

## CLINICAL REVIEW

### Clinical Review Section

disease <sup>d,e</sup>					
Ischemic Cerebrovascular events <sup>f</sup>	31 (1%)	65 (2.1%)	51 (1.6%)	0.47 (0.31,0.73)	0.0006
Endometrial Cancer	2 (0%)	11 (0.5%)	5 (0.2%)	0.18 (0.04,0.82)	0.0267

a Includes arthralgia , arthritis, arthrosis, and joint disorder

b Includes deep thrombophlebitis, pulmonary embolus, retinal vein thrombosis, thrombophlebitis, and thrombosis

c Includes deep thrombophlebitis, pulmonary embolus, and retinal vein thrombosis

d Includes angina pectoris, coronary artery disorder, myocardial infarct, myocardial ischemia

e Myocardial Infarction rates were the same for the anastrozole alone and tamoxifen alone treatment groups (0.7%).

f Includes cerebral embolism, cerebral infarct, cerebral ischemia, and cerebrovascular accident

#### Reviewer's Table

The following table shows the Safety Update results for the pre-specified adverse events.

*Reviewer's Comments: These updated results are similar to those submitted with the original sNDA for all three treatment groups. The adverse events seen with greater frequency for the anastrozole treatment group are: Musculoskeletal disorders, fatigue/asthenia, fractures, fractures of the spine, hip, and wrist/Colles, mood disturbances, and ischemic cardiovascular events.*

**Table 11**

Updated ATAC Prespecified Adverse Events as of January 25, 2002

	Anastrozole (N=3092)	Tamoxifen (N=3093)	Combination (N=3098)
Hot flushes	1082 (35%)	1246 (40.3%)	1261 (40.7%)
Musculoskeletal Disorders	936 (30.3%)	732 (23.7%)	765 (24.7%)
Mood Disturbances	519 (16.8%)	508 (16.4%)	506 (16.3%)
Fatigue/Asthenia	512 (16.6%)	491 (15.9%)	468 (15.1%)
Nausea and Vomiting	346 (11.2%)	339 (11%)	379 (12.2%)
Vaginal Discharge	94 (3%)	378 (12.2%)	368 (11.9%)
Vaginal Bleeding	147 (4.8%)	270 (8.7%)	265 (8.6%)
Fractures	219 (7.1%)	137 (4.4%)	178 (5.7%)
Fractures of spine, hip, or wrist/Colles	87 (2.8%)	55 (1.8%)	60 (1.9%)
Cataracts	124 (4%)	139 (4.5%)	126 (4.1%)
Venous Thromboembolic Events	68 (2.2%)	116 (3.8%)	136 (4.4%)
Deep Venous	35 (1.1%)	57 (1.8%)	70 (2.3%)

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<b>Thromboembolic Events</b>			
Ischemic Cardiovascular Disease	86 (2.8%)	67 (2.2%)	78 (2.5%)
Ischemic Cerebrovascular Disease	34 (1.1%)	70 (2.3%)	60 (1.9%)
Endometrial Cancer	2 (0.1%)	13 (0.6%)	9 (0.4%)

a Includes arthralgia , arthritis, arthrosis, and joint disorder

b Includes deep thrombophlebitis, pulmonary embolus, retinal vein thrombosis, thrombophlebitis, and thrombosis

c Includes deep thrombophlebitis, pulmonary embolus, and retinal vein thrombosis

d Includes angina pectoris, coronary artery disorder, myocardial infarct, myocardial ischemia

e Myocardial Infarction rates were the same for the anastrozole alone and tamoxifen alone treatment groups (0.8%).

f Includes cerebral embolism, cerebral infarct, cerebral ischemia, and cerebrovascular accident

#### Reviewer's Table

#### Fracture Adverse Events

Further exploratory analyses were performed, because fracture adverse events were more numerous for the anastrozole alone group.

The table below shows the number of patients with repeat fracture episodes.

*Reviewer's Comment: Several patients had repeat fracture episodes. The anastrozole treatment group had more patients with a repeat fracture episode than the other treated groups.*

**Table 12 Number of Patients with Repeat Fracture Episodes (June 29, 2001)**

Number of Fracture Episodes	Anastrozole	Tamoxifen	Combination
1	160 (5.2%)	100 (3.2%)	128 (4.1%)
More than 1	23 (0.8%)	15 (0.5%)	14 (0.5%)
2	18 (0.6%)	14 (0.5%)	12 (0.4%)
3	5 (0.2%)	1 (0%)	2 (0.1%)

#### Reviewer's Table

The etiology of fractures is shown in the table below. Etiology information was collected from the adverse event form comments. The adverse event definition excluded those recurrence patients who presented with or developed a fracture.

*Reviewer's Comment: The etiology of most fractures is unknown probably because the Adverse Event form did not specifically query for fracture etiology. This reviewer reviewed all CRFs of patients who developed a fracture and were diagnosed with a recurrence and agrees with the*

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*sponsor's assessment regarding etiology. The majority of patients who were identified as having a skeletal recurrence did not report a fracture.*

**Table 13**

**Etiology of Fractures Occurring During Treatment (Includes those occurring up to 14 days after stopping treatment)**

	Anastrozole	Tamoxifen	Combination
Total Fractures	193	119	144
<b>Etiology of Fractures (% of total fractures)</b>			
Fall/Trauma	62 (32.1%)	36 (30.3%)	36 (25%)
Motor Vehicle Accident	4 (2.1%)	0	2 (1.4%)
Osteoporosis/Osteopenia	4 (2.1%)	3 (2.5%)	1 (0.7%)
Stress Fracture	5 (2.6%)	2 (1.7%)	2 (1.4%)
Unknown	118 (61.2%)	78 (65.5%)	103 (71.5%)

Reviewer's Table

### Raloxifene, Bisphosphonates, and Calcium Use for bone maintenance

#### Raloxifene

The following table shows prophylactic raloxifene use by treatment groups.

*Reviewer's Comment: The groups were well balanced with respect to raloxifene use during the trial. Trial information shows that no patient was placed on raloxifene after withdrawal from the trial; however, this data is severely limited due to the fact that patients were not consistently questioned about medication use after trial withdrawal.*

**Table 14 Number of Patients using Raloxifene to Prevent Bone Events\* (June 29, 2001)**

	Anastrozole	Tamoxifen	Combination
Number of Patients	8	6	5

<sup>a</sup> These numbers do not equal the total numbers of patients who used raloxifene during the trial. Some patients received Raloxifene for other reasons.

Reviewer's Table

### Bisphosphonates and Calcium

The following sponsor's exploratory analyses concern the use of bisphosphonates and calcium.

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The following table shows the treatment group use of bisphosphonates and the fracture incidence within these groups.

*Reviewer's Comment: More anastrozole patients took bisphosphonates during the trial.*

**Table 15**

**Number of Patients Using Bisphosphonates (yes/no) and Fracture Incidence (June 29, 2001)**

	Anastrozole (N=3092)	Tamoxifen (N=3094)	Combination (N=3097)
Bisphosphonates use	185 (6%)	126 (4.1%)	139 (4.1%)
No fracture	149 (80.5%)	109 (86.5%)	121 (87.1%)
Fracture (any) <sup>a</sup>	36 (19.5%)	17 (13.5%)	18 (12.9%)
No Bisphosphonates use	2907 (94%)	2968 (95.9%)	2958 (95.5%)
No fracture	2760 (94.9%)	2870 (96.7%)	2834 (95.8%)
Fracture (any) <sup>a</sup>	147 (5.1%)	98 (3.3%)	124 (4.2%)

<sup>a</sup> Patients had more than 1 fracture.

Reviewer's Table

The table below shows the fracture incidence by bisphosphonate use during the trial and treatment group.

*Reviewer's Comment: The majority of patients who start bisphosphonates do so after the trial has begun. More anastrozole patients took bisphosphonates after the trial began compared with tamoxifen and combination. More anastrozole patients fracture prior to or after the start of bisphosphonates compared with the other groups.*

**Table 16**

**Fracture Incidence by Bisphosphonate use and Treatment Group<sup>a</sup> (June 29, 2001)**

	Anastrozole (N=3092)	Tamoxifen (N=3094)	Combination (N=3097)
Bisphosphonates use starting at or prior to baseline	33/3092 (1.1%)	21/3094 (0.7%)	27/3097 (0.9%)
No fracture	31/33 (93.9%)	18/21 (85.7%)	25/27 (92.6%)
Fracture (any)	2/33 (6.1%)	3/21 (14.3%)	2/27 (7.4%)

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Bisphosphonates started after trial	152/3092 (4.9%)	105/3094 (3.4%)	112/3097 (3.6%)
No fracture	114/152 (75%)	86/105 (81.9%)	95/112 (84.8%)
Fracture prior to start of bisphosphonates (any)	20/152 (13.2%)	12/105 (11.4%)	12/112 (10.7%)
Fracture after bisphosphonates (any)	12/152 (7.9%)	1/105 (1.0%)	3/112 (2.7%)
Missing information about start of bisphosphonates after trial start	6/152 (3.9%)	6/105 (5.7%)	2/112 (1.8%)
Fracture (any)	4	5	1
No Fracture (any)	2	1	1

a Patient may be counted once although they may have had more than 1 fracture.

#### Reviewer's Table

The table below shows fracture incidence by calcium use and treatment group.

*Reviewer's Comment: The fracture incidence was higher in the anastrozole treated group regardless of calcium use compared with the other treatment groups.*

**Table 17 Fracture Incidence by Calcium use and Treatment Group**

	Anastrozole (N=3092)	Tamoxifen (N=3094)	Combination (N=3097)
No Calcium	2327/3092 (75.3%)	2363/3094 (76.4%)	2320/3097 (74.9%)
No Fracture	2222/2327 (95.5%)	2293/2363 (97.0%)	2239/2320 (96.5%)
Fracture	105/2327 (4.5%)	70/2363 (3.0%)	81/2320 (3.5%)
Calcium use	765/3092 (24.7%)	731/3094 (23.6%)	777/3097 (25.1%)
No fracture	687/765 (89.8%)	686/731 (93.8%)	716/777 (92.1%)
Fracture	78/765 (10.2%)	45/731 (6.2%)	61/777 (7.8%)
Calcium use at least 30 days prior to fracture	52/765 (6.8%)	28/731 (3.8%)	49/777 (6.3%)
Calcium use within 29 days prior to fracture	24/765 (3.1%)	14/731 (1.9%)	10/777 (1.3%)
Missing start date for calcium use	2/765 (0.3%)	3/731 (0.4%)	2/777 (0.3%)

Reviewer's Table

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#### Time to Fracture

Fractures were observed in all treatment groups within the first two weeks of trial treatment. For the anastrozole and combination treatment groups, the first person to fracture in those treatment groups did so on study day 6. In the tamoxifen treatment group, the first person to fracture did so on study day 11. The table below shows the mean and median time to fracture events for all treatment groups.

*Reviewer's Comment: The mean and median times to fracture are essentially the same for all three treatment groups.*

**Table 18**

Median and Mean Times to Fracture Events (June 29, 2001) - ITT analysis from adverse events database

Event	Anastrozole	Tamoxifen	Combination
Median Time to Fracture	548 days	548 days	546 days
Mean Time to Fracture	565.4 days	555.9 days	549.3 days

Reviewer's Table

The table below shows the sponsor's time to first fracture event analysis for all fractures occurring during treatment or within 14 days of stopping treatment. Patients who had not had a fracture during trial therapy have been censored after the number of days of trial treatment they received.

*Reviewer's Comment: The analysis shows that time to first fracture events were different for anastrozole compared with tamoxifen favoring tamoxifen.*

**Table 19**

Time to First Fracture Event (June 29, 2001)

Comparison	Hazard Ratio	95% Confidence Interval
Anastrozole versus Tamoxifen	1.58	(1.25, 2.00)
Anastrozole plus Tamoxifen versus Tamoxifen	1.25	(0.98, 1.60)

Reviewer's Table

#### Fracture Site Distribution

The following updated table shows the selected fracture distribution during the trial.

*Reviewer's Comments: The anastrozole alone treatment group had a greater percentage of total and combined hip, spine, and wrist fractures than the tamoxifen alone. These results are consistent with those submitted in the original sNDA. The increase in total fracture rate for the*

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*anastrozole alone group over the 7 month period of the update was 1.2% compared with 0.7% for tamoxifen alone group and 1.1% for the combination group.*

**Table 20**

**Fracture site for events occurring during or within 14 days of the end of Treatment (January 25, 2002)**

Site of fracture	Number (%) of patients *					
	Anastrozole 1 mg (N = 3092)		Tamoxifen 20 mg (N = 3093)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 3098)	
Total fractures	219	(7.1)	137	(4.4)	178	(5.7)
Hip	16	(0.5)	18	(0.6)	12	(0.4)
Vertebral	29	(0.9)	15	(0.5)	16	(0.5)
Wrist/Colles	46	(1.5)	31	(1.0)	33	(1.1)

\* Patients may fall into more than 1 category.

Reviewer's Table

The following table shows the distribution for all other fracture sites.

*Reviewer's Comment: No significant differences for specific fracture sites are seen between the different treatment groups.*

**Table 21 Number of Fractures and Sites of Other Fractures by Treatment Group<sup>a</sup> (June 29, 2001)**

Site of Fracture	Anastrozole (N=130)	Tamoxifen (N=72)	Combination (N=98)
Ankle	18 (13.8%)	10 (13.9%)	18 (18.4%)
Arm	8 (6.2%)	3 (4.2%)	6 (6.1%)
Clavicle	1 (0.1%)	1 (1.4%)	2 (2%)
Elbow	3 (2.3%)	2 (2.8%)	8 (8.2%)
Face	0	0	3 (3.1%)
Femur	4 (3.1%)	3 (4.2%)	2 (2%)
Fibula	2 (1.5%)	3 (4.2%)	2 (2%)
Finger	5 (3.8%)	1 (1.4%)	4 (4.1%)
Foot	9 (6.9%)	7 (9.7%)	8 (8.2%)
Hand	2 (1.5%)	0	2 (2%)
Humerus	10 (7.7%)	5 (6.9%)	6 (6.1%)
Knee	5 (3.8%)	3 (4.2%)	0
Leg	4 (3.1%)	2 (2.8%)	3 (3.1%)
Metacarpal	1 (0.1%)	5 (6.9%)	0
Metatarsal	6 (4.6%)	0	3 (3.1%)
Multiple fractures	0	0	1 (1%)

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Nose	3 (2.3%)	1 (1.4%)	0
Pelvis	2 (1.5%)	1 (1.4%)	1 (1%)
Radius	6 (4.6%)	2 (2.8%)	4 (4.1%)
Ribs	26 (20%)	12 (16.7%)	13 (13.3%)
Sacrum	0	1 (1.4%)	0
Shoulder	5 (3.8%)	3 (4.2%)	4 (4.1%)
Sternum	1 (0.1%)	1 (1.4%)	0
Tibia	1 (0.1%)	3 (4.2%)	4 (4.1%)
Toe	5 (3.8%)	0	4 (4.1%)

a Patients may be counted more than once.

#### Reviewer's Table

The following updated table shows the distribution of fractures reported as serious adverse events.

*Reviewer's Comment: No statistically significant differences occurred between treatment groups for serious fractures. No serious fracture was associated with death; however, serious fractures caused 3 patients to withdraw from the study (1 anastrozole alone, 1 tamoxifen alone and 1 combination).*

**Table 22**

#### Fracture types reported as serious adverse events during or following the withdrawal of treatment (January 25, 2002)

Site of fracture	Number (%) of patients *					
	Anastrozole 1 mg (N = 3092)		Tamoxifen 20 mg (N = 3094)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 3097)	
Fractures of the hip, vertebrae, or wrist/Colles	37	(1.2)	36	(1.2)	34	(1.1)
Hip	13	(0.4)	18	(0.6)	12	(0.4)
Vertebral	8	(0.3)	5	(0.2)	6	(0.2)
Wrist/Colles	16	(0.5)	16	(0.5)	17	(0.5)

\* Patients may fall into more than 1 category.

N Number of patients treated.

#### Reviewer's Table

#### New Primary Cancers

The following table shows the distribution of primary cancers as of the cut off date of January 25, 2002.

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*Reviewer's Comment: No statistically significant difference exists between treated groups for the cancer categories listed below. The results in the table below are similar to the table in the original submission dated June 29, 2001.*

**Table 23**

**New Primary Cancers Occurring with an Incidence of at least 0.1% in any Treatment Group Prior to Recurrence (January 25, 2002)**

Cancer Categories	Number (%) of patients		
	Anastrozole (N = 3092)	Tamoxifen (N = 3093)	Combination (N = 3098)
Skin	45 (1.5%)	37 (1.2%)	36 (1.2%)
Contralateral breast cancer <sup>a</sup>	21 (0.7%)	36 (1.2%)	33 (1.1%)
Colorectal	26 (0.8%)	23 (0.7%)	10 (0.3%)
Ovary	6 (0.2%)	11 (0.4%)	8 (0.3%)
Endometrium <sup>b</sup>	2 (<0.1%)	14 (0.5%)	10 (0.3%)
Lung	9 (0.3%)	8 (0.3%)	4 (0.1%)
Head and neck	7 (0.2%)	5 (0.2%)	6 (0.2%)
Kidney	4 (0.1%)	1 (<0.1%)	5 (0.2%)
Leukemia	4 (0.1%)	3 (<0.1%)	2 (<0.1%)
Gastric	2 (<0.1%)	3 (<0.1%)	4 (0.1%)
Melanoma	0	6 (0.2%)	2 (<0.1%)
Esophagus	0	0	4 (0.1%)

<sup>a</sup> Includes new primary (contralateral) breast cancer occurring after recurrence. There were at least three new primary breast cancers after local recurrence. One patient received the combination and the other two patients received anastrozole alone.

<sup>b</sup> Includes 4 cases reported as serious adverse events following the withdrawal of treatment (patient numbers 0296/0004, 0310/0024, 0322/0011, and 0480/0007) and excludes 2 cases (one [0413/0016] where the event was coded as endometrial carcinoma on the adverse event form and cervical carcinoma on the new primary cancer form and a second [0460/0002] reflecting a recurrence of endometrial cancer). N Number of patients treated.

Reviewer's Table

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The following table shows the updated sponsor's post-hoc analysis of endometrial events by treatment group.

*Reviewer's Comment: The tamoxifen alone and combination treated groups reported spotting, vaginal discharge, and vaginal hemorrhage more frequently than the anastrozole alone treated group. These results are similar to those seen in the original sNDA submission.*

**Table 24**

#### Breakdown of the incidence of vaginal bleeding and discharge (January 25, 2002)

Details of bleeding <sup>a</sup>	Number (%) of patients					
	Anastrozole 1 mg (N = 3092)		Tamoxifen 20 mg (N = 3093)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 3098)	
Spotting	118	(3.8)	187	(6.0)	207	(6.7)
Hemorrhage	41	(1.3)	102	(3.3)	85	(2.7)
Discharge	94	(3.0)	378	(12.2)	369	(11.9)

<sup>a</sup> Patients may fall into more than 1 category.

