positive, progesterone-receptor (PR) positive, or both estrogen- and progesterone-receptor positive breast cancer, and 410 (40.2%) subjects had other combinations of receptor status at entry. Three hundred and five (59.7%) subjects who were randomized to anastrozole treatment and 306 (60.0%) subjects who were randomized to tamoxifen treatment had ER positive, PR positive, or both ER and PR positive breast cancer, respectively. For subjects who had both ER- and PR-negative breast cancer, 1 subject was from Trial 0030 (Subject 0022/0001 who was randomized to anastrozole) and 2 subjects were from Trial 0027 (Subject 0112/0002 who was randomized to anastrozole and Subject 0047/0103 who was randomized to tamoxifen), and were considered to be in violation of the protocol.

Table 4 Previous adjuvant therapy for breast cancer for subjects in Trials 0030 and 0027, separately and combined

Status	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Unknown	1 (0.6)	1 (0.5)	1 (0.3)	0	2 (0.4)	1 (0.2)
Number (%) subjects not receiving prior adjuvant therapy	102 (59.6)	111 (61.0)	234 (68.8)	231 (70.4)	336 (65.8)	342 (67.1)
Number (%) subjects receiving prior adjuvant therapy	68 (39.8)	70 (38.5)	105 (30.9)	97 (29.6)	173 (33.9)	167 (32.7)
Type of adjuvant therapy[a]						
Hormonal	21 (12.3)	20 (11.0)	31 (9.1)	20 (6.1)	52 (10.2)	40 (7.8)
Cytotoxic	32 (18.7)	37 (20.3)	64 (18.8)	62 (18.9)	96 (18.8)	99 (19.4)
Combination hormonal and cytotoxic	15 (8.8)	13 (7.1)	10 (2.9)	15 (4.6)	25 (4.9)	28 (5.5)

[a] Type of adjuvant therapy not available for 1 subject given tamoxifen in Trial 0030.

The percentage of subjects who were given previous adjuvant therapy was similar between the treatment groups. The majority of subjects in both treatment groups did not receive previous adjuvant therapy (65.8% anastrozole and 67.1% tamoxifen subjects). Details of previous adjuvant therapy were unknown for 2 subjects from Trial 0030 (Subject 0094/0004, randomized to anastrozole treatment; and Subject 0115/0001, randomized to tamoxifen treatment) and 1 subject from Trial 0027 (Subject 0099/0116, randomized to anastrozole treatment).

Previous hormonal therapy (either hormonal treatment only or both hormonal and cytotoxic treatment) had been given to 77 (15.1%) subjects who were randomized to anastrozole treatment and 68 (13.3%) subjects who were randomized to tamoxifen treatment. The treatment groups were balanced for the percentage of subjects who were given previous hormonal therapy.

The median duration of previous adjuvant hormonal treatment was 146 weeks for subjects who were randomized to anastrozole treatment and 117 weeks for subjects who were randomized to tamoxifen treatment.

Table 5 summarizes breast cancer disease status at first diagnosis for all randomized subjects in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 5 Breast cancer disease status at first diagnosis for subjects in Trials 0030 and 027, separately and combined

Disease at first diagnosis	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Advanced[a]	52 (30.4)	60 (33.0)	163 (47.9)	169 (51.5)	215 (42.1)	229 (44.9)
Early[b]	118 (69.0)	122 (67.0)	176 (51.8)	158 (48.2)	294 (57.5)	280 (54.9)
Unknown	1 (0.6)	0	1 (0.3)	1 (0.3)	2 (0.4)	1 (0.2)
Total	171 (100.0)	182 (100.0)	340 (100.0)	328 (100.0)	511 (100.0)	510 (100.0)

[a] Subjects with advanced disease at first diagnosis entered trial soon after diagnosis.
[b] Subjects with early disease at first diagnosis entered Trials 0030 and 0027 at disease recurrence.

The percentage of subjects who had advanced breast cancer disease at first diagnosis was similar between the 2 treatment groups. The percentage of subjects who did not have advanced disease at first diagnosis was 57.5% for subjects randomized to anastrozole treatment and 54.9% for subjects randomized to tamoxifen treatment. In Trial 0030, Subject 0096/0004 was withdrawn from the trial on Day 2 because of a protocol violation, had incomplete demographic data, had no baseline disease assessment data and did not start trial treatment. In Trial 0027, 1 subject (Subject 0090/0116) only attended the first visit, had incomplete demographic data, had no baseline disease assessment data, and did not start trial treatment; and for 1 subject (Subject 0048/0101) the investigator stated the disease status was unknown, but the subject had not received adjuvant therapy.

3.1.3 Site and extent of disease at entry

Summary tables:

Subjects with measurable and no measurable disease; Tables T1.7 (Trial 0027), T12.7 (Trial 0030), and T23.7 (Combined)
Site of metastatic disease at entry; Tables T1.8.1 (Trial 0027), T12.8.1 (Trial 0030), and T23.8.1 (Combined)
Extent of metastatic disease at entry; Tables T1.8.2 (Trial 0027), T12.8.2 (Trial 0030), and T23.8.2 (Combined)

Table 6 summarizes disease at entry for all randomized subjects in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 6 Disease measurability at entry for subjects in Trials 0030 and 0027, separately and combined

Category	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Measurable disease[a]	117 (68.4)	140 (76.9)	301 (88.5)	286 (87.2)	418 (81.8)	426 (83.5)
No measurable disease[b]	54 (31.6)	42 (23.1)	39 (11.5)	42 (12.8)	93 (18.2)	84 (16.5)

[a] Measurable disease group included subjects with bidimensionally or unidimensionally measurable lesions as determined by examination, X-ray or CAT scan.
[b] No measurable disease group included subjects with either no lesions or with non-measurable disease only (single metastatic lesions smaller than 0.5 cm, malignant pleural effusions or ascites, positive bone scans, osteoblastic or intratrabecular bone lesions).

The percentage of subjects who had measurable and no measurable disease was similar in the 2 treatment groups. Overall, most subjects who entered the trial (81.8% anastrozole and 83.5% tamoxifen subjects) had measurable disease.

3.1.3.1 Sites of metastatic disease at entry

Table 7 summarizes the sites of metastatic disease for all subjects at entry, by treatment. Subjects with multiple disease sites are included in more than 1 category.

Table 7 Sites of metastatic disease at entry for subjects in Trials 0030 and 0027, separately and combined

Disease sites[a]	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Skin[b]	52 (30.4)	50 (27.5)	183 (53.8)	183 (55.8)	235 (46.0)	233 (45.7)
Lymph nodes	63 (36.8)	64 (35.2)	145 (42.6)	148 (45.1)	208 (40.7)	212 (41.6)
Bone	112 (65.5)	98 (53.8)	156 (45.9)	158 (48.2)	268 (52.4)	256 (50.2)
Viscera	83 (48.5)	87 (47.8)	103 (30.3)	124 (37.8)	186 (36.4)	211 (41.4)
Lung	76 (44.4)	68 (37.4)	74 (21.8)	100 (30.5)	150 (29.4)	168 (32.9)
Liver	13 (7.6)	30 (16.5)	32 (9.4)	31 (9.5)	45 (8.8)	61 (12.0)
Abdomen	7 (4.1)	8 (4.4)	10 (2.9)	5 (1.5)	17 (3.3)	13 (2.5)
Other[c]	0	1 (0.5)	1 (0.3)	2 (0.6)	1 (0.2)	3 (0.6)
No evaluable disease - protocol violators	2 (1.2)	2 (1.1)	2 (0.6)	0	4 (0.8)	2 (0.4)

[a] Subjects may have disease in more than 1 site.
[b] Subjects may have had locally advanced or metastatic disease.

The sites of metastatic disease at entry were similar between the 2 treatment groups. Bone was the most frequent site of metastatic disease at entry in both treatment groups (52.4% anastrozole and 50.2% tamoxifen subjects). In Trial 0030, 2 subjects who were randomized to anastrozole treatment (Subjects 0080/0001 and 0096/0004) and 2 subjects who were randomized to tamoxifen treatment (Subjects 0015/0007 and 0028/0003) had no evaluable disease. In Trial 0027, 2 subjects who were randomized to anastrozole treatment (Subjects 0099/0116 and 0103/0101) had no evaluable disease.

3.1.3.2 Extent of metastatic disease at entry

Table 8 summarizes the extent of metastatic disease for all subjects at entry, by treatment.

Table 8 Extent of metastatic disease at entry for subjects in Trials 0030 and 0027, separately and combined

Disease sites[a]	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Soft tissue and/or lung disease only	39 (22.8)	49 (26.9)	155 (45.6)	132 (40.2)	194 (38.0)	181 (35.5)
All other disease combinations	132 (77.2)	133 (73.1)	185 (54.4)	196 (59.8)	317 (62.0)	329 (64.5)
No visceral disease						
Soft tissue only	18 (10.5)	33 (18.1)	128 (37.6)	106 (32.3)	146 (28.6)	139 (27.3)
Bone[a]	68 (39.8)	60 (33.0)	107 (31.5)	98 (29.9)	175 (34.3)	158 (31.0)
Visceral disease						
Liver involvement	13 (7.6)	30 (16.5)	32 (9.4)	31 (9.5)	45 (8.8)	61 (12.0)
No evidence of liver involvement	70 (40.9)	57 (31.3)	71 (20.9)	93 (28.4)	141 (27.6)	150 (29.4)
Total	169 (98.8)	180 (98.9)	338 (99.4)	328 (100.0)	507 (99.2)	508 (99.6)

[a] Includes subjects who may also have soft tissue disease.

The majority of subjects in both treatment groups had metastatic disease at entry. The extent of metastatic disease at entry was similar between the treatment groups; 194 (38.0%) subjects who were randomized to anastrozole treatment and 181 (35.5%) subjects who were randomized to tamoxifen treatment had soft tissue and/or lung disease only. Some subjects who had disease confined to soft tissue may have had only locally advanced disease. These subjects were considered to have met the requirement for measurable, evaluable disease and were therefore eligible for trial entry, provided that no surgical treatment or radiation therapy to the local disease site was planned.