N Number of patients treated.

Reviewer's Table

### Death

The following table shows information about death attribution and rate from the safety update. The anastrozole treatment group had the fewest deaths. No statistically significant differences occurred between treatment groups for overall death and breast cancer-related deaths. No statistically significant differences occurred between treatment groups for the specific causes of non-breast cancer-related deaths.

*Reviewer's Comment: The table below shows that after treatment deaths for anastrozole were higher than the other treatment groups. This difference is primarily due to adverse events. All case report forms for patients dying as a result of an adverse event were reviewed (during and after treatment). There was no discernable explanation for the slight increase in deaths due to an adverse event occurring after anastrozole treatment is withdrawn.*

**Table 25 Categories of Death (January 25, 2002)**

Category	Number (%) of patients					
	Anastrozole 1 mg (N = 3092)		Tamoxifen 20 mg (N = 3093)		Anastrozole 1 mg tamoxifen 20 mg (N = 3097)	
Number of patients who died <sup>a</sup>	231	(7.5)	245	(7.9)	270	(8.7)
Deaths During treatment <sup>b</sup>	71	(2.3)	90	(2.9)	70	(2.3)

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Related to breast cancer	9 (0.3)	9 (0.3)	16 (0.5)
Adverse event <sup>c</sup>	62 (2.0)	81 (2.6)	70 (2.3)
After treatment	160 (5.2)	155 (5.0)	184 (5.9)
Related to breast cancer	121 (3.9)	136 (4.4)	152 (4.9)
Adverse event <sup>c</sup>	39 (1.3)	19 (0.6)	32 (1.0)

<sup>a</sup> Number of patients who died by treatment first received.

<sup>b</sup> Death during treatment included all deaths occurring within 14 days of treatment cessation and any death as a result of an adverse event (that had an onset within 14 days of treatment cessation).

<sup>c</sup> Information derived from the cause of death form 1094.

N Number of patients treated.

The following table shows the causes of death due to adverse events occurring during treatment or within 14 days of treatment cessation where more than 10 cases were reported. In the table below information on the cause of death came from the main cause of death listed on the Statement of Death case report form or investigator determination. For example, patient #0426/0031 is listed as having sepsis (Body as A Whole) as the main cause of death; however the patient has a contributing cause of death which is acute myelogenous leukemia. The patient is listed in the table below as dying of sepsis.

The most frequent adverse event causes of death were myocardial infarction and other cancers.

*Reviewer's Comment: The information provided in the Statement of Death Adverse Event form was scant. No additional corroborating information was available for most cases. Less than 1% of these patients had autopsies. The trial did not have a separate adjudication committee to review these cases and reclassify them. In general, this reviewer did agree with the sponsor's adjudication given the scant information available.*

**Table 26 Death due to Specific Adverse Events with more than 10 events occurring during the trial or within 14 days of stopping treatment ( January 25, 2002)<sup>a</sup>**

	Anastrozole N=3092 (100%)	Tamoxifen N=3093 (100%)	Combination N=3098 (100%)
Body as a Whole <sup>b</sup>	13	21	22
Carcinoma/neoplasm	3	2	8
Cardiovascular <sup>c</sup>	32	37	35
Cerebrovascular	3	12	8
Accident/Central Nervous System Hemorrhage			
Heart Arrest/Arrhythmia	5	3	5
Heart failure/Congestive Heart Failure/ Left Ventricular Failure	5	5	6
Myocardial Infarction/Ischemia/Occlusion	6	12	11
Digestive <sup>d</sup>	13	13	9

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Gastrointestinal Carcinoma	7	9	3
Heme and Lymphatic Disorders <sup>e</sup>	2	6	4
Respiratory System <sup>f</sup>	10	14	15
Carcinoma of the lung	5	3	3
Pneumonia/Aspiration	4	4	3
Pneumonia			
Urogenital <sup>g</sup>	4	7	5

a Includes all deaths occurring during treatment or within 14 days of treatment cessation. Also includes four patients who developed a recurrence but died of a cause other than breast cancer.

b Includes sudden death, sepsis, carcinoma/neoplasm, suicide, shock, accidental injury, infection-NOS, infection -bacterial (NOS), overdose, abscess, acute abdominal syndrome, death (no other specified cause), anaphylactoid reaction, cachexia, fever

c Includes myocardial infarct/ischemia, cerebrovascular accident/infarct, heart arrest, congestive heart failure, cerebral hemorrhage, deep thrombophlebitis, pulmonary embolism, angina pectoris, arteriosclerosis, coronary artery disease, aortic stenosis, vascular anomaly/catastrophe, hypertension

d Includes gastrointestinal carcinoma, cirrhosis of liver, liver carcinoma, peptic ulcer/hemorrhage/gastrointestinal perforation, pancreatitis, head and neck cancer, cholecystitis, pyloric stenosis, vomiting

e Includes myeloma, leukemia, lymphoma, blood dyscrasia, thrombocythemia

f Includes Pneumonia/aspiration pneumonia, carcinoma of the lung, respiratory distress syndrome, bronchitis, bronchiectasis, asthma, bronchiolitis, respiratory disorder-NOS

g Includes ovarian carcinoma, kidney failure/abnormal kidney function, endometrial carcinoma, bladder carcinoma, pyelonephritis

Reviewer's Table

#### Adverse Events Leading to Withdrawal

The following table shows the specific adverse events with at least a 1% incidence that led to withdrawal of trial treatment. Investigators reported these adverse events on form 1438.

*Reviewer's Comment: The results shown below are similar to those results in the original submission with the cut-off date of June 29, 2001. No significant differences were seen for the adverse events that lead to withdrawal of trial treatment.*

**Table 27**

Specific Adverse Events Leading to Withdrawal with an Incidence of at least 1% as of January 25, 2002<sup>a</sup>

	Anastrozole (N=3092)	Tamoxifen (N=3093)	Combination (N=3098)
Body As a Whole	42 (1.4%)	49 (1.6%)	60 (1.9%)
Cardiovascular <sup>c</sup>	62 (2.0%)	107 (3.5%)	117 (3.8%)
Vasodilatation	33 (1.1%)	47 (1.5%)	54 (1.7%)
Digestive <sup>d</sup>	55 (1.8%)	55 (1.8%)	68 (2.2%)

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Nervous System <sup>e</sup>	29 (0.9%)	44 (1.4%)	44 (1.4%)
Skin and Appendages <sup>f</sup>	39 (1.3%)	49 (1.6%)	32 (1.0%)
Urogenital <sup>g</sup>	32 (1.0%)	56 (1.8%)	45 (1.5%)

a Patients may have had more than 1 adverse event leading to withdrawal.

b Includes asthenia, headache, abdominal pain, generalized edema, pain, enlarged abdomen, carcinoma, chest pain

c Includes vasodilatation, deep thrombophlebitis, thrombophlebitis, pulmonary embolus, cerebrovascular accident, myocardial infarction, hypertension, cerebral infarct,

d Includes nausea, gastrointestinal carcinoma, vomiting, diarrhea, anorexia, dry mouth, dyspepsia, constipation, gamma glutamyl transpeptidase increase

e Includes depression, insomnia, dizziness, anxiety, emotional lability, somnolence, paresthesia, abnormal thinking

f Includes rash, sweating, alopecia, pruritus, dry skin, urticaria

g Includes breast carcinoma (ipsilateral/contralateral/distant), vulvovaginitis, ovarian carcinoma, endometrial carcinoma, endometrial hyperplasia, vaginal hemorrhage, endometrial neoplasm

Reviewer's Table

#### Serious Adverse Events (SAEs)

The following updated table shows the specific serious adverse event categories.

*Reviewer's Comment: The most common serious adverse events were fractures, cataracts, deep thrombophlebitis, and arthritis. Anastrozole was associated with a greater number of fracture, cataracts, and arthritis compared with the other treatment groups. The combination was associated with a greater number of deep thrombophlebitis events than anastrozole and tamoxifen alone. Tamoxifen was associated with more cerebrovascular events than the other groups. No statistically significant differences are seen between the treatment groups in the individual categories. Similar results were observed with the serious adverse events reported as of June 29, 2001.*

**Table 28**

#### Serious Adverse Events Occurring With an Incidence of at least 0.5% in any Treatment Group During or within 14 Days of the End of Treatment (January 25, 2002)

Body system and adverse event by COSTART-preferred term <sup>a</sup>	Number (%) of patients					
	Anastrozole 1 mg (N = 3092)		Tamoxifen 20 mg (N = 3093)		Anastrozole 1 mg plus Tamoxifen 20 mg (N = 3098)	
Body as a whole						
Cellulitis	27	(0.9)	32	(1.0)	32	(1.0)
Sepsis	19	(0.6)	26	(0.8)	22	(0.7)
Accidental injury	18	(0.6)	24	(0.8)	22	(0.7)
Infection	15	(0.5)	22	(0.7)	23	(0.7)
Hernia	13	(0.4)	19	(0.6)	23	(0.7)

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<b>Carcinoma</b>	8	(0.3)	3	(<0.1)	17	(0.5)
<b>Cardiovascular</b>						
Deep thrombophlebitis	21	(0.7)	35	(1.1)	45	(1.5)
Myocardial infarct	23	(0.7)	25	(0.8)	29	(0.9)
Cerebrovascular accident	13	(0.4)		31 (1.0)	27	(0.9)
Pulmonary embolus	10	(0.3)	15	(0.5)	21	(0.7)
Congestive heart failure	17	(0.5)	13	(0.4)	19	(0.6)
Atrial Fibrillation	13	(0.4)	15	(0.5)	16	(0.5)
Angina pectoris	22	(0.7)		(0.3)	12	(0.4)
Thrombophlebitis	2	(<0.1)	5	(0.2)	15	(0.5)
<b>Digestive</b>						
Cholelithiasis	31	(1.0)	31	(1.0)	29	(0.9)
Gastrointestinal carcinoma	29	(0.9)	25	(0.8)	13	(0.4)
Gastrointestinal Disorder	22	(0.7)	10	(0.3)	8	(0.3)
Cholecystitis	8	(0.3)	13	(0.4)	19	(0.6)
<b>Musculoskeletal</b>						
Fracture	77	(2.5)	53	(1.7)	67	(2.2)
Arthritis	44	(1.4)	41	(1.3)	41	(1.3)
Joint Disorder	14	(0.5)	10	(0.3)	9	(0.3)
<b>Nervous System</b>						
Depression	7	(0.2)	6	(0.2)	14	(0.5)
<b>Respiratory system</b>						
Pneumonia	26	(0.8)	29	(0.9)	27	(0.9)
Lung Disorder	18	(0.6)	9	(0.3)	6	(0.2)
Dyspnea	9	(0.3)	4	(0.1)	17	(0.5)
<b>Skin and appendages</b>						
Skin carcinoma	26	(0.8)	24	(0.8)	26	(0.8)
<b>Special senses</b>						
Cataract specified	50	(1.6)	39	(1.3)	55	(1.8)
<b>Urogenital</b>						
Breast carcinoma	15	(0.5)	31	(1.0)	28	(0.9)
Uterine Fibroids, enlarged	4	(0.1)	15	(0.5)	18	(0.6)
Uterine Disorder	6	(0.2)	16	(0.5)	11	(0.4)
Urogenital Disorder	2	(<0.1)	17	(0.5)	12	(0.4)
Endometrial hyperplasia	0		12	(0.4)	18	(0.6)
Endometrial neoplasm	5	(0.2)	30	(1.0)	16	(0.5)

\* A patient may have had more than 1 serious adverse event.

#### Reviewer's Table

#### Adverse Events Following Withdrawal of Trial Treatment

The following updated table shows the serious adverse events that occurred in 5 or more patients after they had withdrawn from the trial (i.e., more than 14 days following cessation of trial treatment).

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*Reviewer's Comment: No statistically significant differences are seen between the treatment groups.*

**Table 29**

**Serious Adverse Events Occurring in at least 5 Patients in any Treatment Group Following Withdrawal of Trial Treatment (January 25, 2002)**

Body system and adverse event by COSTART-preferred term *	Number of patients		
	Anastrozole 1 mg (N = 3092)	Tamoxifen 20 mg (N = 3093)	Anastrozole 1 mg plus Tamoxifen 20 mg (N = 3098)
<b>Body as a Whole</b>			
Sepsis	5	2	4
<b>Cardiovascular</b>			
Pulmonary embolus	5	4	3
Congestive Heart Failure	5	2	3
Deep thrombophlebitis	1	2	7
<b>Digestive</b>			
Gastrointestinal carcinoma	4	6	2
<b>Musculoskeletal</b>			
Fracture	5	9	9
<b>Nervous System</b>			
Depression	2	5	2
<b>Respiratory</b>			
Pneumonia	4	1	7
<b>Skin and appendages</b>			
Skin carcinoma	2	7	4
<b>Urogenital</b>			
Breast Carcinoma	3	5	4

\* A patient may have had more than 1 adverse event following withdrawal of trial treatment.

Reviewer's Table

#### Cardiovascular Adverse Events

The following table shows the ischemic cardiovascular adverse events occurring during treatment or within 14 days after stopping treatment.

*Reviewer's Comment: The Anastrozole treatment group had the greatest number of cardiovascular adverse events. The majority of cardiovascular ischemic events are angina pectoris.*

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**Table 30 Ischemic Cardiovascular Adverse Events Occurring During Treatment or up to 14 Days After Stopping Treatment (June 29, 2001)<sup>a</sup>**

Cardiac Adverse Events	Anastrozole	Tamoxifen	Combination
Total Patients with an Adverse Event	76	59	68
Angina Pectoris	48/76 (63.2%)	27/59 (45.8%)	28/68 (41.2%)
Coronary Artery Disease	9/76 (11.8%)	10/59 (17%)	8/68 (11.8%)
Myocardial Infarction	21/76 (27.6%)	22/59 (37.3%)	24/68 (35.3%)
Myocardial Ischemia	10/76 (13.2%)	9/59 (15.3%)	13/68 (19.1%)

<sup>a</sup> Patients may have had more than 1 event.

#### Reviewer's Table

No significant differences existed between patients who had angina pectoris and who also had a myocardial infarction (anastrozole alone- 4 (0.1%), tamoxifen alone - 3 (0.1%), and combination - 2 (0.1%)).

#### Clinical Laboratory Data

The main ATAC trial did not collect laboratory data on hematological, chemistry, liver function, and cholesterol; however investigators reported laboratory abnormalities as adverse events.

The adverse events seen most frequently in the anastrozole alone group compared to the tamoxifen group were: hypercholesterolemia (6.0% vs. 2.2%,  $p < 0.001$  (FDA statistician) and alkaline phosphatase (1.3% vs. 0.4%).

#### Hypercholesterolemia

*Reviewer's Comment: The information collected on hypercholesterolemia is scant. The visit forms did not specifically ask for this information. The question on the visit form was "Does the patient have any other relevant medical history, Yes/No?"*

*The table below shows the information on the three-hundred and twelve patients who reported hypercholesterolemia as a current medical problem during the trial. Few of these patients (31/312, 9.9%) reported hypercholesterolemia upon trial entry and reported hypercholesterolemia as an adverse event. Thus most patients who reported hypercholesterolemia did so after trial entry and the majority of those patients were in the anastrozole arm. The percentages of the patients reporting hypercholesterolemia by treatment group were: anastrozole- 186/312 (59.6%), tamoxifen (21.8%) and the combination- 18.6%. The percentages of new patients reporting hypercholesterolemia by treatment group during the trial were: anastrozole 168/281(59.8%) tamoxifen 60/281 (21.4%) and combination 53/281(18.9%).*

*Six anastrozole patients, two tamoxifen patients, and five combination patients were on lipid-lowering medication at baseline.*

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**Table 31 Number of Patients with Hypercholesterolemia as an Adverse Event during the Trial (June 29, 2001)**

Event/Treatment Group	Hypercholesterolemia during the trial (N= 312)	Developed Hypercholesterolemia during Trial (N=281)	Hypercholesterolemia Reported Prior to Trial Entry (N=31)
Anastrozole	186 (59.6%)	168 (59.8%)	18
Tamoxifen	68 (21.8%)	60 (21.4%)	8
Combination	58 (18.6%)	53 (18.9%)	5

Reviewer's Table

*Reviewer's Comment: Approximately 65% of hypercholesterolemia patients were started on a lipid lowering medication while on trial treatment. No information exists regarding lipid lowering therapy success and concomitant use of breast cancer hormonal agents.*

The following table shows the incidence of ischemic cardiovascular events by hypercholesterolemia/hyperlipidemia by treatment received.

*Reviewer's Comment: For all treatment groups, patients reporting hypercholesterolemia/hyperlipidemia had an increased risk of an ischemic cardiovascular event.*

**Table 32**

**Number of Patients with Ischemic Cardiovascular Adverse Events, By Treatment Received and Concomitant Hypercholesterolemia and/or Hyperlipidemia**

	Anastrozole	Tamoxifen	Combination
<b>Hypercholesterolemia/Hyperlipidemia (yes)</b>	215	100	90
Had Ischemic Cardiovascular Event (yes)	12/215 (5.6%)	8 (8%)	6 (6.7%)
Had Ischemic Cardiovascular Event (no)	203/215 (94.4 %)	92 (92%)	84 (93.3%)
<b>Hypercholesterolemia/Hyperlipidemia (no)</b>	2877	2994	3007
Had Ischemic Cardiovascular Event (yes)	64/2877 (2.2%)	51/2994 (1.7%)	62/3077 (2.1%)
Had Ischemic Cardiovascular Event (no)	2813/2877 (97.8%)	2943/2994 (98.3%)	2945/3077 (97.9%)

Reviewer's Table

Age subgroup analysis

Higher incidences of hot flushes, leukorrhoea, vaginitis, weight gain, joint symptoms, and depression were observed among younger patients for all 3 treatment groups. Higher incidences of hypertension, cardiac problems related to ischemia, arterial and venous thromboembolic

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events, and fractures were observed with increasing age. No major differences were noted across all three treatment groups in the adverse event categories with respect to age.

#### Ethnic group analysis

Caucasian women accounted for 96.1% of the randomized patients in this trial. An ethnicity analysis could not be performed, because few non-Caucasian patients participated in the trial.

#### Drug-Drug Interaction

The table below shows the sponsor's post-hoc analysis of bisphosphonate use and disease-free survival rates. Bisphosphonate patients did not experience a decrease in disease-free rates compared with those patients who did not receive bisphosphonates.

*Reviewer's Comment: Because concomitant bisphosphonate and Arimidex therapy will likely be necessary for some patients, these post-hoc results should be confirmed in a trial.*

**Table 33**

Disease-free estimate <sup>b</sup>	Disease-Free Estimates According to Bisphosphonate Usage <sup>a</sup>					
	Bisphosphonates			No bisphosphonates		
	Anastrozole 1 mg  (N = 188)	Tamoxifen 20 mg  (N = 125)	Anastrozole 1 mg plus tamoxifen 20 mg  (N = 138)	Anastrozole 1 mg  (N = 2937)	Tamoxifen 20 mg  (N = 2991)	Anastrozole 1 mg plus tamoxifen 20 mg  (N = 2987)
1 year	99.5	98.4	99.3	96.9	96.8	96.5
2 years	97.3	96.8	95.6	93.2	91.8	91.6
3 years	94.3	NC	92.4	89.1	87.1	87.0
4 years <sup>c</sup>	NC	NC	NC	NC	78.6	NC

<sup>a</sup> Estimated using Kaplan-Meier methodology.

<sup>b</sup> Time to disease recurrence was defined as the time from randomization to the earliest of loco-regional or distant recurrence, new primary (contralateral) breast cancer, or death.

<sup>c</sup> All 4-year estimates should be interpreted with caution because of the small numbers of events.

N Number of patients randomized; NC Non-calculable because of a lack of events at, or after, this time point.

Reviewer's Table

#### Subprotocol Studies

For details, see the Appendix.

#### D. Adequacy of Safety Testing

This application is the tenth submission for NDA 20541. Safety data have been collected in previous submissions. The safety information collected to date is satisfactory; however because of the concerns about long term use (> 5 years) and the adverse event profile (musculoskeletal

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adverse events and hypercholesterolemia), additional long term data is important. The ATAC trial is planned for 5 years and additional follow up data beyond completion of the study should be obtained.

#### **E. Summary of Critical Safety Findings and Limitations of Data**

The major limitation of the safety findings is the duration of the study with a median of 3.1 years. The major safety findings of the ATAC trial revealed a statistically significant increase in fractures, musculoskeletal adverse events, and hypercholesterolemia compared with tamoxifen. There were no major differences in this reviewer's and the sponsor's safety analyses. The pharmacokinetic substudy results showed that concomitant administration of anastrozole and tamoxifen resulted in decreased  $C_{min}$  anastrozole levels compared with  $C_{min}$  anastrozole levels obtained when anastrozole was administered alone. Interim results from the Bone substudy demonstrated that the Arimidex patients had the greatest decrease in bone mineral density (BMD) compared with the other treatment groups. The quality of life substudy noted a statistically significant increase in reports of loss of interest in sex, vaginal dryness, and pain or discomfort with sex.

### **VIII. Dosing, Regimen, and Administration Issues**

The recommended dose of Arimidex is 1 mg daily. The ATAC trial is ongoing; thus, the optimal duration of treatment is not known for the early breast cancer indication. There are no other unresolved dosing issues. The current labeling based on previous NDA submissions recommends that the optimal duration of Arimidex therapy in the first or second line locally advanced/metastatic breast cancer treatment is until recurrence. For details concerning how the dose was determined, dose-toxicity, dose-response relationships, and study information that supported the labeling recommendations for renally impaired or hepatically impaired or elderly patients, see the original Pharmacology and Toxicology, Biopharmaceutics, and Medical Officer reviews of NDA 20-541.

### **IX. Use in Special Populations**

#### **A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

All patients enrolled in this clinical trial were postmenopausal women; thus a gender analysis cannot be performed.

#### **B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

Age

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No major differences were noted across all three treatment groups in the adverse event categories with respect to age. The subgroup analyses by age demonstrated higher incidences of hot flushes, leukorrhea, vaginitis, weight gain, joint symptoms, and depression among younger patients for all 3 treatment groups. Higher incidences of hypertension, cardiac problems related to ischemia, arterial and venous thromboembolic events, and fractures were observed with increasing age in all three treatment groups. In the current submission, most adverse events seen with elderly patients in the ATAC trial are similar to those seen in the elderly population.

#### Ethnicity

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

#### **C. Evaluation of Pediatric Program**

The sponsor submitted a pediatric waiver for Arimidex for the adjuvant treatment of postmenopausal women with breast. The Agency agrees with the sponsor request that the requirement for pediatric studies be waived.

#### **D. Comments on Data Available or Needed in Other Populations**

Because aromatase activity is not an important mechanism of estrogen generation in premenopausal women, studies in pregnant women with breast cancer are not necessary. The original NDA submission and other supplements have adequately demonstrated that dosing adjustments are not necessary for the renally impaired, hepatically impaired, or elderly patients. For details, see the original Pharmacology and Toxicology, Biopharmaceutics, and Medical Officer reviews of NDA 20-541.

### **X. Conclusions and Recommendations**

#### **A. Conclusions**

The submission contained preliminary results from one large, international, multicenter, double-blinded, randomized phase 3 trial, A Randomized, Double-blind Trial Comparing ARIMIDEX<sup>®</sup> Alone with NOLVADEX<sup>®</sup> (tamoxifen) Alone with ARIMIDEX<sup>®</sup> and NOLVADEX<sup>®</sup> in Combination, as Adjuvant Treatment in Postmenopausal Women with Breast Cancer (ATAC). Although the trial median duration of follow up of 33 months is preliminary, the trial analysis shows that anastrozole alone results in a statistically significant improvement in recurrence-free survival (recurrence is defined as recurrence (locoregional or distant), new contralateral primary, and death) over tamoxifen alone (Hazard ratio 0.83, 95.2% Confidence Interval (0.71 to 0.96) p=0.014). Results for the hormone receptor population also show a statistically significant improvement in recurrence-free survival over tamoxifen alone in (Hazard ratio 0.78, 95.2% Confidence Interval (0.65 to 0.93)).

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The preliminary efficacy results support the sponsor's first proposed indication that Arimidex is effective for the adjuvant treatment of early breast cancer in postmenopausal women. The preliminary efficacy results do not provide sufficient support for the sponsor's second proposed indication. For details, see Dr. Patricia Cortazar's efficacy review.

The major ATAC trial safety findings included an increase in fractures, musculoskeletal adverse events, and hypercholesterolemia compared with tamoxifen. Tamoxifen has been shown in randomized studies to reduce the incidence of fractures of the hip, spine, and wrist and reduce cholesterol levels. Arimidex is associated with a decrease in hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events (including deep venous thrombosis) and ischemic cerebrovascular events compared with tamoxifen.

Reducing fracture risk associated with Arimidex may be possible with concomitant use of bisphosphonate therapy; therefore, conduction of a double-blind, randomized, comparison trial using Arimidex with and without bisphosphonate therapy in early breast cancer patients with normal bone mineral density at trial entry is recommended.

#### B. Recommendations

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

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

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

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

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

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

#### Additional Risk Management Steps

The sponsor should revise the Tamoxifen label to include information about coadministration of Arimidex and Tamoxifen resulting in lower  $C_{min}$  anastrozole levels compared with  $C_{min}$  anastrozole levels resulting from administration of anastrozole alone.

### XI. Appendix

#### A. Other Relevant Materials

None

#### B. ATAC Substudies

#### Pharmacodynamic and Pharmacokinetic Interactions Substudy

**Pharmacodynamic and Pharmacokinetic Interactions Substudy - "A Randomized, Double-Blind, Trial to Assess the Pharmacokinetics of Arimidex Alone, Nolvadex (Tamoxifen) Alone or Arimidex and Nolvadex in Combination, When Used as Adjuvant Treatment for Breast Cancer in Post-Menopausal Women (10331A/0029)"**

*Reviewer's Comment: This substudy was designed to compare the steady-state trough pharmacokinetics of anastrozole, tamoxifen, and desmethyltamoxifen (major active metabolite of tamoxifen) between treatment groups. After three months of study treatment, the subprotocol required blood samples taken  $24 \pm 4$  hours after the previous dose of study drug. The primary objective was to demonstrate the equivalence of plasma tamoxifen and desmethyltamoxifen levels (between tamoxifen alone and the combination) and the equivalence of plasma anastrozole levels (between anastrozole alone and the combination). Although not prospectively designed, the sponsor performed and reported the results of a post-hoc assessment of estradiol levels in substudy patients who also enrolled in the Bone Mineral Metabolism substudy.*

*Three hundred and fifty-seven women enrolled (138 anastrozole alone, 113 tamoxifen alone and 106 combination). Ten (2.2%) patients were excluded from the analysis, because 8 did not have serum concentrations consistent with the medication they were supposed to be receiving and 2 withdrew their consent. Study results demonstrated that there was a statistically significant reduction in steady-state anastrozole  $C_{min}$  levels in the combination arm compared to the anastrozole alone arm. Coadministration of anastrozole and tamoxifen did not effect steady-state tamoxifen and desmethyltamoxifen  $C_{min}$  levels. The sponsor presented a post-hoc analysis of serum estradiol results from the Bone Mineral Density substudy for those patients enrolled in this substudy. The post-hoc analysis demonstrated similar serum estradiol levels between the anastrozole alone and combination treatment groups. The substudy information about reduced*

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*anastrozole level resulting from co-administration should be part of the anastrozole and tamoxifen labeling.*

#### Substudy Protocol

Patients were enrolled in the substudy after 3 months on the ATAC Trial. Substudy participants had to meet all of the inclusion criteria and none of the exclusion criteria for the main ATAC trial. Additionally, substudy participants had to meet the following inclusion criteria:

- 1) taking ATAC trial treatment for at least 3 months
- 2) taking their trial treatment in the mornings (for at least 3 months)
- 3) 100% compliant with regard to taking their trial treatment over the preceding 14 days
- 4) written informed consent to participate in this pharmacokinetic sub-protocol

Substudy participants were excluded if they had:

- 1) concurrent treatment with diazepam
- 2) concurrent treatment with drugs that might affect tamoxifen steady-state levels or steroid hormone status; these included ketoconazole and related compounds

Patients could withdraw from this pharmacokinetic sub-protocol (but not necessarily from the main trial) if any of the following occurred:

- 1) informed consent for this sub-protocol was withdrawn
- 2) randomized treatment was stopped for any reason other than recurrence
- 3) completion of this sub-protocol

#### Concomitant medications

In addition to the prohibited medications during the main trial, the use of diazepam was prohibited in this sub-protocol.

There were no protocol amendments. There were four administrative changes to the protocol.

*Reviewer's Comment: The administrative changes did not effect the substudy results or interpretation.*

The substudy had a blinding procedure whereby a PK identifier number was assigned to each participant in the substudy. The PK identifier number was different from the main trial number. Zeneca used the PK identifier number to process samples and report results. The sponsor was unable to link the main trial number with the PK identifier number until the main database was locked.

Patients had their blood drawn with their clinic visits.

The primary substudy endpoints were:

the steady state plasma  $C_{min}$  anastrozole concentration

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the steady state plasma  $C_{min}$  tamoxifen concentration

the steady state plasma  $C_{min}$  N-desmethyltamoxifen concentration

For details of how the assays were performed, see the Office of Clinical Pharmacology and Biopharmaceutics review of this supplement.

#### Study Results

The first substudy participant entered on June 8, 1998 and the last one finished on March 3, 1999.

Three hundred and fifty-seven women enrolled (138 anastrozole alone, 113 tamoxifen alone and 106 combination).

#### Demographics

The table below shows the distribution of demographic characteristics between treatment groups.

*Reviewer's Comment: The treatment groups were well-balanced with respect to age, weight, height, and body mass index as shown in the sponsor's table.*

**Table                      Age, sex, height, weight, body mass index, and race of patients at entry for all randomized patients, by treatment received**

Demographic characteristic	Anastrozole 1 mg (N = 138)		Tamoxifen 20 mg (N = 113)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 106)	
<b>Age (years)</b>						
n	138		113		106	
Mean (SD)	65.4 (8.9)		63.1 (9.7)		63.6 (9.3)	
Range	42.3 to 87.7		43.5 to 88.4		40.9 to 84.8	
<b>Age distribution (n [%])</b>						
<60 years	36	(26.1)	42	(37.2)	39	(36.8)
60 to                      70 years	59	(42.8)	41	(36.3)	42	(39.6)
>70 years	43	(31.2)	30	(26.5)	25	(23.6)
<b>Sex (n [%])</b>						
Male	0		0		0	
Female	138 (100.0)		113 (100.0)		106 (100.0)	
<b>Height (cm)</b>						
n	130		110		106	

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Mean (SD)	162.1 (6.7)	162.3 (5.9)	161.3 (6.7)
Range	144 to 176	146 to 178	147 to 185
<b>Weight (kg)</b>			
n	136	112	106
Mean (SD)	71.7 (14.5)	73.0 (13.8)	71.0 (13.1)
Range	47.0 to 170	50.0 to 115	43.9 to 110
<b>Body mass index (kg/m<sup>2</sup>)<sup>a</sup></b>			
n	130	110	106
Mean (SD)	27.4 (5.2)	27.6 (4.8)	27.3 (4.7)
Range			
<b>Race (n [%])</b>			
Caucasian	132 (95.7)	106 (93.8)	103 (97.2)
Black/Afro-Caribbean	2 (1.4)	1 (0.9)	1 (0.9)
Asian	1 (0.7)	1 (0.9)	0
Hispanic	1 (0.7)	1 (0.9)	0
Other <sup>b</sup>	2 (1.4)	4 (3.5)	2 (1.9)

<sup>a</sup> Body mass index was calculated by dividing body weight (in kilograms) by the square of height (in meters).

<sup>b</sup> Other includes patients of mixed race.

N Number of patients receiving treatment; n Number of patients; SD Standard deviation.

#### Reviewer's Table

Approximately 25% were over 70 years of age and 95% were Caucasian. The treatment groups were well-balanced with respect to smoking history, prior hysterectomy, and history of prior hormonal therapy.

The groups were well-balanced with respect to treatment received for breast cancer, hormone receptor status, and nodal status. For details, see sponsor's tables 4, 6, and 7 in the substudy report.

Twelve patients (3.4%) were excluded from the main analyses. Ten patients (2.2%) were excluded because serum results were not consistent with study treatment.

#### Number of excluded patients and reasons for exclusion from the primary analysis

Reason/Type of hormone	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole plus

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	(N=138)	(N=113)	Tamoxifen (N=106)
Withdrew Consent	1	0	1
Had levels of anastrozole detected (trace/clinical)	0	2	0
Had levels of tamoxifen detected (trace/clinical)	6	0	0
No detectable level of any study treatment	1	0	0
No detectable level of tamoxifen	0	0	1

Reviewer's Table

The following steady state plasma concentration results are shown in the table below.

*Reviewer's Comment: Coadministration of anastrozole and tamoxifen resulted in 26% lower mean steady-state anastrozole  $C_{min}$  level which was statistically significant when compared with the mean steady state anastrozole  $C_{min}$  level obtained in the anastrozole alone arm. Coadministration of anastrozole and tamoxifen resulted in 2.5% lower mean steady-state desmethyltamoxifen  $C_{min}$  level compared with the mean steady state desmethyltamoxifen  $C_{min}$  level obtained in the anastrozole alone arm. Coadministration of anastrozole and tamoxifen did not effect mean steady-state tamoxifen  $C_{min}$  level.*

**Table Steady-State Plasma Concentration ( $C_{min}$  [ng/mL]) of anastrozole, tamoxifen, and N-desmethyltamoxifen: main analysis population**

	Anastrozole 1 mg (N = 131)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 105)	Tamoxifen 20 mg (N = 111)
<b>Anastrozole</b>			
n	130	104	
Mean (standard deviation)	37.4 (15.2)	27.7 (11.3)	
Geometric mean (CV%)	34.7 (40.6)	25.5 (44.3)	
Ratio of geometric means.	0.73		
2-sided 90% confidence interval	0.67 to 0.80		
<b>Tamoxifen</b>			
n		99	104
Mean (standard deviation)		103.8 (45.6)	103.8 (40.9)
Geometric mean (CV%)		95.3 (43.7)	94.8 (49.2)
Ratio of geometric means.		1.01	
2-sided 90% confidence interval		0.91 to 1.11	
<b>N-desmethyltamoxifen</b>			
n		76	76
Mean (standard deviation)		293.8 (98.9)	286.6 (107.8)
Geometric mean (CV%)		277.6 (35.7)	265.1 (43.7)

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Ratio of geometric means.	1.05
2-sided 90% confidence interval	0.94 to 1.16
* Combination group:monotherapy group.	
CV Coefficient of variation.	
Sponsor's Table from page 11 of the study report	

The sponsor performed an additional analysis (not protocol specified) of serum estradiol levels for those patients who were enrolled in this substudy and the Bone Mineral Density substudy.

*Reviewer's Comment: This post-hoc analysis suggests that serum estradiol levels were similar between the anastrozole alone and combination treatment groups.*

**Table C Statistical analysis of the comparison of estradiol concentrations.**

Treatment comparison	Ratio of glsmeans <sup>b</sup>	2-sided 90% CI
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg	0.86	0.71 to 1.04
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg (excluding data from 3 outliers)	1.00	0.91 to 1.09

<sup>a</sup> Estradiol concentrations were determined in a subgroup of patients from protocol number 1033ID/0029.

<sup>b</sup> Ratio of the geometric mean concentration at 3 months to the baseline value.

CI Confidence interval; glsmean Geometric least squares mean.

Sponsor's Table from page 12 of the study report

### Lipoprotein and Blood Clotting Factors Substudy

**Lipoprotein and Blood Clotting Factors Substudy - "A Randomized, Double-Blind, Trial to Assess the Effects on Blood Lipids and Clotting Factor Biochemistry of Arimidex Alone, Nolvadex (Tamoxifen) Alone or Arimidex and Nolvadex in Combination (in Comparison to a Control Group), when used as Adjuvant Treatment for Breast Cancer in Post-Menopausal Women"**

*Reviewer's Comment: This subprotocol was opened and then closed after the lipid profile results from the combined analysis of trials -1033IL/0027 and 1033IL/0030-Tamoxifen and Anastrozole Advanced Breast Cancer Trial in Post-Menopausal Women were reviewed by the Steering Committee. Dr. Budzar commented in an Agency meeting on April 19, 2002 that only one patient had ever been enrolled in this subprotocol.*

This subprotocol was designed to assess and quantify study treatment effect on estradiol levels at 3 months and blood lipids (total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides) and clotting factors (antithrombin III, fibrinogen, and von Willebrand's factor

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levels) at 12 months and on substudy participants remaining recurrence-free at 5 and 6 years. The original protocol planned to enroll 330 women (110 in each treatment group) and compare them to an unrandomized Control group of 110 women. The Control group women had to meet the inclusion and exclusion criteria for the ATAC trial, but were neither part of the ATAC trial nor treated with hormone therapy. The primary analyses and endpoints were the change from baseline at one year for the above mentioned blood levels (except estradiol) in the treated patients.

The applicant states that the Steering Committee closed the substudy because lipid data from another study in locally advanced/metastatic breast cancer was available. The lipid results from the locally advanced/metastatic breast cancer studies (Tamoxifen and Anastrozole in Advanced Breast Cancer in Post-Menopausal Women) are below. The table below shows an increase in the mean change in total cholesterol and low density lipoprotein at 84 and 108 weeks for the anastrozole treatment group compared with the tamoxifen treatment group. The table also shows a decrease in the mean change in high density lipoprotein at 84 and 108 weeks for the anastrozole treatment group compared with the tamoxifen treatment group.

#### 164 The Effect of Anastrozole (Arimidex™) on Serum Lipids – Data from a Randomized Comparison of Anastrozole (AN) Vs Tamoxifen (TAM) in Postmenopausal (PM) Women with Advanced Breast Cancer (ABC).