Staging of these subjects was retrospectively performed by Zeneca physicians using the American Joint Committee Staging System (3rd ed) as indicated in Appendix A. In Trial 0030, a total of 340 (96.3%) subjects were stage IV and 6 (1.7%) subjects were stage III. In Trial 0027, a total of 475 (71.1%) subjects were stage IV and 163 (24.4%) were stage III. Similar numbers of subjects in each stage were randomized to anastrozole and tamoxifen. Seven subjects (2.0%) in Trial 0030 and 30 (4.5%) subjects in Trial 0027 could not be assigned to stage IV or stage III; data on mobility of lymph nodes and tumor edema and ulceration, which might have resulted in these subjects being stage III, was not collected.

3.2 Overview of demography

The distribution of age, height, weight, and ethnic origins for the 2 treatment groups were similar for both trials. There were differences between Trials 0030 and 0027 in hormone receptor status, previous hormone therapy, disease status at first diagnosis, and site of disease at entry. More subjects in Trial 0030 were estrogen and/or progesterone receptor positive than in Trial 0027; in Trial 0030, approximately 11% of the subjects were hormone receptor status unknown as compared with more than half of subjects in Trial 0027. Trial 0030 also had proportionally more subjects who received hormonal and combined adjuvant therapy, fewer subjects who first presented with advanced disease, fewer subjects with skin/lymph node disease, and more subjects with bone and visceral disease than Trial 0027.

4 CONTROLLED TRIALS: EFFICACY RESULTS

4.1 Status of randomized subjects

Summary tables:

Randomization and subject status; Tables T1.1 (Trial 0027), T12.1 (Trial 0030), and T23.1 (Combined)
Reason for withdrawal of trial treatment; Tables T2 (Trial 0027), T13 (Trial 0030), and T24 (Combined)
Duration of treatment; Tables T4.1.1 and T4.1.2 (Trial 0027), T15.1.1 and T15.1.2 (Trial 0030), and T26.1.1 and T26.1.2 (Combined)
Duration of follow-up; Tables T4.1.3 (Trial 0027), T15.1.3 (Trial 0030), and T26.1.3 (Combined)

A total of 1021 subjects from 97 centers in the US and Canada (Trial 0030) and 83 centers in Europe, South America, Australia, and South Africa (Trial 0027) were included in the subject population for the primary analysis. Of these subjects, 511 were randomized to receive 1 mg of anastrozole and tamoxifen placebo only daily, and 510 were randomized to receive 20 mg of tamoxifen and anastrozole placebo once daily. Of the 1021 randomized subjects, 1009 subjects were actually given correct randomized treatment. Of the remaining 12 subjects, 8 subjects were misallocated (3 subjects who were randomized to tamoxifen treatment were instead given anastrozole; 5 subjects who were randomized to anastrozole treatment were instead given tamoxifen). Of the 4 remaining subjects, 2 never started trial treatment, and 2 subjects received chemotherapy instead.

The status of randomized subjects as of 10 March 1999, the data cutoff date, is summarized in Table 9.

Table 9 Status of randomized subjects for subjects in Trials 0030 and 0027, separately and combined

Status	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Randomized	171	182	340	328	511	510
Treatment not started	1 (0.6)	0	2 (0.6)	1 (0.3)	3 (0.6)	1 (0.2)
Treatment started	170 (99.4)	182 (100.0)	336 (98.8)	329 (100.3)	506 (99.0)	511 (100.2)
Continuing treatment	48 (28.1)	40 (22.0)	101 (29.7)	88 (26.8)	149 (29.2)	128 (25.1)
Treatment withdrawn						
Subjects who survived	74 (43.3)	90 (49.5)	144 (42.4)	167 (50.9)	218 (42.7)	257 (50.4)
Subjects who died	48 (28.0)	52 (28.6)	91 (26.8)	74 (22.6)	139 (27.2)	126 (24.7)
Treatment misallocation	1 (0.6)	1 (0.5)	4 (1.2)	2 (0.6)	5 (1.0)	3 (0.6)

Of the 1021 randomized subjects, 1017 subjects started trial treatment. At the time of data cutoff, 277 (27.1%) subjects continued on trial treatment, 475 (46.5%) subjects were alive but had been withdrawn from trial treatment, and 265 (26.0%) subjects had died. Subject withdrawals from trial treatment are discussed in the ISS.

Table 10 summarizes the duration of treatment for all treated subjects in Trials 0030 and 0027, separately and combined, by trial treatment received.

Table 10 Duration of treatment for subjects in Trials 0030 and 0027, separately and combined by treatment received (as of data cutoff)

Duration of treatment (weeks)	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=170)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=336)	Tamoxifen 20 mg (n=329)	Anastrozole 1 mg (n=506)	Tamoxifen 20 mg (n=511)
0-12	25 (14.7)	35 (19.2)	52 (15.5)	49 (14.9)	77 (15.2)	84 (16.4)
12-24	28 (16.5)	48 (26.4)	67 (19.9)	69 (21.0)	95 (18.8)	117 (22.9)
24-48	41 (24.1)	45 (24.7)	73 (21.7)	82 (24.9)	114 (22.5)	127 (24.9)
48-96	61 (35.9)	43 (23.6)	107 (31.8)	82 (24.9)	168 (33.2)	125 (24.5)
>96	15 (8.8)	11 (6.0)	37 (11.0)	47 (14.3)	52 (10.3)	58 (11.4)
Minimum (days)	18	12	2	3	2	3
Maximum (days)	932	933	1195	1260	1195	1260
Median (days)	263	182	263	253	263	244

Of these 1017 treated subjects, 506 subjects were given anastrozole and 511 subjects were given tamoxifen. The median duration of treatment was similar between subjects who were given anastrozole (263 days) and subjects who were given tamoxifen (244 days).

Table 11 summarizes the duration of follow-up for all randomized subjects, for subjects alive at the time of data cutoff, in Trials 0030 and 0027, separately and combined, by randomized treatment.

Table 11 Duration of follow-up for subjects in Trials 0030 and 0027, separately and combined by randomized treatment (for subjects alive at data cutoff)

Measurement	Duration (days)					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=124)	Tamoxifen 20 mg (n=129)	Anastrozole 1 mg (n=249)	Tamoxifen 20 mg (n=254)	Anastrozole 1 mg (n=373)	Tamoxifen 20 mg (n=383)
Minimum	1	35	0	106	0	35
Maximum	931	1097	1194	1260	1194	1260
Median	533	538	556	598	547	567

Median duration of follow-up was similar between treatment groups. For the subjects who were known to be alive at the time of data cutoff (10 March 1999), the estimated median duration of follow-up was 547 days for subjects randomized to anastrozole and 567 days for subjects randomized to tamoxifen. Two subjects from Trial 0027 (Subjects 0098/0016 and 0099/0116) who were randomized to anastrozole treatment had no follow up contact post-randomization and hence these 2 subjects had a follow-up time of 0 days. The duration of follow-up in both trials is adequate for efficacy assessment.

4.2 Objective efficacy results

Efficacy analyses of the per protocol population (PP) were performed in the individual trials for time to progression, time to death (survival), and overall response rate. Consistent results were observed between the ITT and PP analyses; therefore, analyses for the ISE were performed for the ITT population only.

4.2.1 Time to disease progression

Summary tables: *Progression status; Tables T4.2.1 and T4.2.3 (Trial 0027), T15.2.1 and T15.2.3 (Trial 0030), and T26.2.1 and T26.2.3 (Combined)*
Time to progression analysis; Table T4.2.5 (Trial 0027), T15.2.5 (Trial 0030), and T26.2.5 (Combined)

Table 12 summarizes the progression status of all randomized subjects by treatment as of 10 March 1999, the data cutoff date.

Table 12 Progression status of randomized subjects for subjects in Trials 0030 and 0027, separately and combined

Progression status	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Randomized subjects	171	182	340	328	511	510
Alive without progression[a]	57 (33.3)	44 (24.2)	91 (26.8)	81 (24.7)	148 (29.0)	125 (24.5)
Progression during treatment	100 (58.5)	121 (66.5)	216 (63.5)	209 (63.7)	316 (61.8)	330 (64.7)
Progression after treatment withdrawal	2 (1.2)	3 (1.6)	15 (4.4)	18 (5.5)	17 (3.3)	21 (4.1)
Death before progression	12 (7.0)	14 (7.7)	18 (5.3)	20 (6.1)	30 (5.9)	34 (6.7)
Median time to progression (days)	338	170	251	252	259	212

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

A total of 748 (73.3%) subjects had disease progression. The subjects who were randomized to anastrozole treatment appeared to have a lower progression rate and longer estimated median time to progression (71.0% and 259 days, respectively) than did subjects who were randomized to tamoxifen treatment (75.5% and 212 days, respectively).

The trial-by-treatment interaction was tested using the Cox regression model with factors for trial, treatment, 4 baseline prognostic covariates, and the trial-by-treatment interaction. The statistical evidence of significant trial-by-treatment interaction was observed at p=0.0169. As

stated in the statistical analysis plan, a likelihood ratio test developed by Gail and Simon (1985) was then used to further examine the nature of the interaction (quantitative or qualitative). The Gail and Simon analysis indicated the statistical evidence of quantitative trial-by-treatment interaction (p=0.0183) but no qualitative interaction with the min less than the critical value of 2.71 . The details of this analysis are described in Appendix B.

The same 4 prespecified baseline covariates which were included in the models for both Trials 0030 and 0027, were fitted into the adjusted model for the combined analysis, and the models were converged. The details for testing the assumptions of the Cox regression model, dealing with missing covariates, and checking the interactions of treatment by baseline covariates are described in Appendix B.

The statistical analysis of time to disease progression is summarized in Table 13 for Trials 0030 and 0027, separately and combined.