Dewar J,<sup>1</sup> Nabholz J-MA,<sup>2</sup> Bonneterre J,<sup>3</sup> Buzdar A,<sup>4</sup> Robertson JFR,<sup>5</sup> Thurlmann B,<sup>6</sup> Clark G,<sup>7</sup> <sup>1</sup>Ninewells Hospital, Dundee, United Kingdom; <sup>2</sup>Cross Cancer Institute, Edmonton, AB, Canada; <sup>3</sup>Centre Oscar Lambret, Lille, France; <sup>4</sup>MD Anderson Cancer Center, Houston, TX; <sup>5</sup>City Hospital, Nottingham, United Kingdom; <sup>6</sup>Medizinische Klinik C Kantonsspital, St Gallen, Switzerland; <sup>7</sup>AstraZeneca Pharmaceuticals, Alderley Park, United Kingdom. Anastrozole is a potent and selective non-steroidal aromatase inhibitor, which reduces estradiol levels in PM women to near undetectable values. A combined analysis of two trials in PM women with ABC has shown AN to have efficacy advantages (time to progression) over TAM in ER+ve patients (Buzdar et al. ASCO 2000 P154a, Abc 609D). The impact of AN and TAM on blood lipids was also monitored during these trials. Blood samples for lipid assessment (total cholesterol (TC), triglycerides, HDL, LDL, apoprotein A, apoprotein B, and lipoprotein a) were taken at baseline, 84, and 108 weeks. Preliminary blood lipid results are shown below. No major differences were seen for the other lipid endpoints.

Blood lipid	Baseline value (mmol/l (n))		Mean change at 84 weeks (n)		Mean change at 108 weeks (n)	
	AN	TAM	AN	TAM	AN	TAM
TC	5.8 (476)	5.9 (511)	-0.3 (67)	-0.6 (55)	-0.3 (24)	-0.2 (21)
HDL	2.4 (304)	3.7 (304)	-1.0 (38)	-2.2 (36)	-2.1 (17)	-2.2 (23)
LDL	3.7 (306)	3.8 (304)	+0.2 (38)	-0.9 (36)	+0.1 (17)	-0.5 (23)

The effects of TAM were similar to that reported previously, but no major differences from effects of AN were observed. Despite its potent estradiol lowering properties, AN had no clinically detrimental effects upon blood lipids. These data suggest that clinical effects of AN due to any changes in lipid profiles are very unlikely.

Breast Cancer Research Treatment 2000; 64:51

#### Endometrial Substudy

**Endometrial Substudy- “A Randomized, Double-Blind, Trial to Assess the Incidence of Endometrial Changes with Arimidex Alone, Nolvadex (Tamoxifen) Alone or Arimidex and**

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#### **Nolvadex in Combination, when used as Adjuvant Treatment for Breast Cancer in Post-Menopausal Women (10331C/0029)"**

*Reviewer's Comment: The substudy was designed to compare the incidence of histologically confirmed endometrial abnormalities occurring after the start of study drug (tamoxifen alone versus anastrozole alone and tamoxifen alone versus the combination). Additional secondary endpoints were comparisons across all treatment groups for uterine and ovarian atypical findings (except fibroids). Odds ratios were used to compare the incidences.*

*This subprotocol study closed when the main study closed; thus, only 285 randomized patients were recruited into this substudy. Because recruitment was low (57% of necessary sample size), the substudy was not sufficiently powered to allow for conclusions to be drawn from the data. Thus, substudy results are exploratory only. No definite conclusions can be drawn to support equivalence or non-inferiority between treatments. No substudy participant developed endometrial cancer. The sponsor plans to re-evaluate the recurrence free patients at 5 and 6 years.*

#### Substudy Protocol

The substudy planned to enroll at least 500 women (sample size calculation). Substudy participants had to meet all of the inclusion criteria and none of the exclusion criteria for the main ATAC trial. Additionally, substudy participants had to meet the following inclusion criteria:

- 1) no prior treatment with tamoxifen (for any reason), unless it was started before the first surgical procedure and was received for less than 29 days
- 2) an intact uterus and no hysterectomy planned within 6 years
- 3) no previous endometrial ablation
- 4) documented written informed consent

Substudy participants underwent their baseline gynecological exam within 8 weeks of their primary therapy completion (surgery or surgery/chemotherapy) and prior to randomization. Baseline examination included transvaginal ultrasound examination for:

- 1) endometrial thickness
- 2) endometrial texture
- 3) uterine dimensions
- 4) ovaries

and hysteroscopy to biopsy any lesions and pipelle sampling.

Substudy participants underwent Year 1, 2, 5, and 6 evaluations with transvaginal ultrasound, hysteroscopy and pipelle sampling.

Substudy participants were withdrawn from this substudy if any of the following occurred:

- 1) they had any baseline endometrial lesion, other than fibroids or uterine polyps without atypia which had been completely excised
- 2) they underwent a hysterectomy for any reason
- 3) the endometrium was not accessible for hysteroscopic investigation at baseline

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- 4) they received alternative hormonal therapy for their breast cancer either in addition to, or instead of, their randomized therapy
- 5) they wished to withdraw at any time (this did not prejudice them remaining in the ATAC main trial)
- 6) they did not start randomized treatment

Thus, substudy participants found on baseline hysteroscopy and transvaginal ultrasound to have endometrial hyperplasia or cancer were excluded from the substudy. The main ATAC trial excluded women with endometrial cancer.

If breast cancer recurrence patients received alternative hormone therapy, these patients were withdrawn. Trial medication cessation did not mandate withdrawal from the substudy although the participant may have withdrawn from the main ATAC trial.

#### Concomitant Therapy

The following medication was not permitted after randomization:

- 1) cytotoxic chemotherapy
- 2) oral administration of ketoconazole (antifungal) or related compounds; topical applications were acceptable
- 3) other hormonal treatments for breast cancer

However, if patients experienced menopausal symptoms, e.g., vaginal dryness or bleeding, hot flushes, abdominal cramps, or dyspareunia, they were permitted the following:

- 1) treatment with progestins for a 3- to 6-month period, if necessary
- 2) if 6 months of progestin treatment failed to control any menopausal symptoms, HRT and/or estrogen creams could be prescribed

The four protocol amendments listed in the revised sponsor's table below.

*Reviewer's Comment: The four endometrial substudy amendments did not significantly impact substudy results. Most amendments increased the number of eligible patients and clarified terms. The fourth amendment outlined the statistical plan.*

#### Table Key details of protocol amendments

Number date	Key details of amendment	Reason for amendment
1 - 18 Apr 1997	Negative cervical cytology removed as an inclusion criterion	Negative cervical cytology results were considered to be unnecessary
	Removal of withdrawal criterion for patients who would require general anesthesia to undergo baseline	To enable patients who would prefer a general anaesthetic for each hysteroscopy to participate

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#### assessments

Grades not previously indicated as required

Update of histopathological grading

2 -11 Nov 1997

To allow centers to enter patients who had undergone hysteroscopy prior to randomization

To remove the need to reassess patients who had recently undergone these invasive procedures

Definition of fibroid type included

Clarification (requested by investigators)

Correction to formula for calculating specificity

Error in original formula

3 - 08 Jul 1998

Update of inclusion criteria

To include only patients who had not previously received tamoxifen

Amendment to visit structure

To obtain a final assessment in patients with recurrence (if none performed within previous 12 months)

Supporting analyses added for the primary endpoint

To evaluate time to endometrial abnormalities and assess robustness of conclusions

4 - 29 Nov 00

Statistical test introduced to detect superiority of anastrozole plus tamoxifen over tamoxifen if non-inferiority was concluded

Evidence from first-line trials suggested anastrozole may be superior to tamoxifen

Revision to withdrawal criteria

Failed hysteroscopies need not necessitate patient withdrawal

No adjustment for multiple comparisons

The incidence of endometrial abnormalities is a safety endpoint adjustment of p-values was not considered to be necessary

Baseline prognostic covariates modified; body mass index to replace

Body mass index provides a better indication of the build of a patient

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weight

and is therefore a more meaningful  
covariate

The first formal analysis was planned when either all patients had completed 2 years of follow-up or one of the three main trial endpoints was reached.

The primary comparison was the incidence of histologically confirmed endometrial abnormality occurring after the start of study drug (tamoxifen alone versus anastrozole alone and tamoxifen versus the combination). The secondary endpoints are the comparisons across all treatment groups for uterine and ovarian atypical findings (except fibroids). Odds ratios were used to compare the incidences.

#### Study Results

The first substudy participant entered on June 13, 1997 and the last one entered on September 3, 1999.

This subprotocol closed when the main study closed; thus, only 285 randomized patients were recruited into this substudy. Six patients did not receive study treatment and seven patients had baseline endometrial abnormalities, thus 279 patients were evaluable.

*Reviewer's Comment: Recruitment was low (57% of necessary sample size).*

The substudy treatment groups were well-balanced with respect to age, mean body weight, and percent Caucasian as shown in the revised sponsor's table below.

**Table Patient population and disposition**

	Anastrozole 1 mg (N = 99)	Tamoxifen 20 mg (N = 92)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 88)
<b>Population</b>			
Mean age (range) (years) <sup>a</sup>	60.2 (45.0 to 78.7)	60.7 (47.0 to 75.1)	59.7 (46.5 to 80.0)
Body weight (range) (kg) <sup>a</sup>	67.0 (45.0 to 101.0)	69.7 (50.0 to 116.0)	69.6 (39.0 to 104.5)
Caucasian (n [%]) <sup>b</sup>	95 (97.9)	88 (98.9)	84 (98.8)
Other	2 (2.0)	1 (1.1)	1 (1.2)
Mean BSA	26.1 ± 4.2	27 ± 4.3	27.3 ± 4.7
<b>Disposition</b>			
Withdrawal (n[%])			
At baseline due to endometrial abnormalities <sup>f</sup>	2 (2.0)	3 (3.3)	3 (3.3)
From subprotocol <sup>b,d</sup>	25 (25.8)	27 (30.3)	23 (27.1)
Primary analysis population (n[%])	97 (98.0)	89 (96.7)	85 (96.6)

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PP population (n[%])            87        (87.9)            81        (88.0)            73        (83.0)

<sup>a</sup> Summaries are for the primary analysis population (for patients with available data).

<sup>b</sup> Percentages calculated with the primary analysis population as the denominator.

<sup>c</sup> The denominator was based upon the 285 patients randomized to treatment.

<sup>d</sup> Number of patients withdrawn (by treatment first received).

N Number of patients receiving treatment.

n Number of patients.

P Per protocol.

#### Reviewer's Table

The treatment groups were well-balanced with respect to prior smoking history, anovulation risk, infertility history, parity and time since last menstrual period. For details, see sponsor's table 5 in the substudy report.

The treatment groups were not well-balanced with respect to prior hormone replacement use and oral contraceptive use as shown in table below.

*Reviewer's Comment: Prior hormone use differences would likely effect the baseline endometrial evaluation. The protocol mandated that the presence of certain baseline endometrial abnormalities required patient withdrawal. Few patients had baseline abnormalities. No significant differences occurred between groups for baseline withdrawal.*

#### Prior Hormone Use Prior to Endometrial Substudy Entry

Treatment/Type of hormone	Anastrozole 1 mg (N=99)	Tamoxifen 20 mg (N=92)	Anastrozole plus Tamoxifen (N=88)
Hormone Replacement Therapy	48 (49.5%)	28 (31.5%)	32 (37.6%)
Oral Contraceptive Use	47 (48.5%)	31 (34.8%)	40 (47.1%)

#### Reviewer's Table

The treatment groups were well-balanced with respect to breast cancer pathology, estrogen receptor (ER) positivity, nodal status, and therapy received. For details, see sponsor's tables 6, 7, 8 and 9 in the substudy report.

The table below shows systemic treatment (e.g., adjuvant chemotherapy and tamoxifen use prior to surgery) prior to randomization. The patient treated with tamoxifen prior to surgery received medication for 6 days.

#### Systemic Breast Cancer Treatment Prior to Randomization and Endometrial Substudy Enrollment

Treatment/Therapy <sup>2</sup>	Anastrozole 1	Tamoxifen 20	Anastrozole plus
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	mg (N=99)	mg (N=92)	Tamoxifen (N=88)
Adjuvant Chemotherapy <sup>1</sup>	28 (28.3%)	19 (21.3%)	26 (29.5%)
CMF	13	9	8
Anthracycline based	11	10	13
CMF + AC	4	0	4
Other	0	0	1
Tamoxifen use prior to surgery	0	0	1 (1.2%)

1 Information missing on types of chemotherapy received

2 Two additional patients are listed as receiving other therapy first followed by chemotherapy. These patients are not listed in table. One patient received CMF and the other received FEC.  
Reviewer's Table

The table below shows that mean baseline estradiol levels were similar across treatment groups. These levels were obtained prior to start of study treatment.

#### Endometrial Substudy -Baseline Estradiol Levels

Levels/Therapy	Anastrozole 1 mg (N=99)	Tamoxifen 20 mg (N=92)	Anastrozole plus Tamoxifen (N=88)
Mean	32.59	27.70	27.03
Standard Deviation	52.47	31.14	18.19
Minimum			
Maximum			

Reviewer's table

The following table shows the reasons for withdrawal from the substudy.

*Reviewer's Comment: The number of patients who withdrew was similar across treatment groups. The most frequent reason patients withdrew was listed as Investigator Discretion. Investigator Discretion withdrawals are explained in a later table.*

#### Endometrial Substudy Withdrawal Reasons

Withdrawal Reasons/Therapy <sup>1</sup>	Anastrozole 1 mg (N=99)	Tamoxifen 20 mg (N=92)	Anastrozole plus Tamoxifen (N=88)
Total	25 (25.3%)	27 (29.3%)	23 (27.1%)
Adverse Event/Intolerant to medication	2	2	3
Hysterectomy/Planned Hysterectomy	1	2	0
Informed Consent Withdrawn	9	7	4
Investigator's Discretion	7	5	10
Protocol Required (endometrial)	0	1	0

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abnormality)			
Protocol Non-Compliance	3	5	6
Technical Difficulties – (e.g., unable to perform hysteroscopy)	3	5	0

1 Five patients listed as having other for their first treatment also withdrew. Three withdrew informed consent. One had a major protocol violation and one did not comply with the protocol.  
Reviewer's Table

The following table shows the Investigator's Discretion Reasons resulting in withdrawal.

*Reviewer's Comment: No significant differences occurred between treatment groups for Investigator Discretion/withdrawal reasons.*

#### Investigator's Discretion Reasons for Endometrial Substudy Withdrawal

Investigator's Discretion/Therapy <sup>1</sup>	Anastrozole 1 mg (N=99)	Tamoxifen 20 mg (N=92)	Anastrozole plus Tamoxifen (N=88)
Total	7	5	10
Breast Cancer Recurrence	3	2	5
Cervicitis	0	0	1
Chemotherapy started	0	0	1
Death	2	0	0
Hysterectomy/Planned Hysterectomy	1	1	0
Intolerant to medication	0	1	0
Metastatic Disease	0	1	1
Stopped hormone therapy	0	0	1
Technical Difficulties – (e.g., performing hysteroscopy)	1	0	1

Reviewer's Table

The following table shows the protocol violations that occurred during the substudy.

*Reviewer's Comment: Although these patients had protocol violations, they were included in the primary analysis.*

#### Number of Patients with Endometrial Substudy Protocol Violations

Protocol Violations/Therapy <sup>A</sup>	Anastrozole 1 mg (N=99)	Tamoxifen 20 mg (N=92)	Anastrozole plus Tamoxifen (N=88)
Major	4 (4.1%)	2 (2.2%)	1 (1.2%)
No histologically proven operable	0	1 (1.1%)	0

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breast cancer			
Not postmenopausal	3 (3.1%)	1 (1.1%)	0
Received an experimental treatment 3 months before randomization	1 (1.0)	0	0
Received Neo-adjuvant Tamoxifen	0	0	1 (1.2%)
Minor	7 (7.2%)	5 (5.6%)	4 (4.7%)
Timing of chemotherapy	2 (2.1%)	1 (1.1%)	2 (2.4%)
Timing of surgery	4 (4.1%)	1 (1.1%)	1 (1.2%)
Lack of Written Informed Consent	1 (1.0%)	3 (3.4%)	1 (1.2%)

a These patients were included in the primary analysis. Major protocol violators were excluded from the per-protocol primary endpoint analyses.

Reviewer's Table

The following table shows the reasons for major protocol deviations.

*Reviewer's Comment: The majority of protocol deviations were due to HRT medication. These patients were included in the primary analysis but excluded from the per-protocol analysis.*

#### Major Protocol Deviations for the Endometrial Substudy

Protocol Deviations/Therapy <sup>1</sup>	Anastrozole 1 mg (N=99)	Tamoxifen 20 mg (N=92)	Anastrozole plus Tamoxifen (N=88)
Prior to confirmation of recurrence patient started on medication which would affect endometrium <sup>1</sup>	2	4	10
Hysteroscopy omitted at baseline	4	2	2

<sup>1</sup> Includes medications for hot flashes

Reviewer's Table

The primary analysis population consisted of all substudy patients who received trial medication and did not withdraw at Visit 1 because of endometrial abnormalities. The per-protocol analysis population consists of all substudy patients who received trial medication and did not have either major protocol violations or deviations. Minor protocol violations or deviations did not result in exclusion from the analysis populations.

#### Endometrial Substudy Patient Accounting

Populations/Therapy	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole plus Tamoxifen	Total Patients
<b>Enrolled Population<sup>a</sup></b>				285
Population that received trial	99	92	88	279

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medication				
Baseline endometrial abnormalities (protocol specified exclusion criteria)	2	3	3	8
Primary analysis population	97	89	85	271
Patients not included in sponsor's Per-protocol analysis	10	8	12	20
Death	1	0	0	1
Hysteroscopy Missing at Baseline/Informed Consent Withdrawn/ Protocol Non-compliance	4	2	2	8
Informed Consent Withdrawn	1	0	0	1
No operation for breast cancer	0	1	0	1
Not postmenopausal according to criteria	2	1	0	3
Received a drug/device that effects the endometrium <sup>b</sup>	2	4	10	16
Per Protocol Population	87	81	73	241

a Six patients who enrolled on the substudy did not receive trial medication.

b Includes Megace (hot flashes), estrogen preparations (hot flashes), chemotherapy, and intrauterine device  
Reviewer's Table

The following table shows the incidence rates for biopsy proven endometrial abnormalities at the end of the second year.

*Reviewer's Comment: The table below shows that 33% substudy patients lacked complete information. Thirty-one substudy patients (17.1%) had histologically confirmed abnormalities at the end of the second year. The combination treatment group had the most patients with abnormal endometrial biopsy results. Anastrozole alone treatment group had the least. Similar results were seen for the per-protocol analysis. Three substudy patients are not included in the table below because they have not reached their 2 year assessment at the time the sponsor's substudy report was written. It is unlikely the results from these three patients would have significantly effected the results.*

#### Table Hysteroscopy/histopathology results: primary analysis population

Hysteroscopy/histopathology in first 2 years

Treatment first received

Anastrozole 1 mg   Tamoxifen 20 mg   Anastrozole 1 mg  
plus tamoxifen 20 mg

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	(N = 97)	(N = 89)	(N = 85)
Patients with complete information	69 (71.1%)	54 (60.7%)	58 (68.2%)
Abnormal <sup>a</sup>	6 (8.7%)	9 (16.7%)	16 (27.6%)
Normal	63 (64.9%)	45 (50.6%)	42 (49.4%)
Patients with Incomplete Information <sup>b</sup>	28 (28.9%)	35 (39.3%)	27 (31.8%)

<sup>a</sup> Percentages calculated with the primary analysis population with complete information as the denominator. Note that if a patient experienced a post-baseline endometrial abnormality prior to their 2-year visit, this patient was considered to have complete information irrespective of their follow-up.

<sup>b</sup> Ninety patients (33%) total had incomplete information.

N Number of patients in the primary analysis population.

Reviewer's table

The table below shows the primary statistical analysis.

*Reviewer's Comment: The results do not show any significant differences between treatment groups. Similar results were seen for the per-protocol population.*

**Table Primary analysis of incidence of any histologically-confirmed endometrial abnormality: primary analysis population<sup>a</sup>**

Treatment comparison	Odds ratio <sup>b</sup>	2-sided 95% CI	p- value
Anastrozole 1 mg versus tamoxifen 20 mg	0.487	0.159 to 1.489	0.2070
Anastrozole 1 mg plus tamoxifen 20 mg versus tamoxifen 20 mg	1.83	0.728 to 4.617	0.1983

<sup>a</sup> Covariate adjusted analysis. <sup>b</sup> An odds ratio of <1.00 indicates that treatment with tamoxifen 20 mg is associated with a greater odds of experiencing an endometrial abnormality than the other group in the treatment comparison.

CI Confidence interval; CL Confidence limit; NA Not applicable.

Reviewer's Table

The following table shows the abnormal endometrial pathology results. The most common endometrial abnormality, a polyp without atypia, was seen in all three treatment groups. The most serious endometrial abnormality was atypical hyperplasia.

*Reviewer's Comments: Similar results were observed for the per-protocol population.*

**Abnormal Endometrial Pathology Observed in Substudy by the end of the Second Year<sup>a</sup>**

Pathology/Therapy	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole plus Tamoxifen	Total Patients
	N=65 (%)	N=48 (%)	N=52 (%)	N=165

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				(%)
Total	6 (9.2)	9 (18.8)	14 (26.9)	29 (17.6)
Abnormal Secretory Endometrium	1 (1.4)	0	3 (5.2)	4 (2.2)
Simple Hyperplasia	0	0	1 (1.7)	1 (0.6)
Complex Hyperplasia	0	0	1 (1.7)	1 (0.6)
Atypical Hyperplasia	0	1 (1.9)	0	1 (0.6)
Polyp (atypia unknown)	0	0	1 (1.7)	1 (0.6)
Polyp (no atypia)	5 (7.2)	8 (14.8)	9 (15.5)	22 (12.2)
Other <sup>b</sup>	0	0	2 (3.4)	2 (1.2)

a Evaluable Population

b Includes benign Mullerian Adenofibroma and granulomatous chronic inflammation

Reviewer's Table

The following table shows the time to first occurrence of an endometrial abnormality.

*Reviewer's Comment: There were no significant differences between treatment groups.*

#### Time to First Occurrence of an Endometrial Abnormality

Treatment Comparison	Hazard Ratio	Lower 95% confidence interval	Upper 95% confidence interval	P-value
Anastrozole versus tamoxifen	0.55	0.19	1.60	0.2715
Combination versus tamoxifen	1.90	0.80	4.51	0.1447

Reviewer's Table

The following table shows the results of the transvaginal ultrasound endometrial thickness evaluation.

*Reviewer's Comment: No significant differences existed between treatment groups for the endometrial thickness data.*

**Table Endometrial thickness (mm) assessed by TVUS: primary analysis population with baseline and 2-year data**

Month	Treatment first received		
	Anastrozole 1 mg (N = 62)	Tamoxifen 20 mg (N = 54)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 52)
Baseline			
N	62	54	52
Median	3.0	3.9	3.0

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Range			
12 months			
n	60	49	50
Median	4.0	6.0	7.0
Range			
24 months			
n	62	54	52
Median	3.0	7.0	7.0
Range			

N Number of patients in the primary analysis population with baseline and 2-year data.  
Data derived from Tables T5.5.1.2.

Sponsor's Table from page 77 of the Endometrial Substudy Report

The following table shows the substudy results for the relationship between vaginal bleeding and endometrial pathology.

*Reviewer's Comment: The substudy results suggest that the absence of bleeding does not imply the absence of pathology.*

**Table Incidence of endometrial abnormalities and vaginal bleeding: primary analysis population with complete information at 2 years**

Category	Treatment first received (n [%])		
	Anastrozole 1 mg (N = 69)	Tamoxifen 20 mg (N = 54)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 58)
Patients with an endometrial abnormality	6 (8.7)	9 (16.7)	16 (27.6)
Patients with an endometrial abnormality and vaginal bleeding	0	0	6 (10.3)

N Number of patients in the primary analysis population with complete information at 2 years.  
Data derived from Table T5.8.

Sponsor's Table from page 84 of the Endometrial Substudy Report

The following table shows the ovarian abnormalities detected at the 12 and 24 month visits.

*Reviewer's Comment: No inferences can be made from the data because there were only 8 abnormalities detected in follow up.*

**Number of Patients with Ovarian Pathology Detected at the 12 and 24 month visits<sup>a</sup>**

Pathology/Therapy	Anastrozole 1 mg N=62	Tamoxifen 20 mg N= 54	Anastrozole plus Tamoxifen N= 52
Cyst	2	3	1

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Ovarian fibroma	1	0	0
Solid mass (Possible dermoid)	0	1	0

a Patients were counted once. One anastrozole patient had a right ovarian cyst and left ovarian fibroma. One anastrozole patient had bilateral ovarian cysts.

Reviewer's Table

### Bone Mineral and Metabolism Substudy

**Bone Mineral and Metabolism Substudy- A Randomized, Double-Blind, Trial to Assess the Effects on Bone Mineral Density and Metabolism of Arimidex Alone, Nolvadex (Tamoxifen) Alone or Arimidex and Nolvadex in Combination (in Comparison to a Control Group), when used as Adjuvant Treatment for Breast Cancer in Post-Menopausal Women (1033ID/0029)**

*Reviewer's Comment: This subprotocol was designed to compare radiological films and laboratory bone turnover markers between the three treatment groups and a control group not receiving hormone therapy. The subprotocol required laboratory evaluation of bone turnover markers (plasma bone alkaline phosphatase, urinary free deoxyypyridolone crosslinks, urinary cross-linked N-telopeptides of type I collagen) at baseline, 3, 6 and 12 months; and dual-energy X-ray absorptiometry (DEXA) scans of total hip and lumbar spine at baseline, 12 and 24 months. DEXA scans were required if patients withdrew or recurred or were recurrence-free at 5 years. Patients were followed for at least two years. The primary endpoint was a comparison of bone mineral density (BMD) in all four arms (including control) at 2 years. Secondary endpoints included biochemical bone turnover markers. The application has data from the 12-month data point only. Two year data will be available in 2003.*

*Three hundred and eight substudy treatment patients and 46 control patients were enrolled. The 308 substudy treatment patients were further subdivided into 92 anastrozole alone patients, 105 tamoxifen alone patients, 103 combination patients, and 8 patients who received no study treatment. The treatment groups in order of greatest decrease to greatest increase in radiological bone mineral density were anastrozole alone, control group, combination and tamoxifen alone. The results show statistically significant differences in favor of tamoxifen alone when compared with anastrozole alone for change in hip and change in lumbar spine bone mineral density at 12 months. Bone biochemical markers showed increased bone resorption and formation with anastrozole when compared with the other treatment groups. The substudy results did not include T scores.*

#### Protocol definitions

Term	Definitions and Commentary
Densitometric osteoporosis	Diagnostic classification of osteoporosis was based on criteria, with bone density values being expressed in relation to the mean reference value in premenopausal women (T-score)

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<b>Osteopenia</b>	a T-score between -1 and -2.5 and could constitute an indication for prophylaxis depending upon the age of the woman and the risks and benefits of the proposed treatment
<b>Osteoporosis</b>	<p>a T-score below -2.5 and included nearly all women who would sustain a fragility fracture. It was regarded as an absolute indication for intervention</p> <p>A reduction in bone mineral density over a 2-year period of either 10% in the lumbar spine and/or 15% in total hip; this included patients who had this reduction after the 1-year scan</p>
<b>Per-protocol population</b>	A secondary per-protocol analysis was performed, excluding patients with major protocol violations and/or deviations
<b>Primary analysis</b>	This population consisted of data from all patients who were in the BMD sub-protocol while receiving trial therapy; ATAC patients who did not receive trial therapy and control patients were not included in this population. Patients withdrawn from this sub-protocol at baseline as a result of osteoporosis (or osteopenia) with no further DEXA-scan measurements available were excluded from this population.

#### Substudy Protocol

This subprotocol, "A Randomized, Double-Blind, Trial to Assess the Effects on Bone Mineral Density and Metabolism of Arimidex Alone, Nolvadex (Tamoxifen) Alone or Arimidex and Nolvadex in Combination (in Comparison to a Control Group), when used as Adjuvant Treatment for Breast Cancer in Post-Menopausal Women (1033ID/0029)", planned to enroll 260 ATAC trial participants and a control group of 86 postmenopausal early breast cancer patients not on hormone therapy.

The ATAC/Bone Mineral Density subprotocol patients and control patients had to meet the inclusion and exclusion criteria for the main ATAC trial. Substudy protocol did not require the control patients to have completed surgery or chemotherapy to enroll. The following additional exclusion criteria were required for both the treatment and control groups:

- 1) patients who had received HRT within the 12 months prior to randomization
- 2) patients who had received bisphosphonate therapy within the 12 months prior to randomization
- 3) patients who had a bone fracture within the 6 months prior to randomization
- 4) patients who had chronic renal/liver impairment
- 5) patients with malabsorption syndrome
- 6) patients with any of the following endocrine disorders: hyperparathyroidism, untreated thyroid disease, Cushing's syndrome, pituitary disease
- 7) patients who took anti-convulsant therapy
- 8) patients who took corticosteroids

Patients could withdraw from the substudy for the following reasons:

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- 1) Patients developed osteoporosis, defined as a reduction in BMD over a 2-year period either 10% in the lumbar spine and/or 15% in total hip: this included patients who had this reduction after the 1-year scan.
- 2) Patients were confirmed as having severe osteoporosis at baseline, 1 year, or 2 years defined in the criteria for the diagnosis of osteoporosis. However, if a patient had a T-score of -2.5, that patient was considered to be borderline and the presence of associated fragility fractures was to be ruled out. If the presence fragility fractures was confirmed, the patient was to be withdrawn. However, patients who had a T-score of -2.5 without associated fragility fractures were permitted to continue in the sub-protocol. (T-scores were calculated based upon BMD assessments of a 30-year-old healthy woman at the time of her peak bone mass.)
- 3) Patients commenced any of the prohibited concomitant treatments as defined in the protocol.
- 4) Patients wished to withdraw at any time.
- 5) Patients developed skeletal metastases in any part of the L1 to L4 lumbar spine or total hip region.
- 6) Patients received bisphosphonate therapy.
- 7) Patients did not receive randomized treatment (for patients from the ATAC main trial only)
- 8) Patients died.

#### Concomitant Medication

The substudy protocol excluded any concomitant medication that was excluded from use during the ATAC main trial and the concomitant use of bone resorption inhibitors, HRT (unless permitted in the main ATAC trial), and corticosteroids.

There were three protocol amendments and two administrative changes during the substudy.

*Reviewer's Comment: The administrative changes and most protocol amendments did not impact on the endpoints or their analysis. However, the third protocol amendment permitted data analysis at one year and removed the adjustments for multiplicity because there were only safety analyses in this subprotocol. These changes did not effect the interim substudy results.*

**Table 3 Key details of protocol amendments**

Number	Effective date	Key details of amendment	Reason for amendment
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1	15 Jan 1999	<p>Baseline assessments should be carried out after primary surgery and chemotherapy (if given) but must be prior to the start of randomized therapy; patients not receiving chemotherapy would start treatment within 8 weeks of surgery</p> <p>Patients who are recurrence-free at 5 years will have a further DEXA scan</p> <p>Added criteria for the diagnosis of osteoporosis</p>	<p>Clarification</p> <p>To add to the respective safety databases for anastrozole and tamoxifen</p> <p>Clarification</p>
2	21 Jan 2000	<p>To amend sub-protocol endpoints from the completion of 24-month DEXA scan to completion of 60-month DEXA scan and include withdrawal of patients if their disease recurred after the 24-month DEXA scan</p> <p>To clarify that patients who are confirmed as having severe osteoporosis at baseline, 1 year, or 2 years with associated fragility fractures or who developed osteoporosis after 1 or 2 years or metastases in any part of the L1 to L4 lumbar region should be withdrawn</p> <p>To amend sections on statistical comparison and endpoints, and statistical methods</p>	<p>Interim data available to support 5-year treatment option</p> <p>Clarification of reasons for withdrawal of patients</p> <p>Clarification of the statistical methods to be used for the primary analysis of BMD and the secondary analyses</p>

**Table 3 Key details of protocol amendments**

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Number	Effective date	Key details of amendment	Reason for amendment
3	25 Sep 2000	<p>Two secondary objectives deleted (i. to assess at 2 years, the change in BMD associated with adjuvant therapy with anastrozole or anastrozole plus tamoxifen followed by any prescribed treatment post-recurrence, compared to adjuvant therapy with tamoxifen followed by any prescribed treatment post-recurrence; ii. to explore the profiles of the change in BMD over time for each treatment group during the 2-year trial period)</p> <p>Timing of the first formal analysis will be performed when all patients in the sub-protocol have completed the 1-year visit or reached one of the other sub-protocol end points</p> <p>Remove the adjustments for multiple comparisons since BMD is a safety endpoint</p> <p>To amend sections on statistical comparisons and endpoints, and statistical methods.</p>	<p>Objectives deleted for the following reasons; i. the population was the same as the primary objective; ii. no additional information would be gained from the analysis</p> <p>Clarification</p> <p>Adjusting the resulting p-values to allow for multiple comparisons may result in the rejection of an important safety difference</p> <p>Clarification</p>

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The primary endpoint was the change in BMD (for lumbar spine and total hip) from baseline while receiving trial therapy as measured by DEXA. The secondary endpoints were changes in the following biochemical markers:

- 1) immunoreactive free urinary deoxypyridoline crosslinks (iFDPD)
- 2) urinary crosslinked N-telopeptides of type I bone collagen (NTX)
- 3) serum bone isoform of alkaline phosphatase (i Bone ALP)

Bone resorption biomarkers are urinary iFDPD and NTX levels and bone formation biomarker is serum i Bone ALP.

#### BMD measurements

The lumbar spine DEXA measurement was the average of the L1, L2, L3, and L4 values. If measurement of 1 of the components was not possible, then BMD was calculated using the remaining components.

The total hip BMD was the average of the values for the trochanteric, intertrochanteric, and femoral neck regions of the hip. If subsequent measurements of 1 of these components was not possible, then BMD was calculated using the other components.

#### Study Results

The first substudy participant entered on June 10, 1998 and the last one entered on June 24, 2000.

Three hundred and eight substudy treatment patients and 46 control patients were enrolled. The 308 substudy treatment patients were 92 anastrozole patients, 105 tamoxifen patients, 103 combination patients, and 8 patients who received no study treatment. These 8 patients were excluded from the analyses.

#### Demographics

The sponsor's table below shows the distribution of demographic characteristics between treatment groups for patients in the primary analysis. Most patients were Caucasian.

*Reviewer's Comment: The treatment groups were fairly well-balanced with respect to age, weight, height, body mass index, and race. Fewer patients aged less than 60 were in the anastrozole alone treatment group.*

**Table**            **Age, sex, height, weight, body mass index, and race of patients at entry: primary analysis population and eligible controls**

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Demographic characteristic	Anastrozole 1 mg (N = 80)		Tamoxifen 20 mg (N = 87)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)		Control (N = 39)			
<b>Age (years)</b>										
n	80		87		82		39			
Mean (SD)	64.7 (8.8)		63.6 (8.2)		64.4 (8.5)		64.2 (7.6)			
Range	46.0 to 86.1		46.8 to 81.2		42.2 to 84.0		52.2 to 79.2			
<b>Age distribution (n [%])</b>										
<60 years	21	(26.3)	32	(36.8)	22	(26.8)	16	(41.0)		
60 to 70 years	34	(42.5)	29	(33.3)	41	(50.0)	13	(33.3)		
>70 years	25	(31.3)	26	(29.9)	19	(23.2)	10	(25.6)		
<b>Sex (n [%])</b>										
Male	0		0		0		0			
Female	80 (100.0)		87 (100.0)		82 (100.0)		39 (100.0)			
<b>Height (cm)</b>										
n	75		84		80		39			
Mean (SD)	162.0 (6.7)		160.0 (6.7)		162.0 (7.8)		164.2 (6.1)			
Range	151 to 180		149 to 178		136 to 185		148 to 175			
<b>Weight (kg)</b>										
n	75		85		80		39			
Mean (SD)	75.9 (16.4)		75.6 (14.0)		76.9 (14.9)		73.5 (9.9)			
Range	47 to 140		41 to 117		48 to 124		54 to 95			
<b>Body mass index (kg/m<sup>2</sup>)</b>										
n	74		84		79		39			
Mean (SD)	29.0 (6.3)		29.5 (5.8)		29.4 (6.0)		27.3 (3.6)			
Range										
<b>Race (n [%])</b>										
Caucasian			70	(87.5)	78	(89.7)	75	(91.5)	39	(100)
Black/Afro-Caribbean			0		1	(1.1)	2	(2.4)	0	
Hispanic			2	(2.5)	0		0		0	

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Others <sup>a</sup>	6	(7.5)	7	(8.0)	4	(4.9)	0
Not recorded	2	(2.5)	1	(1.1)	1	(1.2)	0

<sup>a</sup> Body mass index was calculated by dividing body weight (in kilograms) by the square of height (in meters).

<sup>b</sup> Other includes patients of mixed race.

N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients; SD Standard deviation.

#### Reviewer's Table

The table shows the distribution according to pertinent prior medical history for those patients included in the primary analysis. Smoking history is associated with increased osteoporosis risk. Estrogen therapy is associated with decreased risk.