Table 13 Statistical analysis of time to disease progression in Trials 0030 and 0027, separately and combined

Comparison	Statistical analysis	
	Hazard ratio[a]	Lower 95% CL
Tamoxifen:anastrozole		
Trial 0030		
Adjusted analysis[b]	1.44	1.16
Unadjusted analysis[c]	1.42	1.15
Trial 0027		
Adjusted analysis[b]	0.99	0.86
Unadjusted analysis[c]	1.01	0.87
Combined trials		
Primary analysis (adjusted)[d]	1.13	1.00
Support analysis (adjusted)[e]	1.12	1.00
Support analysis (unadjusted)[c]	1.13	1.00

[a] Hazard ratio >1.00 indicates that anastrozole is associated with longer time to progression than is tamoxifen.
[b] The primary analysis (adjusted) was performed for individual trials using a Cox regression model including factors of treatment, extent of disease at entry, previous hormonal therapy, estrogen/progesterone receptor status, and age.
[c] The support analysis (unadjusted) was performed using a Cox regression model including treatment factor only.
[d] The adjusted analysis was repeated for combined trials using trial as a stratification factor - primary analysis.
[e] The adjusted analysis was repeated for combined trials by adding trial as an additional covariate - support analysis.
CL Confidence limit.

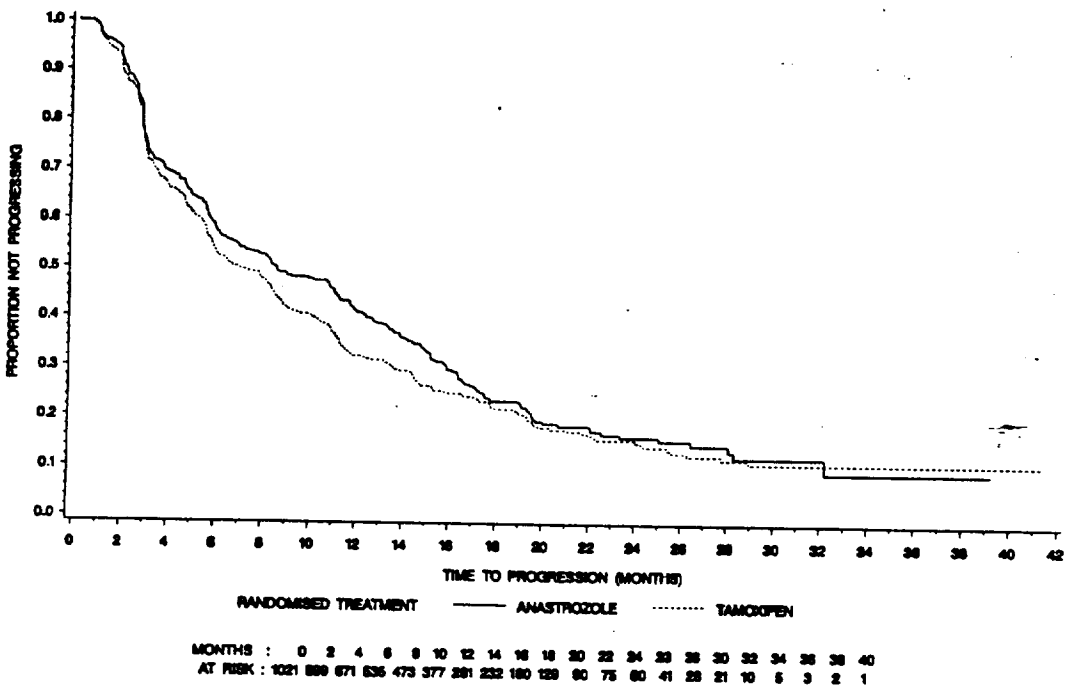
In Trial 0030, the median time to progression was 338 days for subjects randomized to anastrozole treatment compared to 170 days for subjects randomized to tamoxifen treatement. In the primary analysis, the hazard ratio was 1.44, and the unadjusted analysis was supportive. Both analyses met the prespecified criteria for non–inferiority (lower 95% confidence limits greater than 0.8) and showed numerical superiority for anastrozole (lower 95% confidence limits greater than 1.00). Therefore, Trial 0030 showed anastrozole to be at least as effective as tamoxifen in time to progression. In Trial 0027, the median time to progression was 252 days for subjects randomized to anastrozole treatment compared to 251 days for subject randomized to tamoxifen treatment. All analyses met prespecified criteria for non-inferiority.

From the primary combined analysis, the hazard ratio of 1.13 favors anastrozole. The lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen:anastrozole) was 1.00, which was greater than the statistical criterion of 0.8 to declare noninferiority. Consistent results were observed from the 2 support analyses; the hazard ratios were 1.12 and 1.13 from the support adjusted analysis and the support unadjusted analysis, respectively. The lower 95% confidence limit for the hazard ratio was 1.00 from the 2 supporting analyses.

The consistent results show that anastrozole is at least as efficacious as tamoxifen in terms of time to progression. Even though the trials were not designed to demonstrate superiority, in Trial 0030, there is a numerical superiority for anastrozole.

The Kaplan-Meier plot of time to progression is presented in Figure 1.

Figure 1 Kaplan-Meier probability of time to progression, combined trials



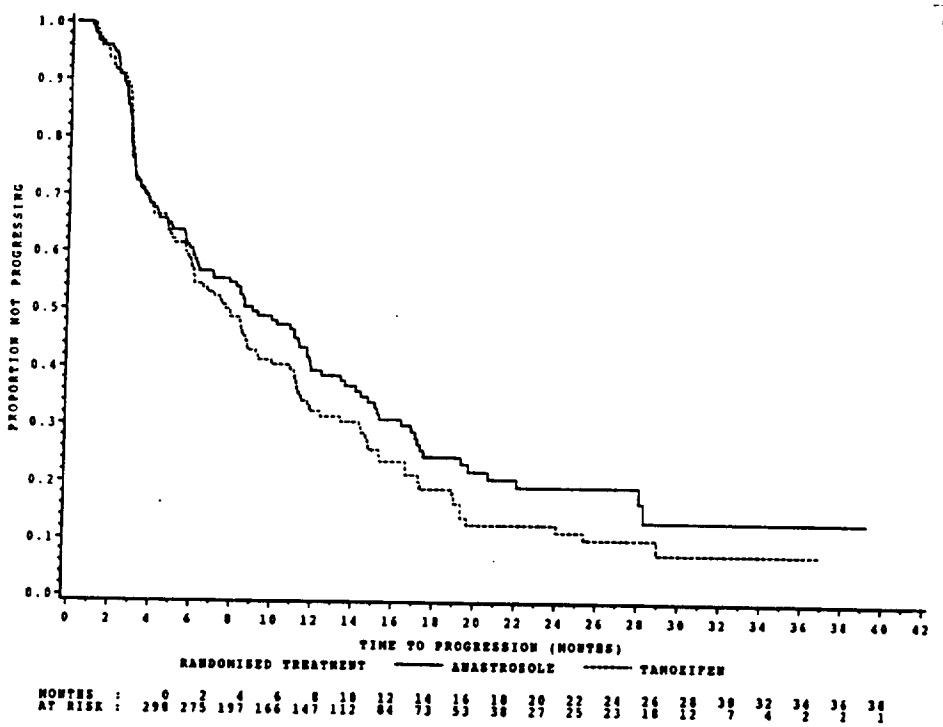
As described in Appendix B, the trial-by-covariate interactions were tested and no statistically significant interaction was found. However, because of the suggestion of a differing result between Trial 0030 and Trial 0027 in time to progression (259 days in Trial 0030 versus 212 days in Trial 0027), retrospective data reviews of certain demographic subgroups were performed.

Disease state at first diagnosis, prior hormonal therapy and site of disease did not affect the relative efficacy of anastrozole versus tamoxifen. Subjects from Trial 0027 who were known to be estrogen/progesterone receptor positive form a subgroup (n=298 [44.6%]), which demographically resembles the overall population in Trial 0030 (in which subjects were known to hormone receptor positive). When this subgroup of subjects from Trial 0027 was reviewed separately, those randomized to anastrozole achieved numerically longer median times to progression (271 days) than those randomized to tamoxifen (237 days) (see Figure 2). Thus the results of this subgroup review are consistent with the results of Trial 0030 in suggesting numerical superiority for anastrozole over tamoxifen.

In the subgroup of subjects in Trial 0027 who were not known to be estrogen/progesterone receptor positive (n=370 [55.4%]), median time to progression was slightly shorter for anastrozole (223 days) compared to tamoxifen (253 days). Because few subjects in Trial 0030 were not known to be receptor positive (n=40 [11.3%]), the presence of such subjects would be expected to have little effect on the Trial 0030 results.

Although these data reviews are retrospective, they may explain the apparent differences in the performance of anastrozole relative to that of tamoxifen in Trials 0027 and 0030.

Figure 2 Kaplan-Meier probability of time to progression for the subgroup of subjects in Trial 0027 who were estrogen and/or progesterone receptor positive



4.2.2 Objective response

Summary tables:

Best object response; Tables T4.3.1 and 4.3.3 (Trial 0027), T15.3.1 and T15.3.3 (Trial 0030), and T26.3.1 and T26.3.3 (Combined)
Objective response: extent of disease covariate; Tables T4.3.4 (Trial 0027), T15.3.4 (Trial 0030), and T26.3.4 (Combined)
Clinical benefit - Tables T4.3.5 (Trial 0027), T15.3.5 (Trial 0030), and T26.3.5 (Combined)
Objective response analysis; Tables T4.3.6 (Trial 0027), T15.3.6 (Trial 0030), and T26.3.6 (Combined)

4.2.2.1 Objective response for all subjects

Best objective response was determined using a computer algorithm that strictly applied the protocol definition of response which was based on UICC criteria. The categories of objective response are defined in Section 2.6.2 of this ISE. Table 14 summarizes the tumor responses for all randomized subjects in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 14 Objective response for all subjects in Trials 0030 and 0027, separately and combined

Objective response	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Responders	36 (21.1)	31 (17.0)	112 (32.9)	107 (32.6)	148 (29.0)	138 (27.1)
Complete response (CR)	5 (2.9)	5 (2.7)	19 (5.6)	16 (4.9)	24 (4.7)	21 (4.1)
Partial response (PR)	31 (18.1)	26 (14.3)	93 (27.4)	91 (27.7)	124 (24.3)	117 (22.9)
Non-responders	135 (78.9)	151 (83.0)	228 (67.1)	221 (67.4)	363 (71.0)	372 (72.9)
Stable disease (SD)	72 (42.1)	56 (30.8)	88 (25.9)	83 (25.3)	160 (31.3)	139 (27.3)
≥24 weeks	65 (38.0)	52 (28.6)	79 (23.2)	75 (22.9)	144 (28.2)	127 (24.9)
<24 weeks	7 (4.1)	4 (2.2)	9 (2.6)	8 (2.4)	16 (3.1)	12 (2.4)
Progression (PROG)	63 (36.8)	95 (52.2)	140 (41.2)	138 (42.1)	203 (39.7)	233 (45.7)

The objective response rate was defined as the percentage of subjects showing best objective response of complete response (CR) or partial response (PR). The best objective response rate of CR or PR was similar for subjects randomized to anastrozole treatment (29.0%) and for subjects randomized to tamoxifen treatment (27.1%). The percentage of subjects with a best response rate of stable disease greater than or equal 24 to weeks was greater for subjects randomized to anastrozole treatment (28.2%) compared with subjects randomized to tamoxifen treatment (24.9%).