*Reviewer's Comment: While differences exist between treatment groups for smoking history and prior HRT, it is unclear whether the differences would have effected the study results.*

**Table Medical history: primary analysis population and eligible controls**

Medical history	Anastrozole 1 mg (N = 80)	Tamoxifen 20 mg (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)	Control (N = 39)
<b>Ever smoked</b>				
Yes	38 (47.5)	37 (42.5)	45 (54.9)	13 (33.3)
No	42 (52.5)	50 (57.5)	37 (45.1)	26 (66.7)
<b>Hysterectomy</b>				
Yes	18 (22.5)	21 (24.1)	21 (25.6)	11 (28.2)
No	62 (77.5)	66 (75.9)	61 (74.4)	28 (71.8)
<b>Previous HRT</b>				
Yes	9 (11.3)	16 (18.4)	16 (19.5)	1 (2.6)
No	71 (88.8)	71 (81.6)	66 (80.5)	38 (97.4)

N Number of patients in the primary analysis population or number of eligible control patients.

#### Reviewer's Table

The following table below shows the time since the last menstrual period (LMP) for all four groups for those patients included in the primary analysis.

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*Reviewer's Comment: There is an imbalance in the time since last menstrual period < 1 year. More anastrozole alone patients had their LMP within the year prior to substudy entry.*

**Table Time since last menstrual period: primary analysis population and eligible controls**

Time since last menstrual period	Anastrozole 1 mg (N = 80)		Tamoxifen 20 mg (N = 87)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)		Control (N = 39)	
	<1 year	11	(13.8)	2	(2.3)	4	(4.9)	0
1 to 2 years	2	(2.5)	3	(3.4)	3	(3.7)	1	(2.6)
2 to 3 years	1	(1.3)	4	(4.6)	0		1	(2.6)
3 to 4 years	0		3	(3.4)	1	(1.2)	0	
>4 years	66	(82.5)	75	(86.2)	74	(90.2)	36	(92.3)
Unknown	0		0		0		1	(2.6)

N Number of patients in the primary analysis population or number of eligible control patients.

Reviewer's Table

The treatment groups were fairly well-balanced with respect to treatment received for breast cancer (except primary breast surgery), hormone receptor status, and nodal status. A greater percentage of anastrozole patients received breast conservation therapy compared with other treatment groups and fewer anastrozole patients had positive nodes; however, these differences are unlikely to have effected substudy results. For details, see sponsor's tables 8, 9, 10, and 11.

The table below shows the numbers of patients and their status. Most patients were withdrawn at baseline because they were osteopenic or osteoporotic.

**Table Status of randomized patients as of the data cut-off (1-year visit)**

Patient status	Number (%) of patients							
	Anastrozole 1 mg		Tamoxifen 20 mg		Anastrozole 1 mg plus tamoxifen 20 mg		Control	
Randomized to treatment	94	(100.0)	109	(100.0)	105	(100.0)	46*	(100.0)
Received trial treatment	92	(97.9)	105	(96.3)	103	(98.1)	NA	
Withdrawn at baseline	14	(14.9)	22	(20.2)	23	(21.9)	7	(15.2)
Treatment not started	2	(2.1)	4	(3.7)	2	(1.9)	NA	
Withdrawn from sub-protocol	10	(10.6)	17	(15.6)	17	(16.2)	1	(2.2)
Continuing sub-protocol	70	(74.5)	70	(64.2)	65	(61.9)	38	(82.6)

\* The control group consisted of non-randomized patients who did not receive hormonal therapy.

NA Not applicable.

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#### Reviewer's Table

The primary analysis included two hundred and forty-nine patients (80.8% enrolled). The per-protocol analysis included two hundred and fifteen patients (69.8%). The table below gives the numbers of patients and reasons for exclusion.

*Reviewer's Comment: The sponsor did not always differentiate osteoporosis from osteopenia consistently. In some cases patients with a T score less than 2.5 were called osteopenic and in others osteoporotic.*

#### Number of patients and reasons for which patients were excluded from the primary analysis

Reason/Type of hormone	Anastrozole 1 mg (N=94)	Tamoxifen 20 mg (N=109)	Anastrozole plus Tamoxifen (N=105)	Control (N=46)
Total excluded from primary analysis	14 (14.9%)	22 (20.2%)	23 (21.9%)	7 (15.2%)
Did not receive trial medication/withdrew consent	2	3	2	N/A
Patient Osteopenic or Osteoporotic at Baseline	12	19	21	7
Primary Analysis Population	80	87	82	39
Additional patients excluded from per-protocol analysis <sup>a,b</sup>	11	12	11	0 <sup>d</sup>
Another malignancy	1	0	0	0
Baseline Data Missing	1	3	2	0
Not post-menopausal	0	0	1	0
Received Chemotherapy	1	0	0	0
Received Corticosteroids	3	6	5	0 <sup>d</sup>
Received experimental or non-approved medication within last 3 months for a medical condition	2	1	1	0
Received hormone replacement therapy within the last 12 months prior to start of trial	0	3	1	0
Received Medication for Hot flashes	1	0	1	0
Received medication likely to effect bone mineral density <sup>f</sup>	2	1	0	0
Per Protocol Population	69	75	71	39

<sup>a</sup> Most patients had a major protocol violation.

<sup>b</sup> Patients could have more than 1 reason.

<sup>c</sup> One tamoxifen alone patient also received Evista.

<sup>d</sup> One control patient (0210/5009) who received corticosteroids was not excluded from the per-protocol analysis.

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#### Reviewer's Table

The primary endpoint was a comparison of bone mineral density (BMD) in all four arms (including control). The table below shows the results for the primary endpoint of change in lumbar spine.

*Reviewer's Comment: The revised sponsor's table shows that the change in BMD was the greatest for the anastrozole. Anastrozole alone patients had 2.3% median decrease in bone mineral density. Control patients had 1.3% median decrease in bone mineral density. Tamoxifen patients had 1.1% median increase in bone mineral density.*

**Table Percentage change in lumbar spine BMD from baseline to 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Anastrozole 1 mg (N = 80)	Tamoxifen 20 mg (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)	Control (N = 39)
n	73	71	64	38
Median	-2.27	1.06	0.09	-1.27
Range	—————			

N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients with data at baseline and Month 12.

#### Reviewer's Table

The sponsor's analysis of the geometric means of the change in lumbar spine BMD demonstrated a statistically significant difference between anastrozole and tamoxifen ( $p < 0.0001$ ). The sponsor's analysis of the geometric means of the change in lumbar spine BMD did not demonstrate a statistically significant difference between anastrozole and the combination.

*Reviewer's Comment: The sponsor's analysis may have minimized the change difference in lumbar spine density because it uses geometric means. Nonetheless, the data show that the difference in percentage change in lumbar spine density with anastrozole alone is statistically significantly different compared with tamoxifen.*

The sponsor's table below shows the percent change in lumbar spine BMD.

*Reviewer's Comment: Anastrozole alone patients were more likely to experience bone loss than patients in other treatment groups. The table below shows that the percentages of patients in each treatment arm having a decrease in BMD were 75.4%-anastrozole, 65.3%-control, 45.3%-*

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combination, and 40.9%-tamoxifen. The table below shows that the percentages of patients having an increase in BMD were 24.7% -anastrozole, 36.9%-control, 54.7%-combination, and 59.2%-tamoxifen.

**Table                    Extent of change in lumbar spine BMD from baseline to 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline		Number (%) of patients							
		Anastrozole 1 mg (N = 80)		Tamoxifen 20 mg (N = 87)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)		Control (N = 39)	
<b>n</b>		73		71		64		38	
<b>Increase</b>									
0% to < 3%	3%	14	(19.2)	21	(29.6)	21	(32.8)	8	(21.1)
3% to < 6%	6%	3	(4.1)	14	(19.7)	11	(17.2)	2	(5.3)
		1	(1.4)	7	(9.9)	3	(4.7)	4	(10.5)
<b>Decrease</b>									
>0% to 3%		24	(32.9)	18	(25.4)	17	(26.6)	15	(39.5)
>3% to 6%		23	(31.5)	9	(12.7)	10	(15.6)	7	(18.4)
>6%		8	(11.0)	2	(2.8)	2	(3.1)	2	(5.3)

\* Percentages derived from numbers of patients with data at both time points.

N Number of patients in the primary analysis population or number of eligible control patients;

n Number of patients with data at baseline and Month 12.

Data derived from Table T5.1.3.

Sponsor's Table from p. 78 of the Bone Mineral Density substudy report

The sponsor's table below shows the percentage change in total hip BMD for the treatment groups and control group.

*Reviewer's Comment: Anastrozole alone treated patients experience a decrease in total hip BMD compared to the other patients.*

**Table                    Percentage change in total hip BMD from baseline to 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Anastrozole	Tamoxifen	Anastrozole	Control
	1 mg (N = 80)	20 mg (N = 87)	1 mg plus tamoxifen 20 mg (N = 82)	(N = 39)
<b>N</b>	73	71	62	39

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Median            -1.50                      0.85                      1.16                      0.21

Range

N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients with data at baseline and Month 12.

Data derived from Table T5.2.2.

Sponsor's Table from p. 86 of the Bone Mineral Density substudy report

The sponsor's analysis of the geometric means of the change in total hip BMD demonstrated a statistically significant difference between anastrozole and tamoxifen ( $p < 0.0002$ ). The sponsor's analysis of the geometric means of the change in total hip BMD did not demonstrate a statistically significant difference between anastrozole and the combination.

*Reviewer's Comment: The sponsor's analysis may have minimized the change difference in total hip density because it uses geometric means. Nonetheless, the data show that the difference in percentage change in total hip density with anastrozole alone is significant compared with tamoxifen.*

The sponsor's table below shows the distribution of percent change in total hip BMD.

*Reviewer's Comment: Anastrozole alone patients were more likely to experience bone loss than patients in other treatment groups. The table below shows that the percentages of patients in each arm having a decrease in total hip BMD were 74.0%-anastrozole, 41.0%-control, 37.1%-combination, and 36.6%-tamoxifen. The table below shows that the percentages of patients in each arm having an increase in BMD were 26.0%-anastrozole, 58.9%-control, 62.9%-combination, and 63.4%-tamoxifen.*

**Table                      Extent of change in total hip BMD from baseline to 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Number (%) of patients							
	Anastrozole 1 mg (N = 80)		Tamoxifen 20 mg (N = 87)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)		Control (N = 39)	
n	73		71		62		39	
<b>Increase</b>								
0% to < 3%	3%	15 (20.5)	31 (43.7)	25 (40.3)	19 (48.7)			
3% to < 6%	6%	4 (5.5)	11 (15.5)	12 (19.4)	2 (5.1)			
6%		0	3 (4.2)	2 (3.2)	2 (5.1)			
<b>Decrease</b>								

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>0% to 3%	34	(46.6)	17	(23.9)	16	(25.8)	10	(25.6)
>3% to 6%	17	(23.3)	6	(8.5)	7	(11.3)	5	(12.8)
>6%	3	(4.1)	3	(4.2)	0		1	(2.6)

\* Percentages derived from numbers of patients with data at both time points

N Number of patients in the primary analysis population or number of eligible control patients;

n Number of patients with data at both time points.

Data derived from Table T5.2.3.

Sponsor's Table from p. 88 of the Bone Mineral Density substudy report

The sponsor performed adjusted and unadjusted secondary analyses of the change in geometric means of the lumbar spine and total hip BMD using the primary and per-protocol populations. The analyses demonstrated a statistically significant difference between anastrozole and tamoxifen but not between tamoxifen and the combination. For details, see sponsor's tables 25 and 32 in the study report.

The sponsor performed additional exploratory analyses assessing percent change in total hip BMD by treatment group and years since LMP or age. The results support the observation that anastrozole use is associated with a tendency for a decrease in BMD over 12 months. For details see sponsor's tables 33 and 34 in the study report.

Substudy secondary endpoints included biochemical bone turnover markers. Urinary levels of iFDPD and NTX are markers of bone resorption and i bone ALP is a marker of bone formation.

Baseline levels of iFDPD, NTX and i bone ALP were comparable for all groups. For details, see sponsor's tables 35, 38, and 41 in the study report. The following three sponsor's tables demonstrate the changes over time for all three biochemical bone markers.

*Reviewer's Comment: The final result from the bone remodeling processes of resorption and formation depends upon which process predominates. The anastrozole treatment arm was associated with the greatest number and percentage of patients with increases in iFDPD, NTX and i bone ALP.*

**Table                      Extent of change in iFDPD levels from baseline to 3, 6, and 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Number (%) of patients *			
	Anastrozole 1 mg  (N = 80)	Tamoxifen 20 mg  (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg  (N = 82)	Control   (N = 39)

**3 months**

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n	69	70	68	31
<b>Increase</b>				
0% to <30%	28 (40.6)	10 (14.3)	12 (17.6)	10 (32.3)
30% to <60%	2 (2.9)	2 (2.9)	2 (2.9)	0
60%	6 (8.7)	1 (1.4)	1 (1.5)	0
<b>Decrease</b>				
>0% to 30%	25 (36.2)	34 (48.6)	35 (51.5)	15 (48.4)
>30% to 60%	8 (11.6)	23 (32.9)	17 (25.0)	6 (19.4)
>60%	0	0	1 (1.5)	0
<b>6 months</b>				
n	66	68	64	30
<b>Increase</b>				
0% to <30%	20 (30.3)	4 (5.9)	7 (10.9)	10 (33.3)
30% to <60%	7 (10.6)	4 (5.9)	4 (6.3)	1 (3.3)
60%	5 (7.6)	1 (1.5)	1 (1.6)	0
<b>Decrease</b>				
>0% to 30%	25 (37.9)	30 (44.1)	34 (53.1)	13 (43.3)
>30% to 60%	8 (12.1)	27 (39.7)	18 (28.1)	5 (16.7)
>60%	1 (1.5)	2 (2.9)	0	1 (3.3)
<b>12 months</b>				
n	60	63	59	31
<b>Increase</b>				
0% to <30%	21 (35.0)	5 (7.9)	10 (16.9)	6 (19.4)
30% to <60%	5 (8.3)	1 (1.6)	0	2 (6.5)
60%	4 (6.7)	1 (1.6)	2 (3.4)	1 (3.2)
<b>Decrease</b>				
>0% to 30%	22 (36.7)	18 (28.6)	27 (45.8)	16 (51.6)
>30% to 60%	8 (13.3)	38 (60.3)	19 (32.2)	6 (19.4)
>60%	0	0	1 (1.7)	0

\* Percentages derived from numbers of patients with data at both time points.

iFDPD Free urinary deoxypyridoline crosslinks; N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients with data at both time points.

Data derived from Table T6.1.3.

Sponsor's Table from p. 99 of the Bone Mineral Density substudy report

**Table                    Extent of change in NTX levels from baseline to 3, 6, and 12 months: primary**

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### analysis population and eligible controls with data at both time points

Percentage change from baseline	Number (%) of patients.							
	Anastrozole 1 mg (N = 80)		Tamoxifen 20 mg (N = 87)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)		Control (N = 39)	
<b>3 months</b>								
n	71		71		68		34	
<b>Increase</b>								
0% to <30%		35 (49.3)	14 (19.7)	7 (10.3)	6 (17.6)			
30% to <60%	60%	9 (12.7)	1 (1.4)	0	6 (17.6)			
60%		4 (5.6)	0	0	1 (2.9)			
<b>Decrease</b>								
>0% to 30%		21 (29.6)	24 (33.8)	30 (44.1)	14 (41.2)			
>30% to 60%		2 (2.8)	31 (43.7)	30 (44.1)	7 (20.6)			
>60%		0	1 (1.4)	1 (1.5)	0			
<b>6 months</b>								
n	69		68		66		31	
<b>Increase</b>								
0% to <30%		24 (34.8)	4 (5.9)	6 (9.1)	8 (25.8)			
30% to <60%	60%	16 (23.2)	0	1 (1.5)	1 (3.2)			
60%		6 (8.7)	0	0	0			
<b>Decrease</b>								
>0% to 30%		17 (24.6)	29 (42.6)	21 (31.8)	12 (38.7)			
>30% to 60%		5 (7.2)	30 (44.1)	33 (50.0)	10 (32.3)			
>60%		1 (1.4)	5 (7.4)	5 (7.6)	0			
<b>12 months</b>								
n	63		66		61		35	
<b>Increase</b>								
0% to <30%		16 (25.4)	6 (9.1)	8 (13.1)	9 (25.7)			
30% to <60%	60%	15 (23.8)	1 (1.5)	2 (3.3)	2 (5.7)			
60%		8 (12.7)	3 (4.5)	1 (1.6)	2 (5.7)			
<b>Decrease</b>								
>0% to 30%		22 (34.9)	17 (25.8)	18 (29.5)	15 (42.9)			
>30% to 60%		1 (1.6)	33 (50.0)	24 (39.3)	7 (20.0)			
>60%		1 (1.6)	6 (9.1)	8 (13.1)	0			

\* Percentages derived from numbers of patients with data at both time points.

N Number of patients in the primary analysis population or number of eligible control patients; n Number

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of patients with data at both time points; NTX Urinary crosslinked N-telopeptides.

Data derived from Table T6.2.3.

Sponsor's Table from p. 104 of the Bone Mineral Density substudy report

**Table                    Extent of change in i Bone ALP levels from baseline to 3, 6, and 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline		Number (%) of patients							
		Anastrozole 1 mg (N = 80)		Tamoxifen 20 mg (N = 87)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)		Control (N = 39)	
<b>3 months</b>									
n		72		74		68		32	
<b>Increase</b>									
0% to <30%	60%	39	(54.2)	28	(37.8)	23	(33.8)	19	(59.4)
30% to <60%		9	(12.5)	3	(4.1)	3	(4.4)	2	(6.3)
>60%		2	(2.8)	1	(1.4)	0		0	
<b>Decrease</b>									
>0% to 30%		20	(27.8)	37	(50.0)	39	(57.4)	10	(31.3)
>30% to 60%		2	(2.8)	5	(6.8)	3	(4.4)	1	(3.1)
<b>6 months</b>									
n		69		69		67		30	
<b>Increase</b>									
0% to <30%	60%	30	(43.5)	17	(24.6)	16	(23.9)	15	(50.0)
30% to <60%		17	(24.6)	4	(5.8)	4	(6.0)	2	(6.7)
>60%		6	(8.7)	0		0		0	
<b>Decrease</b>									
>0% to 30%		15	(21.7)	42	(60.9)	38	(56.7)	12	(40.0)
>30% to 60%		1	(1.4)	6	(8.7)	9	(13.4)	1	(3.3)
<b>12 months</b>									
n		67		65		62		31	
<b>Increase</b>									
0% to <30%		30	(44.8)	12	(18.5)	17	(27.4)	15	(48.4)

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30% to <	60%	11	(16.4)	1	(1.5)	2	(3.2)	2	(6.5)
60%		13	(19.4)	2	(3.1)	2	(3.2)	1	(3.2)
<b>Decrease</b>									
>0% to 30%		11	(16.4)	38	(58.5)	29	(46.8)	13	(41.9)
>30% to 60%		2	(3.0)	12	(18.5)	12	(19.4)	0	

\* Percentages derived from numbers of patients with data at both time points.

i Bone ALP Serum bone isoform of alkaline phosphatase; N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients with data at both time points.

Data derived from Table T6.3.3.