The trial-by-treatment interaction was tested using the logistic regression model with factors for treatment, 4 baseline prognostic covariates, and the trial-by-treatment interaction. There was no statistical evidence of trial-by-treatment interaction (p=0.25).

Table 15 summarizes the statistical analysis of objective response rate in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 15 Statistical analysis of objective response rate in Trials 0030 and 0027, separately and combined

Comparison	Statistical analysis			
	Odds ratio[a]	Lower 95% CL	Difference in response rate[b]	Lower 95% CL
Anastrozole:tamoxifen				
Trial 0030				
Adjusted analysis[c]	1.38	0.87	5.01	−1.90
Unadjusted analysis[d]	1.30	0.83	4.02	−2.47
Trial 0027				
Adjusted analysis[c]	0.95	0.72	−1.01	−6.74
Unadjusted analysis[d]	1.01	0.77	0.32	−5.37
Combined trials				
Primary analysis (adjusted)[e]	1.06	0.83	1.08	−3.49
Support analysis (unadjusted)[d]	1.10	0.87	1.90	−2.58

[a] Odds ratio >1.00 indicates that anastrozole is associated with higher response rate than is tamoxifen.
[b] Difference in response rate (anastrozole - tamoxifen) was calculated from odds ratio using the formula stated in Section 2.7.4.1. A difference >0 indicates that anastrozole is associated with a higher response rate than is tamoxifen.
[c] The primary analysis (adjusted) was performed for individual trials using a logistic regression model including factors of treatment, site of disease at entry, previous hormonal therapy, estrogen/progesterone receptor status, and age.
[d] The support analysis (unadjusted) was performed using a logistic regression model including treatment factor only.
[e] The adjusted analysis was repeated for combined trials by adding trial as an additional covariate.
CL Confidence limit.

For Trial 0030, the difference in response rate was 5.01 for the adjusted analysis (with lower 95% confidence limit –1.90%) and 4.02 for the unadjusted analysis (with lower 95% confidence limit –2.47%). For Trial 0027, the difference in response rate was –1.01 for the adjusted analysis (with lower 95% confidence limit –6.74%) and 0.32 for the unadjusted analysis (with lower 95% confidence limits –5.37%). The prespecified criteria for noninferiority of anastrozole was a lower 95% confidence limit greater than –10%. For the combined trials, the difference in response rate was 1.08 for the adjusted analysis (lower 95% confidence limit –3.49%) and 1.90 for the unadjusted analysis (lower 95% confidence limit –2.58%).

All analyses yielded results that met the criterion for noninferiority of anastrozole. Anastrozole was therefore shown to be at least as efficacious as tamoxifen in objective response.

4.2.2.2 Objective response for subjects with measurable disease

The above intention-to-treat (ITT) analysis included all subjects regardless of whether they had measurable disease, nonmeasurable disease, or both. Although a complete response is unlikely for nonmeasurable disease, and nonmeasurable lesions could not be assigned a partial response; the prespecified criteria for objective response rate stated that all subjects with nonmeasurable disease would be included as part of the denominator. Subjects with measurable lesions were also analyzed separately.

A total of 418 (81.8%) subjects randomized to anastrozole treatment and 426 (83.5%) subjects randomized to tamoxifen treatment had measurable disease from which an objective response could be assigned on the basis of objective bidimensional measurements. Table 16 summarizes the objective tumor response for all randomized subjects with measurable disease in Trials 0030 and 0027, separately and combined.

Table 16 Objective response for subjects with measurable disease in Trials 0030 and 0027, separately and combined

Objective response	Number (%) of subjects [a]					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=117)	Tamoxifen 20 mg (n=140)	Anastrozole 1 mg (n=301)	Tamoxifen 20 mg (n=286)	Anastrozole 1 mg (n=418)	Tamoxifen 20 mg (n=426)
Responders	38 (32.5)	31 (22.1)	115 (38.2)	111 (38.8)	153 (36.6)	142 (33.3)
Complete Response (CR)	11 (9.4)	12 (8.6)	34 (11.3)	31 (10.8)	45 (10.8)	43 (10.1)
Partial Response (PR)	27 (23.1)	19 (13.6)	81 (26.9)	80 (28.0)	108 (25.8)	99 (23.2)
Non-responders	79 (67.5)	109 (77.9)	186 (61.8)	175 (61.2)	265 (63.4)	284 (66.7)
Stable disease (SD)	37 (31.6)	31 (22.1)	70 (23.3)	59 (20.6)	107 (25.6)	90 (21.1)
≥24 weeks	30 (25.6)	26 (18.6)	58 (19.3)	48 (16.8)	88 (21.1)	74 (17.4)
<24 weeks	7 (6.0)	5 (3.6)	12 (4.0)	11 (3.8)	19 (4.5)	16 (3.8)
Progression (PROG)	42 (35.9)	78 (55.7)	116 (38.5)	116 (40.6)	158 (37.8)	194 (45.5)

[a] Only includes subjects with measurable disease at entry.

Of the subjects with measurable disease, CR or PR was 36.6% for subjects randomized to anastrozole treatment and 33.3% for subjects randomized to tamoxifen treatment. The overall response rate was higher for this subgroup of subjects compared to that for all subjects. The reasons were: (a) partial response cannot be assigned to nonmeasurable disease, and (b) for a subject with CR or PR on measurable disease, combination with nonmeasurable disease may result in no longer meeting criteria for objective response. In addition, measurable disease may be more likely to be soft tissue disease and less likely to be bone, and thus may actually carry a better prognosis.

4.2.2.3 Objective response by extent of disease

Table 17 summarizes the objective tumor response by extent of disease for all randomized subjects in Trials 0030 and 0027, separately and combined.

Table 17 Objective response by extent of disease for all randomized subjects in Trials 0030 and 0027, separately and combined

Extent of disease	Trial Randomized treatment					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Soft tissue and/or lung disease only						
Number of subjects with extent of disease	39	49	155	132	194	181
Number (%) of subjects with objective response (CR or PR)	13 (33.3)	16 (32.7)	73 (47.1)	55 (41.7)	86 (44.3)	71 (39.2)
All other disease combinations						
Number of subjects with extent of disease	132	133	185	196	317	329
Number (%) of subjects with objective response[a]	23 (17.4)	15 (11.3)	39 (21.1)	52 (26.5)	62 (19.6)	67 (20.4)

[a] Numbers given refer to number of subjects with objective response (complete or partial) per number of subjects with extent of disease.

Of the 375 subjects who had soft tissue and/or lung disease only, the percentage of subjects with CR or PR was 44.3% for subjects randomized to anastrozole treatment compared to 39.2% for subjects randomized to tamoxifen treatment. Of the 646 subjects who had all other disease combinations, the best objective response rate was similar between the treatment groups (19.6% of subjects who were randomized to anastrozole treatment and 20.4% of subjects who were randomized to tamoxifen treatment). The literature suggests that subjects with soft tissue disease are more likely to respond to hormonal therapy than subjects with other disease combinations (Muss 1992).

4.2.3 Time to treatment failure

Summary tables:

Reason for treatment failure; Tables T4.4.1 (Trial 0027), T15.4.2 (Trial 0030), and T26.4.1 (Combined)
Median time to treatment failure; Tables T4.4.2 (Trial 0027), T15.4.2 (Trial 0030), and T26.4.2 (Combined)
Time to treatment failure analysis; Tables T4.4.3 (Trial 0027), T15.4.3 (Trial 0030), and T26.4.3 (Combined)

Table 18 summarizes the reasons for treatment failure for all randomized subjects in Trials 0030 and 0027 combined by trial treatment up to the date of the last objective response assessment before the data cutoff date. For the majority of subjects who reached treatment failure in each treatment group across trials, the reason for treatment failure was disease progression.

Table 18 Reasons for treatment failure for subjects in Trials 0030 and 0027, separately and combined

Reason	Number (%) of subjects[a]					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Death without evidence of progression	3 (1.8)	3 (1.6)	5 (1.5)	3 (0.9)	8 (1.6)	6 (1.2)
Disease progression (objective)	100 (58.5)	121 (66.5)	216 (63.5)	208 (63.4)	316 (61.8)	329 (64.5)
Treatment stopped because of disease progression (investigator's opinion)	13 (7.6)	13 (7.1)	15 (4.4)	16 (4.9)	28 (5.5)	29 (5.7)
Subject lost to follow-up	0	0	2 (0.6)	1 (0.3)	2 (0.4)	1 (0.2)
Adverse event	8 (4.7)	6 (3.3)	13 (3.8)	15 (4.6)	21 (4.1)	21 (4.1)
Protocol noncompliance	2 (1.2)	2 (1.1)	3 (0.9)	6 (1.8)	5 (1.0)	8 (1.6)
Unwilling to continue	2 (1.2)	4 (2.2)	5 (1.5)	10 (3.0)	7 (1.4)	14 (2.7)
Never started randomized treatment	1 (0.6)	0	2 (0.6)	1 (0.3)	3 (0.6)	1 (0.2)
Other reason	6 (3.5)	3 (1.6)	6 (1.8)	6 (1.8)	12 (2.3)	9 (1.8)
Total number of subjects with treatment failure	135 (78.9)	152 (83.5)	267 (78.5)	266 (81.1)	402 (78.7)	418 (82.0)

Of the subjects randomized in this trial, 702 (68.8%) subjects had treatment failure resulting from disease progression (645 [63.2%] subjects from the objective algorithm and 57 [5.6%] subjects from the investigator's opinion). One hundred four (10.2%) subjects were withdrawn from trial treatment for reasons other than disease progression, and 14 (1.4%) subjects died before progression.

A total of 820 (80.3%) subjects had treatment failure. A smaller percentage of subjects who were randomized to anastrozole treatment (78.7%) had treatment failure when compared with subjects who were randomized to tamoxifen treatment (82.0%). Subjects who were randomized to anastrozole treatment also had a longer estimated median time to treatment failure (208 days) when compared with subjects who were randomized to tamoxifen treatment (176 days). (See Table A in the Summary section of this ISE.)

Formal treatment comparisons were analyzed using a Cox regression model in the same way that was done for time to progression.

The trial-by-treatment interaction was tested using the Cox regression model with factors for treatment, 4 baseline prognostic covariates, and the trial-by-treatment interaction. There was no statistical evidence of trial-by-treatment interaction (p=0.07).

Table 19 summarizes the statistical analysis of time to treatment failure in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 19 Statistical analysis of time to treatment failure in Trials 0030 and 0027, separately and combined

Comparison	Statistical analysis	
	Hazard ratio[a]	Lower 95% CL
Tamoxifen:anastrozole		
Trial 0030		
Adjusted analysis[b]	1.35	1.11
Unadjusted analysis[c]	1.33	1.10
Trial 0027		
Adjusted analysis[b]	1.03	0.89
Unadjusted analysis[c]	1.04	0.90
Combined trials		
Primary analysis (adjusted)[d]	1.13	1.01
Support analysis (adjusted)[e]	1.13	1.01
Support analysis (unadjusted)[c]	1.13	1.01

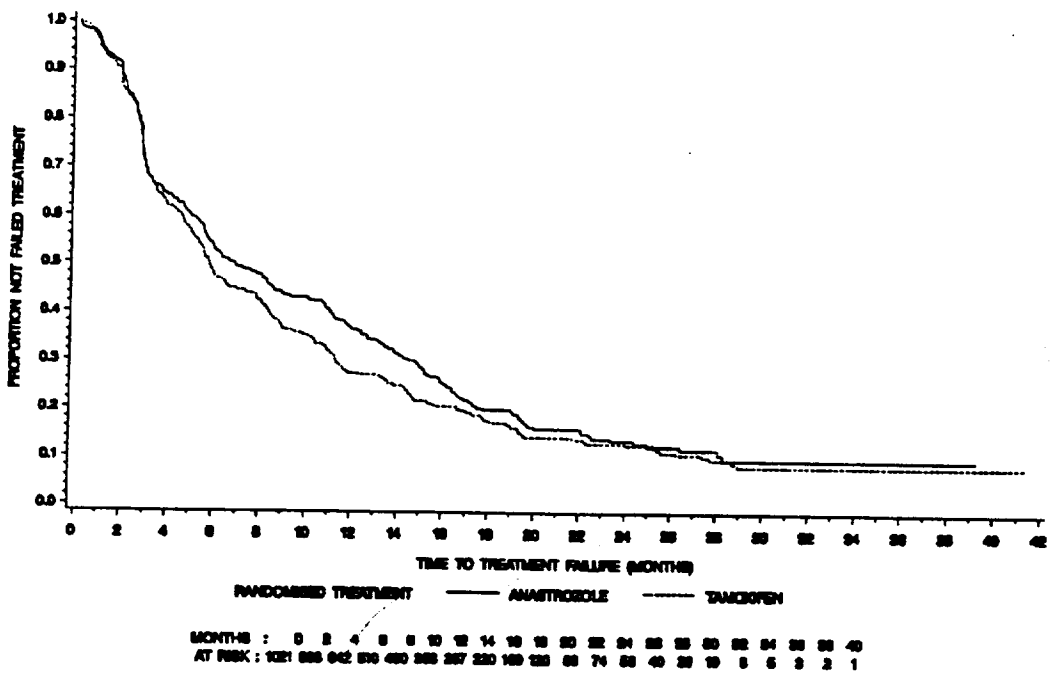
[a] Hazard ratio >1.00 indicates that anastrozole is associated with longer time to progression than is tamoxifen.
[b] The primary analysis (adjusted) was performed for individual trials using a Cox regression model including factors of treatment, extent of disease at entry, previous hormonal therapy, estrogen/progesterone receptor status, and age.
[c] The support analysis (unadjusted) was performed using a Cox regression model including treatment factor only.
[d] The adjusted analysis was repeated for combined trials using trial as a stratification factor - primary analysis.
[e] The adjusted analysis was repeated for combined trials by adding trial as an additional covariate - support analysis.
CL Confidence limit

In Trial 0030, the hazard ratio for time to treatment failure was 1.35 with lower 95% confidence limit of 1.11, indicating numerical superiority for anastrozole. The unadjusted analysis was supportive. Non-inferiority for anastrozole was also seen in Trial 0027.

In the combined trials, consistent hazard ratios and associated lower 1-sided 95% confidence limits (tamoxifen:anastrozole) were obtained from the primary analysis and the 2 support analyses. The hazard ratio of 1.13 favors anastrozole. The lower 1-sided 95% confidence limit was 1.01, which was greater than the statistical criterion of 0.8 to declare noninferiority; thus proving that anastrozole is at least as efficacious as tamoxifen in terms of time to treatment failure. There was numerical superiority for anastrozole in Trial 0030 and the combined trials; however, these trials were not designed to demonstrate superiority.

The Kaplan-Meier plot of time to treatment failure is presented in Figure 3.

Figure 3 Kaplan-Meier probability of time to treatment failure, combined trials



4.2.4 Time to death (survival)

Summary tables: *Survival status; Tables T4.6.1 (Trial 0027), T15.6.1 (Trial 0030), and T26.6.1 (Combined)*
Survival at 2 years; Tables T4.6.3 (Trial 0027), T15.6.3 (Trial 0030), and T26.6.3 (Combined)

All deaths, regardless of cause (whether due to progression or an adverse event), are included in this section. Specific causes of death are presented in the ISS.

Table 20 summarizes the survival status for all randomized subjects in Trials 0030 and 0027, separately and combined, by trial treatment.

Table 20 Survival status for subjects in Trials 0030 and 0027, separately and combined

Survival status	Number (%) of subjects[a]					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Alive[a]	124 (72.5)	129 (70.9)	249 (73.2)	254 (77.4)	373 (73.0)	383 (75.1)
Dead	47 (27.5)	53 (29.1)	91 (26.8)	74 (22.6)	138 (27.0)	127 (24.9)

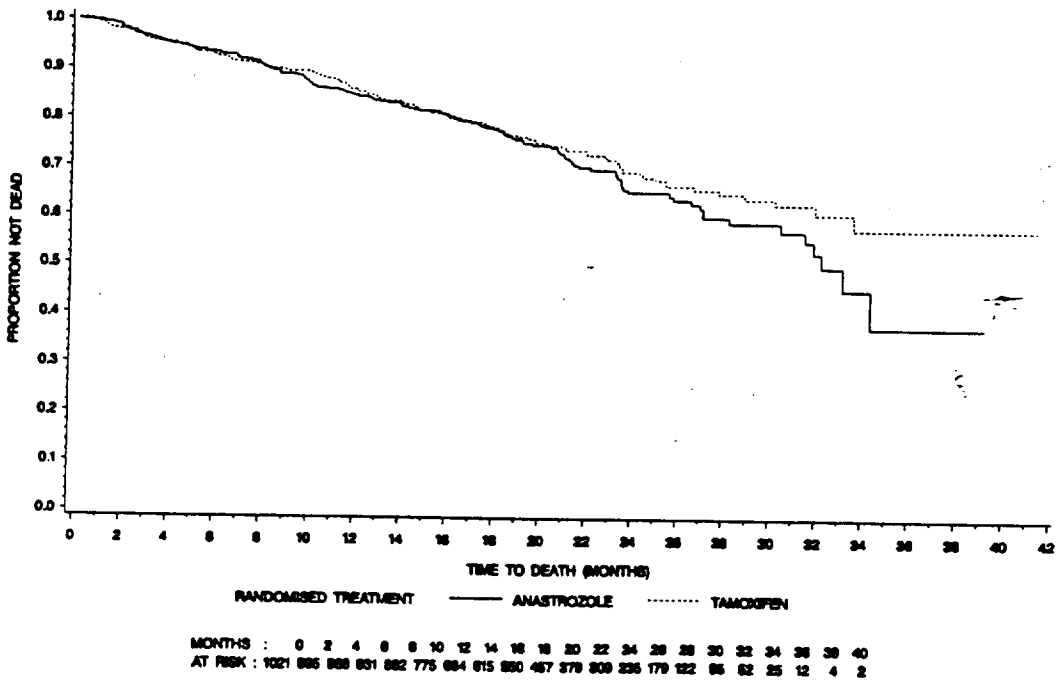
[a] Data for these subjects were censored at the last known observation.

Subjects randomized to anastrozole treatment appeared to have a higher death rate (138 [27.0%] than subjects randomized to tamoxifen (127 [24.9%]), but this is not a cause for concern since survival data are still immature.

The percentage of subjects who were alive longer than 2 years was 65.2% for subjects who were randomized to anastrozole treatment and 69.4% for subjects who were randomized to tamoxifen treatment. (See Table A in the Summary section of this ISE.) A statistical analysis of survival was not performed because only 265 (26.0%) subjects in this trial had died at the time of data cutoff.

The Kaplan-Meier plot of time to death (survival) is presented in Figure 4.

Figure 4 Kaplan-Meier probability of time to death (survival), combined trials



4.2.5 Duration of response

Summary tables: *Duration of response; Tables T4.5.1 and T4.5.3 (Trial 0027), T15.5.1 and T15.5.2 (Trial 0030), and T26.5.1 and T26.5.2 (Combined)*

Table 21 summarizes the duration of response for all randomized subjects who had a best objective response of complete or partial.