Sponsor's Table from p. 106 of the Bone Mineral Density substudy report

#### Fractures

Five patients in the substudy sustained fractures in the first year (tamoxifen 20 mg: 2 [patient numbers 0416/0080 (hip) and 0486/0100 (ankle)]; anastrozole 1 mg plus tamoxifen 20 mg: 2 [patient numbers 0489/0060 (rib) and 0527/0017 (radius)]; control: 1 [patient number 0210/5005 (distal forearm)]).

*Reviewer's Comment: The sponsor argues that the substudy results may be due to the fact that more anastrozole patients were less than 1 year from their LMP. The WHO Technical Report entitled Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis 1994 on page 16 states "bone loss accelerates around menopause and averages 2% per year over the next 5-10 years". The sponsor did not provide an analysis, which suggested the number/percentage of patients less than 10 years from their LMP was greater in the anastrozole treatment group. The overall conclusion from the data presented is that anastrozole is associated with a statistically significant decrease in BMD than tamoxifen at 12 months. Additional substudy follow up is crucial. A post-marketing study in the ATAC patient population combining anastrozole alone and oral calcium plus bisphosphonate may be prudent.*

#### Quality of Life substudy

**Quality of Life substudy -A Randomized, Double-Blind, Trial to Assess the Quality of Life with Arimidex Alone, Nolvadex (Tamoxifen) Alone or Arimidex and Nolvadex in Combination when used as Adjuvant Treatment for Breast Cancer in Post-Menopausal Women (1033IE/0029)**

*Reviewer's Comment: This substudy's primary objective was to compare differences in quality of life between the treatment groups as assessed by the Functional Assessment of Cancer Therapy - Breast (FACT-B) Treatment Outcome Index (TOI). Secondary objectives were to compare responses for the specific endocrine symptoms, Endocrine subscale (ES), FACT B Emotional Well-Being (EWB) and Social Well-Being (SWB), QOL one-month post-recurrence, and most bothersome endocrine symptoms. The FACT-B and Endocrine Subscale were administered at baseline, 3, 6, 9, 12, and 24 months, at suspected recurrence/withdrawal, and one month post recurrence. The primary substudy comparison is between the anastrozole alone patients and the*

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*tamoxifen alone patients. The second substudy comparison is between the combination patients and the tamoxifen alone patients. The primary efficacy endpoint is the difference in the longitudinal analysis of FACT-B TOI at 2 years. A difference of 5 in the TOI between the treatment groups was considered clinically relevant. The substudy protocol proposed that evaluation of the specific endocrine symptoms and the most bothersome endocrine symptoms would consider only those items with a greater than 10% incidence in any one of the treatment arms and the comparison would use Fisher's Exact Test. Statistical adjustments would be made according to the procedure described by Holm. The two analysis populations were: 1) all patients enrolled in the QOL substudy and another substudy 2) all patients enrolled in the QOL. The primary analysis was performed on the first analysis population (all patients enrolled in the QOL and another substudy). The second analysis was performed on the second population with the above endpoints. Additional analyses excluded those patients who had significant protocol violations. If 50% or more of the subscale items were answered then missing values were prorated ((sum of subscale multiplied by the number of items in the subscale)/number of items answered). If less than 50% of the subscale items were answered, then the subscale is considered missing.*

*One thousand one hundred and five patients enrolled and one thousand twenty-one were evaluable (335 anastrozole alone, 347 tamoxifen alone, 339 combination) Study results demonstrated no differences in the longitudinal analysis of Fact-B TOI scores at 2 years between anastrozole and tamoxifen treatment groups or tamoxifen and the combination treatment groups. Substudy results revealed no differences between treatment groups for the Endocrine subscale, EWB subscale, and the SWB subscale. Statistically significant differences were noted between treatment groups in several responses on the most bothersome endocrine symptoms question against anastrozole for the following symptoms- vaginal dryness, pain/discomfort with intercourse, loss of interest in sex, and diarrhea. The triad of symptoms: loss of interest in sex, vaginal dryness, and pain or discomfort with sex are concerning for a real finding of an anastrozole drug effect.*

#### Substudy Protocol

This subprotocol, "A Randomized, Double-Blind, Trial to Assess the Quality of Life (QOL) with Arimidex Alone, Nolvadex (Tamoxifen) Alone or Arimidex and Nolvadex in Combination when used as Adjuvant Treatment for Breast Cancer in Post-Menopausal Women (1033IE/0029)", planned to enroll 1000 women. Patients enrolled in other substudies (except the endometrial and bone substudies) could enroll in this one.

The primary objectives of this trial were to compare QOL between the anastrozole (1 mg) group, the tamoxifen (20 mg) group, and the anastrozole (1 mg) plus tamoxifen (20 mg) combination group during the first 2 years of treatment.

The secondary objectives of this trial were to:

- 1) compare the incidence of specific endocrine symptoms between the 3 treatment groups

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- 2) compare the Emotional Well Being (EWB) and Social Well Being (SWB) values between the 3 treatment groups at each scheduled visit
- 3) determine the patients' most bothersome endocrine symptoms in each of the 3 treatment groups
- 4) provide information about QOL 28 days post recurrence.

The ATAC QOL substudy patients had to meet the inclusion and exclusion criteria for the main ATAC trial. In addition, substudy patients had to consent to participate in the QOL trial and complete a baseline questionnaire. Patients were excluded from the substudy if the investigator considered that the patients would be unable to comply with the sub-protocol due to psychiatric or literacy reasons.

Patients were withdrawn from the substudy for the following reasons:

- 1) completion of this QOL sub-protocol
- 2) ceased trial therapy for any reason other than recurrence of disease
- 3) completed the 28 day post-recurrence follow-up
- 4) wished to withdraw from this sub-protocol at any time (this did not prejudice them remaining in the main ATAC trial (1033IL/0029)
- 5) did not start trial therapy

There were three amendments to this substudy protocol.

*Reviewer's Comment: Although amendment number 1 increased the number of eligible patients, prolonged treatment duration and accordingly changed the timing of endpoints and analysis populations, it is not clear that these changes effected the overall results of the study. Amendment 2 changed the primary endpoint from using the entire FACT-B questionnaire to selected subsections of the FACT-B. Since this change was performed prior to completion of enrollment and there were no interim analyses, it is unclear the impact this change would have. Amendment 2 also added a secondary endpoint, clarified analysis populations, and clarified how missing data would be analyzed. Amendment 3 revised the primary objectives, revised the criteria for demonstrating non-inferiority, dropped analyses that were redundant, revised the definitions of the analysis populations, discussed multiplicity and clarified the planned longitudinal analysis at 2 years.*

Table Number	Key details of all protocol amendments	Key details of amendment	Reason for amendment
1	24-Nov-97	• Restriction for excluding patients	• Desire of patients in the endometrial

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2	07-Jan-99	<p>enrolled in the endometrial sub-protocol (1033IC/0029) was removed. Goal of 1000 patients is exclusive of those participating in either the endometrial or bone sub-protocols.</p> <ul style="list-style-type: none"> <li>• Treatment duration extended from 2 to 5 years</li> <li>• The analysis populations will reflect changes made to the eligibility criteria.</li> <li>• Section 3.3 has been changed from Trial Endpoints to Trial Completion.</li> <li>• Timing of baseline questionnaire and definition of unscheduled visit revised in Trial Plan and section 7.2.3 of protocol.</li> <li>• Revision of the primary endpoint.</li> <li>• Definition of the secondary statistical endpoint QOL 28 days Post-Recurrence revised.</li> <li>• Definition of analysis population and analyses to be performed revised.</li> <li>• Explanation of how missing data will be handled and references describing the procedures to be used have been added.</li> </ul>	<p>sub-protocol to participate in the Quality of Life (QOL) sub-protocol.</p> <ul style="list-style-type: none"> <li>• Interim data available to support 5-year treatment option.</li> <li>• Clarification of the analysis populations.</li> <li>• As advised by regulatory authorities.</li> <li>• Clarification of timing of baseline questionnaire and definition of unscheduled visit.</li> <li>• Clarification of the term TOI.</li> <li>• Clarification of the secondary statistical endpoint.</li> <li>• Clarification of the analysis population and analyses.</li> <li>• Clarification of how missing data will be handled from a statistical perspective.</li> </ul>
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Number	Effective date	Key details of amendment	Reason for amendment
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- 3            30-Apr-01
- Primary Objectives revised.
  - Revised Trial Plan footnotes to indicate that post-recurrence questionnaires should be completed for recurrences over the 5 year period.
  - Criteria for showing non-inferiority have been reversed for Trial Outcome Index (TOI) and Endocrine subscale (ES) with no impact on actual sample size calculations which are correct.
  - Analysis of Specific Endocrine Symptom Response was dropped.
  - Specific Endocrine Symptom Response revised.
  - ITT analyses will not be performed.
  - Definition of analysis population revised
  - Rationale for handling of multiplicity amended in line with other sub-protocols.
  - The longitudinal analysis of TOI score at 2 years has been revised with respect to handling of missing data, removal of recurrence as a time dependent covariate, dropping investigation of a center
  - Comparisons of interest clarified.
  - Footnote was inconsistent with other sections of the Protocol.
  - Criteria for showing non-inferiority were incorrectly stated and have been reversed.
  - To avoid duplication of analyses addressing the most bothersome symptoms.
  - Since a statistical response is not proposed, data will not be collapsed into a dichotomous variable.
  - Because few patients received incorrect randomized therapy or did not start treatment at all, the ITT analyses have been dropped.
  - Clarification of analysis populations and the analyses to be performed.
  - Since the subprotocols address different safety aspects, no adjustments for multiple testing will be performed.
  - Clarification of the longitudinal analysis of TOI score at 2 years.

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effect  
and a center by treatment effect, the  
addition of prognostic covariates,  
clarification that the model  
including  
baseline covariates will be the  
primary  
model for consistency with the other  
ATAC subprotocols, a proposal to  
conduct an unadjusted analysis to  
assess  
the robustness of the primary model  
conclusions, and the addition of the  
method to test for a difference if  
non-inferiority is concluded for the  
comparison between the anastrozole  
arm  
and the combination arm.

- The final five references will be removed as they are no longer cited in the Protocol.
- The reference list has been amended to reflect the changes to the protocol.

The FACT-B subscales were administered at baseline, 3, 6, 9, 12, and 24 months, at suspected recurrence/withdrawal, one month post recurrence, and at unscheduled visits. The following instructions concerning the questionnaire were given: it had to be completed by the patient herself without the help of staff or relatives, it had to be completed before any investigations or discussions about the status of the patient's disease with the clinic staff, and there was only one answer to every question which was to be circled. All completed questionnaires were to be placed by the patient in a sealed pre-paid envelope and given to an appointed individual for subsequent mailing to AstraZeneca.

The primary substudy comparison was the FACT-B TOI questionnaire at 2 years between the anastrozole alone patients and the tamoxifen alone patients. The TOI is the sum of the physical well being (PWB), functional well being (FWB), and breast cancer subscale (BCS) components of the questionnaire, i.e.,  $TOI = PWB + FWB + BCS$ . The second substudy comparison is between the combination patients and the tamoxifen alone patients. The primary efficacy endpoint is a difference in the longitudinal analysis of FACT-B TOI at 2 years. A difference of 5 in the TOI between the treatment groups was considered clinically relevant. The sample size calculation predicted that to show superiority in the comparison with 95% power and a 2-sided 5% confidence interval, the study needed 235 evaluable patients who completed the questionnaires at 2 years.

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Secondary objectives were to compare responses for:

- 1) the specific endocrine symptoms, Endocrine subscale (ES)
- 2) FACT B Emotional Well-Being (EWB)
- 3) Social Well-Being (SWB)
- 4) TOI QOL one-month post-recurrence
- 5) most bothersome endocrine symptoms

The substudy protocol proposed that evaluation of the specific endocrine symptoms and the most bothersome endocrine symptoms would consider only those items with a greater than 10% incidence in any one of the treatment arms and the comparison would use Fisher's Exact Test. For the comparison of the Endocrine Subscale (ES) overall score, with 235 evaluable patients per arm and a 2-sided 5% significance level, the trial had 98% power to detect a difference of 4 between the treatment groups. Analysis of the most bothersome endocrine symptoms was to be conducted for those symptoms which had a greater than 10% incidence in any 1 of the treatment arms in the comparison. With 235 evaluable patients per group, this trial had 80% power to show a reduction from 20% to 10% in the proportion of patients with these symptoms.

Statistical adjustments would be made according to the procedure described by Holm. The two analysis populations were: 1) all patients enrolled in the QOL substudy and another substudy 2) all patients enrolled in the QOL. The primary analysis was performed on the first analysis population (all patients enrolled in the QOL and another substudy). The second analysis was performed on the second population with the above endpoints. Additional analyses will be performed excluding those patients who had significant protocol violations. If 50% or more of the subscale items were answered then missing values were prorated ((sum of subscale multiplied by the number of items in the subscale)/number of items answered). If less than 50% of the subscale items were answered, then the subscale is considered missing. If any one of the subscales contributing to TOI (PWB, FWB, or BCS) were considered missing by the above 50% rule then the TOI was also considered missing.

For details of the planned statistical analysis of the primary and secondary endpoints, see the Statistical review of this supplemental NDA.

#### Sample size calculation

The sponsor projected that 13-14% of patients would develop a recurrence during the 2 years and 15-16% were expected to drop out/fail to complete forms. Thus, it was calculated that 330 patients per treatment group be recruited in order to have 235 evaluable patients.

#### Study Results

The first patient was recruited on April 28, 1998 and the last patient was recruited on April 28, 1999.

The sponsor's table below shows the demographics of the participants.

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*Reviewer's Comment: The treatment groups were fairly well-balanced with respect to demographics. There were more anastrozole patients less than 60 years of age compared to the other treatment groups. Nearly all participants were Caucasian.*

**Table Age, height, weight, body mass index, and race of patients at entry for primary population**

Demographic characteristic	Anastrozole 1 mg (N = 335)	Treatment (n [%]) Tamoxifen 20 mg (N = 347)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 339)
<b>Age (years)</b>			
n	335	347	339
Mean (SD)	62.8 (8.7)	63.7 (8.6)	64.2 (9.0)
Median	61.8	63.4	63.2
Range <sup>a</sup>	43.4 to 86.4	45.5 to 90.7	45.2 to 89.5
<b>Age distribution (n [%])</b>			
< 60 years	142 (42.4)	129 (37.2)	123 (36.3)
≥ 60 to ≤ 70 years	122 (36.4)	136 (39.2)	126 (37.2)
> 70 years	71 (21.2)	82 (23.6)	90 (26.5)
<b>Sex (n [%])</b>			
Male	0	0	0
Female	335 (100.0)	347 (100.0)	339 (100.0)
<b>Height (cm)</b>			
n	313	332	325
Mean (SD)	161.3 (6.8)	161.1 (6.9)	160.8 (6.4)
Median	161.0	160.5	160.0
Range	137.8 to 178.0	137.2 to 180.3	143.5 to 182.0
<b>Weight (kg)</b>			
n	332	343	335
Mean (SD)	71.5 (13.9)	71.1 (14.3)	71.9 (13.7)
Median	70.0	69.0	70.0
Range	41.3 to 120.2	36.2 to 127.0	38.0 to 145.3
<b>Body mass index (kg/m<sup>2</sup>)</b>			
n	312	331	324
Mean (SD)	27.5 (5.1)	27.4 (5.7)	27.9 (5.3)
Median	26.9	26.3	27.5
Range			
<b>Race (n [%])</b>			
Caucasian	331 (98.8)	342 (98.6)	331 (97.6)
Black/Afro-Caribbean <sup>b</sup>	1 (0.3)	1 (0.3)	3 (0.9)
Asian	1 (0.3)	0	1 (0.3)
Hispanic	0	3 (0.9)	0



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No                                      329 (98.2)                                      345 (99.4)                                      333 (98.2)

\* Including wide local excision.

N Number of patients enrolled in the QOL sub-protocol by treatment first received.

Reviewer's Table

The following tables show the numbers of patients and reasons for which patients were excluded from all the analyses.

#### Numbers of patients and reasons for which patients were excluded from all analyses

Reason or Population/Type of hormone	Anastrozole 1 mg (N=357)	Tamoxifen 20 mg (N=375)	Anastrozole plus Tamoxifen (N=373)	Total
Randomized	357	375	373	1105
Excluded -did not receive any hormone treatment	1	2	3	6
Excluded-received at least one dose of any treatment	356	373	370	1099
Excluded-received incorrect hormone treatment	2	3	1	6

Reviewer's Table

The primary analysis population included all substudy participants whom either only participated in the QOL substudy or who participated in the QOL and PK substudy.

#### Numbers of patients and reasons for which patients were excluded from the primary analysis<sup>a</sup>

Reason or Population/Type of hormone	Anastrozole 1 mg (N=335)	Tamoxifen 20 mg (N=347)	Anastrozole plus Tamoxifen (N=339)
Total excluded from primary analysis	49 (14.6%)	67 (19.3%)	66 (17.7%)
Death	3	2	2
Withdrawn from treatment in main trial	38	58	60
Patient lost to follow up	0	1	2
Informed Consent Withdrawn	4	3	0
Investigator's Discretion	4	3	2

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a Excludes six patients who did not receive any trial medication. Six patients who received the wrong treatment. Excludes 78 patients who participated in the bone and endometrial substudies.  
Reviewer's Table

The secondary analysis population included all substudy participants who started their randomized treatment.

Numbers of patients and reasons for which patients were excluded from the secondary analysis population<sup>a</sup>

Reason/Type of hormone	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole plus Tamoxifen	Total
Randomized	357	375	373	1105
Secondary analysis population	357	371	371	1099
Total excluded from secondary analysis	0	4	2	6

a Excludes six patients who did not receive any trial medication.  
Reviewer's Table

The per-protocol analysis population included all substudy participants who started their randomized treatment and:

- 1) enrolled in either the QOL substudy or the QOL substudy and the PK substudy
- 2) did not have either a major protocol violation or deviation

Numbers of patients and reasons for which patients were excluded from the per protocol analysis<sup>a</sup>

Reason or Population/Type of hormone	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole plus Tamoxifen	Total
Per Protocol Population	326	344	333	703
Total excluded from per-protocol analysis because of major protocol violation	5	1	3	9
Another malignancy	1	0	1	2
Baseline Data Missing	2	1	1	4
Not post-menopausal	1	0	1	2
Received treatment with non-approved or experimental drug during the 3 months prior to randomization	1	0	0	1
Excluded from the Per protocol analyses because of major protocol deviation	10	4	8	22

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Took medication such as cytotoxics, HRT for hot flashes, or other hormonal treatment for breast cancer	6	2	5	13
Received a different trial treatment for > 3 months than that which was originally received	2	2	2	6
Had continuous interruption of trial treatment for > 3 months	2	0	1	3

a Excludes six patients who did not receive any trial medication and those six patients who received the wrong treatment.

#### Reviewer's Table

Patients who recurred before the end of the 2-year follow-up were included in the respective analyses up to and including the final visit before recurrence was confirmed. This may have included a visit in between the 6 monthly scheduled visits. Patients who died or withdrew from trial therapy were included up to and including their final visit (whether scheduled or unscheduled) while still on study treatment.