Table 21 Duration of response for all randomized subjects who had a best objective response of CR or PR for subjects in Trials 0030 and 0027, separately and combined

Response data	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Number (%) of subjects with objective response	36 (21.1)	31 (17.0)	112 (32.9)	107 (32.6)	148(29.0)	138 (27.1)
Duration of response from randomization						
Median (days)	490	546	498	518	498	524
Range (days)	63-917	84-924	111-1194	83-1124	63-1194	83-1124
Duration of response from first documentation of response						
Median (days)	376	332	378	421	378	406
Range (days)	34-833	54-784	35-1027	56-1037	34-1027	54-1037

Two hundred eighty six (28.0%) subjects were considered to be responders (subjects 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, appeared to be lower for subjects who randomized to anastrozole treatment (498 and 378 days, respectively), compared with subjects who were randomized to tamoxifen treatment (524 and 406 days, respectively). The medians must be interpreted cautiously since they are estimated based upon responders only, which represent a small portion (28.0%) of the total population. No statistical analysis of treatment comparison was performed.

Kaplan-Meier plots for duration of response are presented in Figures 5 and 6 (duration of response from randomization and from first response, respectively).

Figure 5 **Kaplan-Meier probability of duration of response (responding subjects only) from randomization, combined trials**

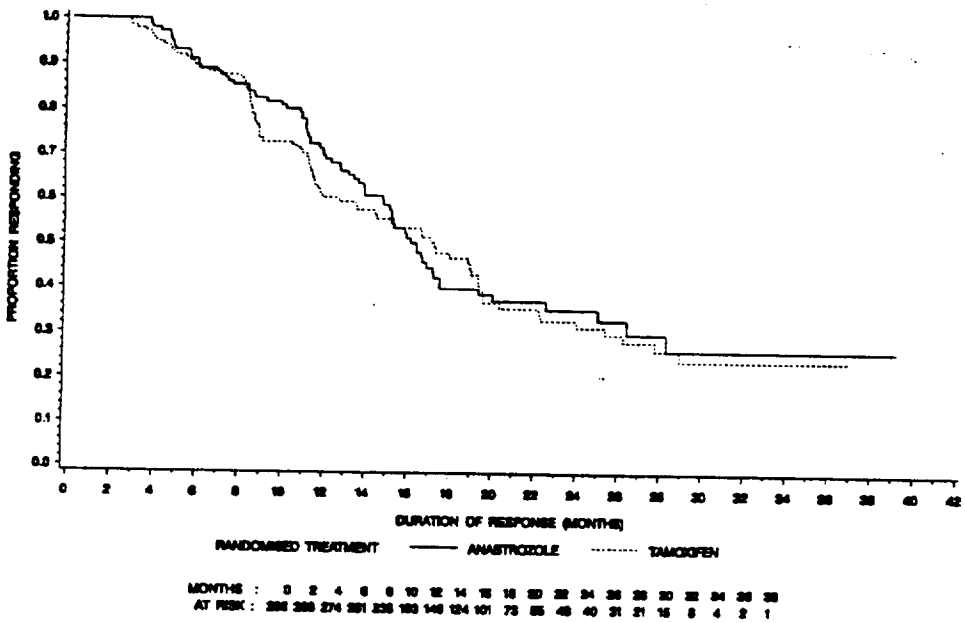
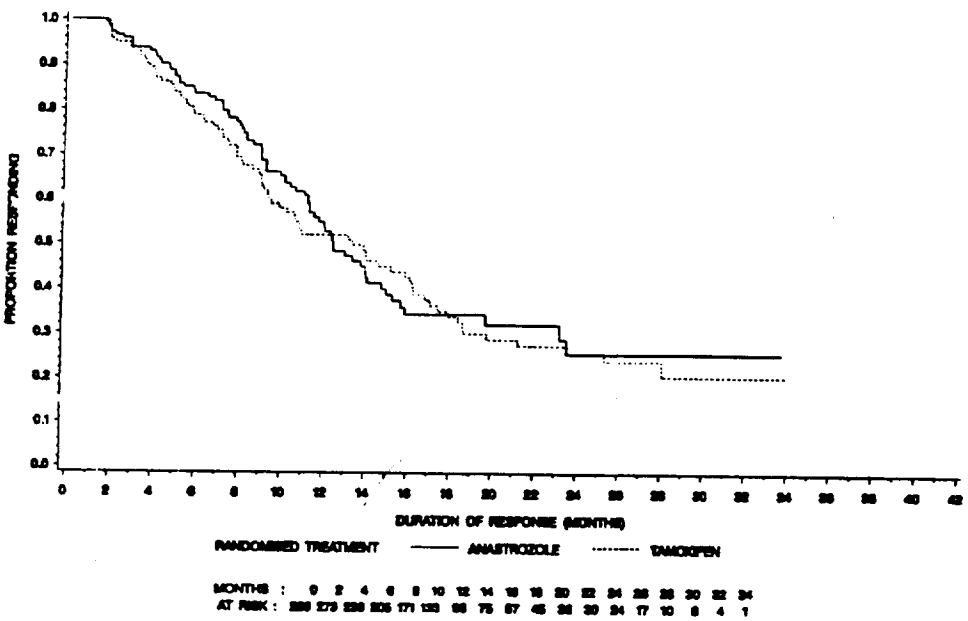


Figure 6 **Kaplan-Meier probability of duration of response (responding subjects only) from first response, combined trials**



4.2.6 Duration of clinical benefit

Summary table: *Duration of clinical benefit; Tables T4.5.3 (Trial 0027), T15.5.3 (Trial 0030), and T26.5.3 (Combined)*

Table 22 summarizes the duration of clinical benefit for those subjects who were CR, PR, or SD 24 weeks from the date of randomization to the date of first determined progression or death from any cause.

Table 22 Duration of clinical benefit for subjects in Trials 0030 and 0027, separately and combined

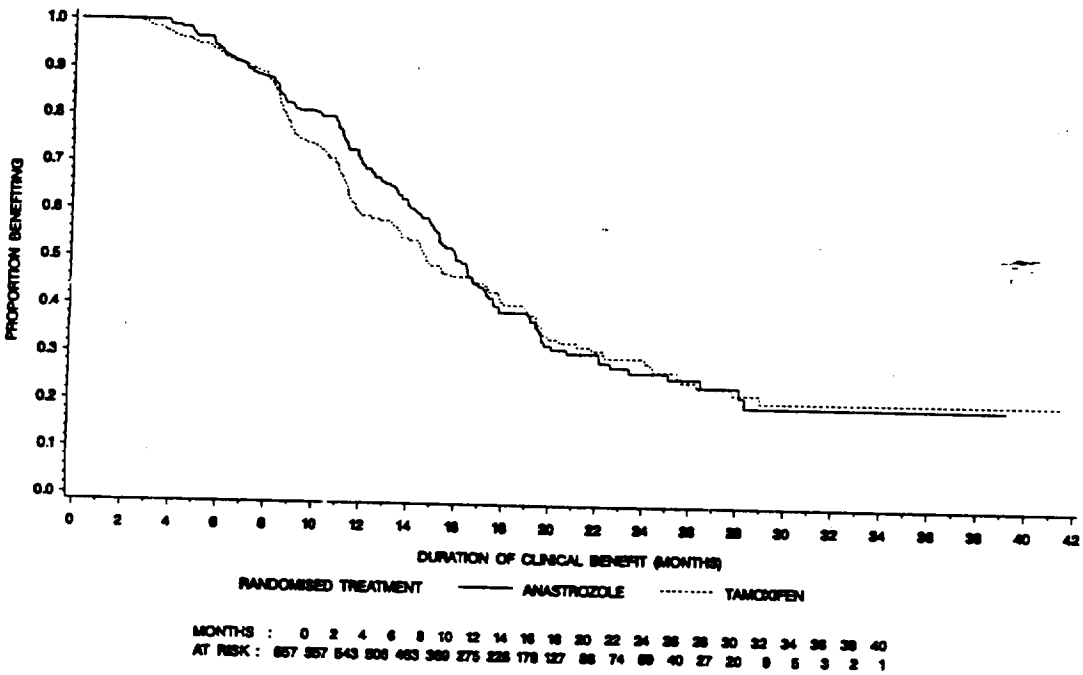
Duration of clinical benefit data	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Number (%) of subjects with CR, PR, or SD ≥24 weeks	101 (59.1)	83 (45.6)	191 (56.2)	182 (55.5)	292 (57.1)	265 (52.0)
Duration of clinical benefit						
Median (days)	503	442	462	448	483	445
Range (days)						

CR Complete response.
PR Partial response.
SD Stable disease.

The subjects who were randomized to anastrozole treatment appeared to have a higher percentage of clinical benefit and longer estimated median time to progression (57.1% and 483 days, respectively) than did subjects who were randomized to tamoxifen treatment (52.0% and 445 days, respectively). No statistical analysis of treatment comparison was performed.

A Kaplan-Meier plot for duration of clinical benefit is presented in Figure 7.

Figure 7 **Kaplan-Meier probability of duration of clinical benefit (subjects with clinical benefit), combined trials**



4.2.7 Health economics

Summary table:

Proportion of subjects who received further breast cancer therapy; Tables T6.1 (Trial 0027), T17.1 (Trial 0030), and T28.1 (Combined)
Duration of further breast cancer therapy; Tables T6.2 (Trial 0027), T17.2 (Trial 0030), and T28.2 (Combined)

Table 23 summarizes the number of subjects who received radiotherapy, chemotherapy, or hormonal therapy after withdrawal of trial treatment.

Table 23 Therapy received after withdrawal of trial treatment for subjects in Trials 0030 and 0027, separately and combined

Therapy[a]	Number (%) of subjects					
	Trial 0030		Trial 0027		Combined trials	
	Anastrozole 1 mg (n=122)	Tamoxifen 20 mg (n=142)	Anastrozole 1 mg (n=235)	Tamoxifen 20 mg (n=241)	Anastrozole 1 mg (n=357)	Tamoxifen 20 mg (n=383)
Radiotherapy	34 (27.9)	28 (19.7)	73 (31.1)	77 (32.0)	107 (30.0)	105 (27.4)
Chemotherapy	36 (29.5)	53 (37.3)	106 (45.1)	105 (43.6)	142 (39.8)	158 (41.3)
Hormonal therapy	55 (45.1)	80 (56.3)	117 (49.8)	142 (58.9)	172 (48.2)	222 (58.0)
Other	31 (25.4)	29 (20.4)	52 (22.1)	49 (20.3)	83 (23.2)	78 (20.4)

[a] Subjects may have received more than 1 type of treatment.
N Number of subjects.

A smaller percentage of subjects who were given anastrozole received further hormonal therapy after withdrawal (48.2%) as compared with subjects who were given tamoxifen (58.0%). The percentage of subjects who were given therapies after withdrawal that were other than hormonal, was similar between the 2 treatment groups.

5 DISCUSSION AND CONCLUSIONS

5.1 Interpretation of efficacy results

The anastrozole first-line clinical program included 2 core trials that provided information on the efficacy of anastrozole. Both were randomized, double-blind trials, which compared anastrozole with tamoxifen in postmenopausal women with advanced breast cancer who had not received any systemic therapy for advanced disease. The primary efficacy end points were time to progression and objective response rate, while the secondary end points were time to treatment failure, duration of response, duration of clinical benefit, survival, and health economics. Time to progression and objective response rate are recognized end points for assessing the efficacy of cancer therapies (Grossman 1988, Therasse 1998). In particular, time to progression is an accepted surrogate end point for overall survival given the public interest in rapid access to cancer therapies, whereas mature survival data may require many years of follow-up. Success in these trials required that anastrozole meet criteria for noninferiority versus tamoxifen for both primary end points.

Trial 0030 enrolled 353 subjects in the US and Canada, while Trial 0027 enrolled 668 subjects in Europe, South America, Australia, and South Africa. Median duration of follow up for alive subjects was 547 days for subjects randomized to anastrozole and 567 days for subjects randomized to tamoxifen. At the time of data cutoff, 73.3% of the subjects had progressed, sufficient for clinically relevant statistical analysis.

Response categories were assigned by a Zeneca-developed algorithm that strictly applied the protocol definition of response, which was based on UICC criteria.

Intent-to-treat analyses (both adjusted for covariates and unadjusted) found that both Trials 0030 and 0027 met the prespecified criterion for noninferiority for time to progression. A per protocol analysis, which was performed for individual trials by excluding major protocol violators and deviators, also found that Trials 0030 and 0027, individually, met the prespecified noninferiority criterion for time to progression. These analyses are presented in the individual trial CTRs. The consistent results from all analyses indicate that anastrozole is at least as efficacious as tamoxifen for the end point of time to progression. Trial 0030 and the combined trial data suggest that anastrozole might be superior to tamoxifen with the lower 95% confidence limit greater than or equal to 1.00.

Intent to treat analyses (both adjusted and unadjusted) also found that both Trials 0030 and 0027 met the prespecified criterion for noninferiority for objective response rate. Per-protocol analyses also found that Trials 0030 and 0027, individually, met the prespecified noninferiority criterion for objective response rate. The consistent results from all analyses indicate that

anastrozole is at least as effective as tamoxifen for the end point of objective response rate. Anastrozole therefore met both efficacy objectives for both trials.

Anastrozole was also demonstrated to be at least as efficacious as tamoxifen in time to treatment failure. There was numerical superiority for anastrozole in Trial 0030 and the combined trials; however, the trials were not designed to assess superiority. The primary reason for treatment failure was progression of disease, as would be expected in trials of hormonal agents which are well-tolerated.

Duration of response and duration of clinical benefit gave differing results, with tamoxifen having longer duration of response and anastrozole having longer duration of clinical benefit. Statistical analyses of treatment comparison were not planned in the protocols, and were not performed. The median durations of response must be interpreted cautiously, as they are estimated based upon responders only, which represent a small portion (28.0%) of the total trial population. The category of clinical benefit included both subjects with objective response and those with stable disease longer than 24 weeks, which may explain the difference in results. Achievement of durable stable disease has been shown to benefit subjects treated with hormonal therapy for breast cancer (Howell 1988, Robertson 1994).

At the time of data cutoff, only 26.0% of the subjects had died; therefore, statistical analysis of survival was not performed. The death rate was 27.0% for subjects randomized to anastrozole treatment and 24.9% for subjects randomized to tamoxifen treatment. The numbers of deaths due to breast cancer was similar in the 2 treatment groups (This information is presented in detail in the ISS.). Non-breast cancer deaths in the period after treatment may reflect comorbid conditions and the effects of further therapies. Review of the therapies received after trial treatment did not reveal major differences between the anastrozole and tamoxifen treatment groups, but could not rule out therapy-related effects.

Although the results from Trials 0030 and 0027 did not differ qualitatively, quantitative differences were seen. Response rates for both therapies were lower in Trial 0030 than Trial 0027. This may be partly due to the greater proportion of subjects with measurable disease and with soft tissue disease in Trial 0027. Response rates for both trials fell within a range of what has been observed in previous trials of first line hormonal therapy (Ingle 1986, Hayes 1995, Pyrrhonen 1997, Ingle 1999).

In time to progression and time to treatment failure, there was numerical superiority for anastrozole in Trial 0030 and the combined trials. A retrospective data review showed similar numerical superiority for anastrozole among subjects in Trial 0027 who were known to be estrogen and/or progesterone receptor positive

5.2 Efficacy conclusions

Anastrozole was shown to have met prespecified criteria for equivalence to tamoxifen with regard to the 2 primary end points of time to progression and objective response rate. Data from Trials 0030 and 0027, and the combined trials show that anastrozole is at least as efficacious as tamoxifen in time to progression, and there is numerical superiority for anastrozole in Trial 0030 and the combined trials. In Trials 0030 and 0027, and in the combined trials, anastrozole was also shown to be at least as efficacious as tamoxifen in objective response rate. In the secondary end point of time to treatment failure, anastrozole was shown to be at least as efficacious as tamoxifen, again with numerical superiority.

Anastrozole was numerically superior to tamoxifen in duration of clinical benefit and inferior in duration of response. The median durations of response must be interpreted cautiously, since they are estimated based upon responders only, which represent a small portion (28.0%) of the total population. No statistical analysis of treatment comparison was performed. Statistical analysis of death rate was not done because too few subjects had died at the time of data cutoff.

The results presented in this supplemental application support the claim that anastrozole is indicated for first-line treatment of advanced breast cancer in postmenopausal women.

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[1] Note: references are available upon request.

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TABLE T1.1 RANDOMIZATION AND SUBJECT STATUS - 1033IL/0027

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

TREATMENT GIVEN	RANDOMISED TREATMENT					
	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N = 340		N = 328		N = 668	
	N	%	N	%	N	%
ANASTROZOLE	334	98.2	2	0.6	336	50.3
TAMOXIFEN	4	1.2	325	99.1	329	49.3
OTHER	1	0.3	1	0.3	2	0.3
NONE	1	0.3	0	0.0	1	0.1
TOTAL	340	100.0	328	100.0	668	100.0

SUBJECT STATUS AT DATA CUT-OFF	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N	%	N	%	N	%
STARTED TRIAL TREATMENT	336	98.8	329	100.3	665	99.6
ON TREATMENT	101	29.7	88	26.8	189	28.3
WITHDRAWN FROM TREATMENT (ALIVE)	144	42.4	167	50.9	311	46.6
DEAD	91	26.8	74	22.6	165	24.7

PERCENTAGE CALCULATED USING NUMBER OF SUBJECTS RANDOMIZED AS DENOMINATOR

TABLE T1.2 AGE, HEIGHT, WEIGHT AND BODY MASS INDEX AT ENTRY - 1033IL/0027
(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

		ANASTROZOLE	TAMOXIFEN	TOTAL
		N = 340	N = 328	N = 668
AGE (YEARS)	N	340	328	668
	MEAN	67	66	66
	MEDIAN	67	66	67
	SD	11.0	10.6	10.8
	MAX	91	92	92
	MIN	34	41	34
HEIGHT (CM)	N	320	310	630
	MEAN	159	159	159
	MEDIAN	160	160	160
	SD	7.1	7.2	7.1
	MAX	174	180	180
	MIN	139	125	125
WEIGHT (KG)	N	333	318	651
	MEAN	68	68	68
	MEDIAN	67	67	67
	SD	13.2	12.9	13.0
	MAX	121	111	121
	MIN	40	42	40
BMI (KG/M2)	N	317	308	625
	MEAN	27	27	27

(CONTINUED)

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TABLE T1.2 AGE, HEIGHT, WEIGHT AND BODY MASS INDEX AT ENTRY - 1033IL/0027
(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

		ANASTROZOLE	TAMOXIFEN	TOTAL
		N = 340	N = 328	N = 668
BMI (KG/M2)	MEDIAN	26	26	26
	SD	4.9	5.0	4.9
	MAX	42	44	44
	MIN	16	16	16

ST3

TABLE T1.3 AGE GROUP, ETHNIC ORIGIN AND GENDER - 1033IL/0027
(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

		ANASTROZOLE		TAMOXIFEN		TOTAL	
		N = 340		N = 328		N = 668	
		N	%	N	%	N	%
AGE GROUP	<= 65	160	47.1	160	48.8	320	47.9
	> 65	180	52.9	168	51.2	348	52.1
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	0.0	2	0.6	2	0.3
	HISPANIC	9	2.6	9	2.7	18	2.7
	MIXED	13	3.8	16	4.9	29	4.3
	OTHER	2	0.6	3	0.9	5	0.7
GENDER	FEMALE	340	100.0	328	100.0	668	100.0
	MALE	0	0.0	0	0.0	0	0.0

TABLE T1.4 BREAST CANCER DISEASE STATUS AT FIRST DIAGNOSIS - 1033IL/0027
(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

DISEASE STATUS AT FIRST DIAGNOSIS	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N = 340		N = 328		N = 668	
	N	%	N	%	N	%
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	100.0	328	100.0	668	100.0

TABLE T1.5.1 PRIOR ADJUVANT THERAPY (HORMONAL OR CYTOTOXIC) FOR BREAST CANCER - 1033IL/0027
(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

PRIOR ADJUVANT THERAPY	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N = 340		N = 328		N = 668	
	N	%	N	%	N	%
YES	105	30.9	97	29.6	202	30.2
NO	234	68.8	231	70.4	465	69.6
UNKNOWN	1	0.3	0	0	1	0.1

TYPE OF ADJUVANT THERAPY	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N	%	N	%	N	%
HORMONAL ONLY	31	9.1	20	6.1	51	7.6
CYTOTOXIC ONLY	64	18.8	62	18.9	126	18.9
BOTH	10	2.9	15	4.6	25	3.7

TABLE T1.5.2 DURATION OF ADJUVANT HORMONAL TREATMENT - 1033IL/0027

(SUBJECTS INCLUDED: ALL SUBJECTS IN TRIAL 1033IL/0027 WHO WERE GIVEN PREVIOUS ADJUVANT HORMONAL TREATMENT)

DURATION OF ADJUVANT TREATMENT (WEEKS)	ANASTROZOLE	TAMOXIFEN	TOTAL
	N =41	N =35	N =76
MEDIAN	105	141	113
MIN	3	4	3
MAX	315	351	351

TABLE T1.6.1 MOST RECENT HORMONAL RECEPTOR STATUS: ER AND PR GROUPED - 1033IL/0027
(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

GROUPED ER AND PR STATUS	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N =340		N =328		N =668	
	N	%	N	%	N	%
ER AND/OR PR POSITIVE	154	45.3	144	43.9	298	44.6
ALL OTHER COMBINATIONS	186	54.7	184	56.1	370	55.4

ER AND/OR PR POSITIVE IS ONE OF THE FOLLOWING: ER+
PR+
ER+ AND PR+

ALL OTHER COMBINATIONS INCLUDE UNKNOWN RECEPTOR STATUS

TABLE T1.6.2 MOST RECENT HORMONAL RECEPTOR STATUS: ER AND PR SEPARATELY - 1033IL/0027
(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

ER	PR	ANASTROZOLE N =340		TAMOXIFEN N =328		TOTAL N =668	
		N	%	N	%	N	%
+	+	80	23.5	85	25.9	165	24.7
	–	30	8.8	27	8.2	57	8.5
	UNKNOWN	36	10.6	30	9.1	66	9.9
–	+	8	2.4	1	0.3	9	1.3
	–	1	0.3	1	0.3	2	0.3
	UNKNOWN	0	0.0	0	0.0	0	0.0
UNKNOWN	+	0	0.0	1	0.3	1	0.1
	–	0	0.0	0	0.0	0	0.0
	UNKNOWN	185	54.4	183	55.8	368	55.1

TABLE T1.7 SUBJECTS WITH MEASURABLE AND NO MEASURABLE DISEASE AT ENTRY - 1033IL/0027
(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N =340		N =328		N =668	
	N	%	N	%	N	%
MEASURABLE DISEASE	301	88.5	286	87.2	587	87.9
NO MEASURABLE DISEASE	39	11.5	42	12.8	81	12.1

MEASURABLE DISEASE INCLUDES SUBJECTS WITH ANY BIDIMENSIONALLY OR UNIDIMENSIONALLY MEASURABLE LESIONS

NO MEASURABLE DISEASE INCLUDES SUBJECTS WITH EITHER NO LESIONS OR NON-MEASURABLE DISEASE ONLY

TABLE T1.8.1 SITE OF METASTATIC DISEASE AT ENTRY - 1033IL/0027

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

SITE OF DISEASE	ANASTROZOLE N = 340		TAMOXIFEN N = 328		TOTAL N = 668	
	N	%	N	%	N	%
SKIN	183	53.8	183	55.8	366	54.8
LYMPH	145	42.6	148	45.1	293	43.9
BONE	156	45.9	158	48.2	314	47.0
VISCERAL	103	30.3	124	37.8	227	34.0
LUNG	74	21.8	100	30.5	174	26.0
LIVER	32	9.4	31	9.5	63	9.4
ABDOMEN	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	0.0	2	0.3

SUBJECTS WITH METASTATIC DISEASE MAY APPEAR IN MORE THAN ONE HOW

PLEURAL EFFUSIONS ARE CONSIDERED VISCERAL LUNG DISEASE

TABLE T1.8.2 EXTENT OF METASTATIC DISEASE AT ENTRY - 1033IL/0027

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

EXTENT OF DISEASE		ANASTROZOLE N = 340		TAMOXIFEN N = 328		TOTAL N = 668	
		N	%	N	%	N	%
EXTENT COVARIATE	SOFT TISSUE AND/OR LUNG DISEASE ONLY	155	45.6	132	40.2	287	43.0
	ALL OTHER DISEASE COMBINATIONS	185	54.4	196	59.8	381	57.0
NO VISCERAL DISEASE	SOFT TISSUE ONLY	128	37.6	106	32.3	234	35.0
	BONE ONLY	55	16.2	44	13.4	99	14.8
	BONE AND SOFT TISSUE ONLY	52	15.3	54	16.5	106	15.9
VISCERAL DISEASE	NO EVIDENCE OF LIVER INVOLVEMENT	71	20.9	93	28.4	164	24.6
	LIVER INVOLVEMENT	32	9.4	31	9.5	63	9.4
NO EVALUABLE DISEASE	NO EVALUABLE DISEASE	2	0.6	0	0	2	0.3

PLEURAL EFFUSIONS ARE CONSIDERED VISCERAL LUNG DISEASE

TABLE T2 REASON FOR WITHDRAWAL OF TRIAL TREATMENT - 1033IL/0027

(SUBJECTS INCLUDED : ALL TREATED SUBJECTS IN TRIAL 1033IL/0027)

PRIMARY REASON FOR WITHDRAWAL	ANASTROZOLE N = 336		TAMOXIFEN N = 329		TOTAL N = 665	
	N	%	N	%	N	%
DEATH	6	1.8	3	0.9	9	1.4
DISEASE PROGRESSION (INVESTIGATOR'S OPINION)	193	57.4	197	59.9	390	58.6
PATIENT LOST TO FOLLOW UP	2	0.6	1	0.3	3	0.5
ADVERSE EVENT	15	4.5	15	4.6	30	4.5
PROTOCOL NON-COMPLIANCE	3	0.9	6	1.8	9	1.4
PATIENT UNWILLING TO CONTINUE	10	3.0	12	3.6	22	3.3
OTHER REASON	6	1.8	7	2.1	13	2.0
TOTAL	235	69.9	241	73.3	476	71.6

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TABLE T4.1.1 DURATION OF TREATMENT - 1033IL/0027

(SUBJECTS INCLUDED : ALL TREATED SUBJECTS IN TRIAL 1033IL/0027)

DURATION OF TREATMENT (DAYS)	ANASTROZOLE	TAMOXIFEN
	N = 336	N = 329
MEDIAN	263	253
MIN	2	3
MAX	1195	1260

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TABLE T4.1.2 DURATION OF TREATMENT IN WEEKS - 1033IL/0027

(SUBJECTS INCLUDED : ALL TREATED SUBJECTS IN TRIAL 1033IL/0027)

DURATION OF TREATMENT (WEEKS)	ANASTROZOLE N = 336		TAMOXIFEN N = 329	
	N	%	N	%
<0 TO 12	52	15.5	49	14.9
<12 TO 24	67	19.9	69	21.0
<24 TO 48	73	21.7	82	24.9
<48 TO 96	107	31.8	82	24.9
>96	37	11.0	47	14.3

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TABLE T4.1.3 DURATION OF FOLLOW-UP TO DATE LAST SEEN ALIVE - 1033IL/0027

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027
WHO WERE ALIVE AT DATA CUTOFF)

DURATION OF FOLLOW-UP (DAYS)	ANASTROZOLE	TAMOXIFEN	TOTAL
	N = 249	N = 254	N = 503
MEDIAN	556	598	572
MIN	0	106	0
MAX	1194	1260	1260

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TABLE T4.2.1 PROGRESSION STATUS - 1033IL/0027

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

SUBJECT STATUS		ANASTROZOLE N = 340		TAMOXIFEN N = 328		TOTAL N = 668	
		N	%	N	%	N	%
NOT PROGRESSED	ALIVE NO PROGRESSION	91	26.8	81	24.7	172	25.7
PROGRESSED	TOTAL PROGRESSED	249	73.2	247	75.3	496	74.3
	PROGRESSION DURING TREATMENT	216	63.5	209	63.7	425	63.6
	PROGRESSION AFTER TREATMENT WITHDRAWAL	15	4.4	18	5.5	33	4.9
	DEATH BEFORE PROGRESSION	18	5.3	20	6.1	38	5.7

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TABLE T4.2.3 MEDIAN TIME TO PROGRESSION - 1033IL/0027

(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

	ANASTROZOLE	TAMOXIFEN
	N = 340	N = 328
TIME TO PROGRESSION (DAYS)	251	252

MEDIAN TIMES TO EVENT WERE ESTIMATED USING KAPLAN-MEIER METHOD

TABLE T4.2.5 TIME TO PROGRESSION : ANALYSIS RESULTS - 1033IL/0027

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIAL 1033IL/0027)

TAMOXIFEN:ANASTROZOLE	HAZARD RATIO	LOWER 95% CONFIDENCE LIMIT
ADJUSTED ANALYSIS	0.99	0.86
UNADJUSTED ANALYSIS	1.01	0.87

A HAZARD RATIO >1 INDICATES THAT ANASTROZOLE IS ASSOCIATED WITH A LONGER TIME TO PROGRESSION(TREATMENT FAILURE) THAN IS TAMOXIFEN

THE ADJUSTED ANALYSIS WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING FACTORS FOR TREATMENT, AGE, PREVIOUS HORMONAL THERAPY, ER/PR STATUS AND EXTENT OF DISEASE AT ENTRY

THE UNADJUSTED ANALYSIS WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING TREATMENT FACTOR ONLY