#### Primary endpoints

The following table shows the percentage of patients who completed a baseline questionnaire and those who completed a baseline questionnaire plus had one additional visit.

*Reviewer's Comments: Similar percentages of patients completed questionnaires.*

**Table Percentage of Patients with evaluable TOI scores at scheduled visits - primary population**

Treatment first received	Visit						
	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24	
Two visits <sup>a</sup>	%	%	%	%	%	%	%
Anastrozole 1 mg	95.2	84.9	88.2	84.3	83.3	83.7	93.4
Tamoxifen 20 mg	95.4	88.9	91.2	84.4	82.9	84.7	93.4
Combination	95.6	84.9	86.5	83.2	83.6	85.7	93.8

N Number of patients enrolled in the QOL sub-protocol by treatment first received. n Number of patients with sufficiently completes questionnaires.

TOI Trial outcome index, defined as the sum of physical well being, functional well being, and breast cancer subscale.

<sup>a</sup>Baseline plus one additional visit.

## CLINICAL REVIEW

### Clinical Review Section

#### Reviewer's Table

The following table and diagram show the longitudinal analysis of TOI for the primary population.

*Reviewer's Comment: There were no statistically significant differences between treatment groups as shown in the table below and illustrated by the overlapping confidence intervals in the diagram.*

**Table Longitudinal analysis of TOI - primary population**

Treatment comparisons	Difference in TOI	Two-sided 95% confidence interval		Lower limit of 1-sided 95% confidence interval	p-value
		Lower	Upper		
Anastrozole 1 mg vs tamoxifen 20 mg	-0.75	-1.98	0.47	NA	0.2272
Anastrozole 1 mg + Tamoxifen 20 mg vs tamoxifen 20 mg <sup>a</sup>	-0.10	-1.32	1.12	-1.12	0.8707

NA Not applicable.

TOI Trial outcome index, defined as the sum of physical well being, emotional well being, and breast cancer subscale scores.

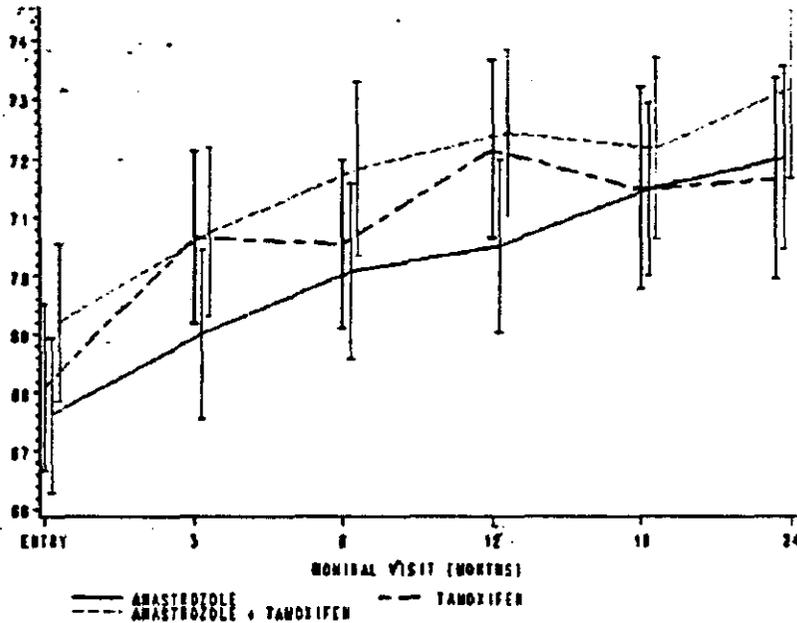
Reviewer's Table

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# CLINICAL REVIEW

## Clinical Review Section

**Figure 2 Mean (95% CI) Trial Outcome Index over time**



Sponsor's diagram p. 62 of study report

The following sponsor's table shows the number of patients with recurrences and completed questionnaires at recurrence and 28 days post confirmation of recurrence.

Reviewer's Comment: Few patients recurred in the ATAC QOL substudy.

**Table Patients with evaluable TOI scores at recurrence and 28 days post confirmation of recurrence**

Treatment first received	Confirmation of recurrence <sup>a</sup>		28 days post confirmation <sup>b</sup>		Both	
	n	%	n	%	n	%
Anastrozole 1 mg (N = 9)	6	66.7	3	33.3	3	33.3
Tamoxifen 20 mg (N = 20)	10	50.0	7	35.0	5	25.0
Anastrozole (1 mg od) + Tamoxifen (20 mg od) (N = 22)	11	50.0	9	40.9	5	22.7

<sup>a</sup> Questionnaire was to be completed prior to seeing the doctor.

<sup>b</sup> Questionnaire was to be completed at 28 days ± 7 days post confirmation of recurrence visit.

n Number of patients with sufficiently completed questionnaires.

N Number of patients in the primary population with a confirmed recurrence by treatment first received.

## CLINICAL REVIEW

### Clinical Review Section

TOI Trial outcome index, defined as the sum of physical well being, functional well being, and breast cancer subscale.

Data derived from Table T5.2.

Sponsor's Table from p. 68 of the QOL substudy report

The following sponsor's table shows the results from the patients who recurred by treatment group. There were no statistically significant differences between treatment groups.

**Table                      Functional assessment of cancer therapy: QOL 28 days post-recurrence  
FACT-B (TOI) - primary  
population**

Treatment first received	Parameter	TOI score <sup>a</sup>		
		Confirmation of recurrence	28 days post-recurrence	Change <sup>b</sup>
Anastrozole 1 mg n (N = 9)		6	3	3
	Mean (SD)	68.0 (13.3)	66.8 (11.7)	8.1 (10.3)
	Median	71.5	62.3	10.0
	Range			
Tamoxifen 20 mg n (N = 20)		1	0	7
	Mean (SD)	62.4 (15.9)	63.3 (11.3)	1.6 (10.9)
	Median	63.5	63.0	0.0
	Range			
Anastrozole 1 mg n + tamoxifen 20 mg (N = 22)		11	9	5
	Mean (SD)	64.4 (16.9)	57.8 (17.6)	-0.7 (9.0)
	Median	63.2	52.8	-2.0
	Range			

<sup>a</sup> TOI Trial outcome index, defined as the sum of physical well being, emotional well being, and breast cancer subscale scores.

<sup>b</sup> Change represents TOI score post-recurrence minus TOI score at confirmed recurrence.

n Number of patients.

N Number of patients in the primary population with a confirmed recurrence by treatment first received.

SD Standard deviation.

Data derived from Table T5.15.

Sponsor's Table from p. 71 of the QOL substudy report

Secondary endpoints

Endocrine subscale

## CLINICAL REVIEW

### Clinical Review Section

Similar percentages of patients completed the Endocrine subscale as completed the baseline questionnaire. Few patients in the substudy developed a recurrence. No significant differences occurred between treatment groups. For details, see Table 20 of the study report.

The following table shows the longitudinal analysis of Endocrine total subscores. There were no statistically significant differences between treatment groups.

**Table Longitudinal analysis of ES total scores - primary population**

Treatment comparisons	Difference in ES	Two-sided 95% confidence interval		Lower limit of the 1-sided 95% confidence interval	p-value
		Lower	Upper		
Anastrozole 1 mg vs tamoxifen 20 mg	-0.15	-1.02	0.73	NA	0.7384
Anastrozole 1 mg + Tamoxifen 20 mg vs tamoxifen 20 mg*	-0.59	-1.46	0.29	-1.32	0.1884

\* If the lower limit of the 2-sided 95% confidence interval is > -4 but ≤ 0, then non-inferiority of Anastrozole + tamoxifen compared to tamoxifen alone may be concluded. This analysis adjusts for the following covariates: baseline ES, receptor status, age (<65/≥ 65), chemotherapy (Y/N), mastectomy (Y/N), and axillary clearance (Y/N).  
ES Endocrine symptom subscale total score.

NA Not applicable.

Data derived from Table T5.12.

Sponsor's Table from p. 77 of the QOL substudy report

Similar percentages of patients who recurred completed questionnaires at recurrence and 28 days post confirmation of recurrence. There were no significant differences between treatment groups. For details, see Table 21 of the study report.

The following table shows the analysis of Endocrine total subscores for the recurrence population. There were no statistically significant differences between treatment groups.

**Table Functional assessment of cancer therapy: QOL 28-day post-recurrence FACT-B (ES) - primary population**

Treatment first Received	Parameter	ES score <sup>a</sup>		
		Confirmation of recurrence	28-day post-recurrence	Change <sup>b</sup>
Anastrozole 1 mg n (N = 9)	Mean (SD)	5 60.1 (9.5)	3 64.9 (5.1)	3 10.4 (8.2)

## CLINICAL REVIEW

### Clinical Review Section

	Median	63.5	67.8	7.0
	Range			
Tamoxifen 20 mg n (N = 20)	1		0	7
	Mean (SD)	54.1 (12.0)	64.1 (5.1)	2.6 (5.0)
	Median	56.0	65.6	1.0
	Range			
Anastrozole 1 mg +				
Tamoxifen 20 mg n (N = 22)	1		2	9
	Mean (SD)	59.8 (8.3)	64.0 (4.8)	4.7 (8.0)
	Median	61.7	64.0	1.1
	Range			

<sup>a</sup> ES Endocrine symptom subscale score.

<sup>b</sup> Change represents ES score post-recurrence minus ES score at confirmed recurrence.

n Number of patients with sufficiently completed questionnaires.

N Number of patients in the primary population with a confirmed recurrence by treatment first received.

SD Standard deviation.

Data derived from Table T5.17.

Sponsor's Table from p. 78 of the QOL substudy report

The sponsor analyzed the worst endocrine symptom response, the physical well-being scores, the emotional well-being scores, social well-being scores, and functional well-being, by treatment group. No significant differences occurred between treatment groups. For details, see Tables 26-30 of the study report.

The sponsor's analyses of patient responses to the question of which symptoms were most bothersome are listed in the table below.

*Reviewer's Comment: The anastrozole treated patients reported more loss of interest in sex, vaginal dryness, pain or discomfort with intercourse, and diarrhea.*

**Table Analysis of incidence of most bothersome endocrine symptoms: comparison of anastrozole to tamoxifen - primary population**

Most bothersome endocrine symptom	Anastrozole incidence	Tamoxifen incidence	Odds ratio <sup>a</sup>	95% confidence Interval		p-value
				Lower	Upper	
Hot flushes	0.6078	0.6398	0.89	0.64	1.26	0.5220
Night sweats	0.4431	0.5101	0.79	0.57	1.08	0.1371
Gained weight	0.5210	0.5331	0.92	0.67	1.25	0.5814
Breast sensitivity/ tenderness	0.3982	0.3948	1.06	0.77	1.46	0.7138
Irritability	0.3713	0.3660	1.07	0.77	1.48	0.6999
Bloated feeling	0.3503	0.3833	0.87	0.63	1.20	0.3971
Mood swings	0.4042	0.3631	1.23	0.89	1.70	0.2052
Headaches	0.2635	0.2478	1.16	0.81	1.67	0.4210
Loss of interest in sex	0.3443	0.2392	1.878	1.31	2.70	0.0006
Vaginal dryness	0.2994	0.1960	1.94	1.33	2.83	0.0006

## CLINICAL REVIEW

### Clinical Review Section

Lightheaded/dizzy	0.2545	0.3256	0.77	0.54	1.10	0.1475
Cold sweats	0.2156	0.2651	0.745	0.52	1.08	0.1170
Pain or discomfort with intercourse	0.1946	0.1326	1.76	1.13	2.75	0.0121
Vaginal itching/irritation	0.1587	0.2363	0.57	0.39	0.85	0.0062
Diarrhea	0.1347	0.0922	1.601	0.98	2.64	0.0601
Vaginal discharge	0.0868	0.2161	0.33	0.20	0.52	0.0001

\* An odds ratio of  $< 1$  suggests a lower incidence with anastrozole. Incidence is defined as the proportion of patients for whom the symptom had ever been bothersome.

Only symptoms with an incidence of greater than 10% in any treatment group were analyzed.

This analysis adjusts for the presence of the symptom at baseline.

Data derived from Table T5.20.

Reviewer's Table

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/s/

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Ann Farrell  
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MEDICAL OFFICER

Grant Williams  
9/5/02 01:56:20 PM  
MEDICAL OFFICER

Consult

## Clinical Consultation

**FROM:** Patricia Beaston-Wimmer, M.D., Ph.D.  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products

**THROUGH:** David Orloff, MD Director, DMEDP

**TO:** Amy Baird, CSO, DODP, HFD-150

**SUBJECT:** Arimidex (anastrozole) tablets, NDA 20-541/S-10.

**DATE CONSULT RECEIVED:** June 11, 2002

**DATE CONSULT COMPLETED:** August 12, 2002

### **MATERIAL RECEIVED FOR REVIEW<sup>1</sup>**

The consultation package included Dr. Farrell's Safety Review, the link to the NDA submission, and the request for consultation form with specific questions. The Efficacy Review and supplemental information from the Company were forwarded as they became available.

### **BACKGROUND**

Administrative—The Division of Oncologic Drug Products is requesting comment on supplemental NDA 20-541. Arimidex is currently approved for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy (October 1995) and for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer (September 2000). This supplemental NDA seeks an indication for Arimidex as adjuvant treatment in postmenopausal women with breast cancer.

#### Drugs in study—

Anastrozole (Arimidex) is a non-steroidal orally active, highly selective aromatase inhibitor. It suppresses estrogen levels via aromatase inhibition and is devoid of partial estrogenic activity.

Tamoxifen (Nolvadex) is listed as a nonsteroidal antiestrogen but falls into a relatively new class of drugs, SERMS or selective estrogen receptor modulators. As such, tamoxifen has been found to be effective in the treatment breast cancer (due to its anti-

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<sup>1</sup> Note for the reader. Direct quotes from the sNDA are *italicized*. Specific comments from this consultant are **bolded**. Unless noted, tables are copied directly from the submission.

Consult

estrogenic properties) but having a relatively positive effect on maintaining bone mineral density in postmenopausal women (due to its estrogenic properties).

**Safety Issues**— 'The ATAC trial (A Randomized, Double-Blind Trial Comparing Arimidex Alone, with Nolvadex, with Arimidex and Nolvadex in combination, as Adjuvant Treatment in Post-menopausal Women with Breast Cancer) is a large and important trial in post-menopausal women with early breast cancer and the trial may impact the practice of care for patients with early stage breast cancer. Anastrozole, an aromatase inhibitor, was shown to be superior to tamoxifen for disease-free survival rate. This sNDA may be approved and shortly thereafter physicians may preferentially use anastrozole for 5 years in all early stage breast cancer patients. Anastrozole has some safety issues - statistically significant differences in musculoskeletal events, fractures and possibly hypercholesterolemia.' (Dr. Farrell)

**QUESTIONS FOR DMEDP:** The questions for DMEDP are provided in the outlined sections. Answers or comments to the questions are provided in the body of this consult.

**Bone concerns**

Please review the main ATAC trial and substudy concerning bone events.

- a) Are you in agreement with the sponsor's conclusions from the main ATAC trial? If so, why?
- b) Are you in agreement with the sponsors conclusions from the substudy? If so, why?
- c) What is your critique of the trial and substudy from the perspective of the bone safety data? Consider definitions and endpoints.
- d) Do you consider the data robust or hypothesis generating?
- e) How long should the trial/bone substudy last in order to collect adequate information to label this drug safely?
- f) Do you have any additional suggestions for further study?  
We have asked for the following analyses:
  - 1) a table showing numbers of patients and incidence rates: Bisphosphonate use (yes/no labor) by fracture (yes/no) by treatment group: Calcium use (yes/no) by fracture (yes/no) by treatment group and;
  - 2) a table for all patients who developed a fracture listing each patient with the following information: patient number, treatment received, length of study treatment (exposure) when patient developed fracture and type of fracture
- g) Do you have any recommendations for women who may have osteoporosis and need hormonal therapy?

Consult

## SUMMARY OF STUDIES:

**Main Clinical Study:** "A Randomized, Double-Blind Trial Comparing ARIMIDEX Alone with NOLVADEX Alone, with ARIMIDEX and NOLVADEX in Combination, as Adjuvant Treatment in Postmenopausal Women with Breast Cancer" (ATAC).

A large multi-center trial enrolling 9,366 post-menopausal patients with operable breast cancer. The patients were randomized to one of the following three treatment arms: Arimidex 1 mg daily, tamoxifen 20 mg daily, or a combination of the two treatments for five years or until recurrence of the disease.

**Objectives**— The primary endpoints were recurrence-free survival and safety. The secondary endpoints were time to distant recurrence, the incidence of new breast primaries and survival. The inclusion and exclusion criteria for patients in this study are listed in Appendix A.

**Duration of treatment**— The planned duration of treatment was 5 years. A summary of the exposure to trial drug and duration of treatment for the main study is in the following table:

**Table 39 Exposure to trial drug and duration of treatment**

Duration of treatment	Number (%) of patients		
	Anastrozole 1 mg (N = 3092)	Tamoxifen 20 mg (N = 3094)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 3097)
>0 to <12 months	330 (10.7)	373 (12.1)	385 (12.4)
≥12 to <24 months	391 (12.6)	422 (13.6)	421 (13.6)
≥24 to <36 months	1363 (44.1)	1288 (41.6)	1328 (42.9)
≥36 to <48 months	937 (30.3)	927 (30.0)	887 (28.6)
≥48 to <60 months	71 (2.3)	84 (2.7)	76 (2.5)
Median (months)	30.9	30.7	30.4
Range (months)			

N Number of patients treated.

Data derived from Table T10.1.

**Sub-Study:** A Randomised, Double-blind Trial to Assess the Effects on Bone Mineral Density and Metabolism of ARIMIDEX Alone, NOLVADEX Alone, or ARIMIDEX and NOLVADEX in Combination, (in Comparison to a Control Group) When Used as Adjuvant Treatment for Breast Cancer in Postmenopausal Women. (1033ID/0029) A safety sub-study was performed to evaluate the effect of anastrozole treatment on bone mineral density (BMD).

This sub-study was planned because although both estrogen and tamoxifen are known to increase BMD in post-menopausal women, anastrozole would, in contrast, lower estrogen and could worsen BMD. Patients randomized into this sub-study had to meet the general inclusion and exclusion criteria for the main study (Appendix A) and additional exclusion criteria as listed in Appendix B.

Consult

A fourth arm was added to this sub-study and consisted of a control group. These patients were postmenopausal early breast cancer patients with good prognosis following primary surgery who remained untreated and had not been randomized to treatment in the ATAC main trial. (Patients with invasive breast cancer who, as part of normal clinical practice, were not receiving treatment following primary surgery.) This group was added to provide a comparator for change in BMD over time in a similar population of women who have not had exogenous hormonal manipulation. These patients had to meet the same inclusion and exclusion criteria as patients randomized into the sub-study.

Objectives– *The primary objectives of this sub-protocol were to assess and quantify the changes in bone mineral density (BMD) of patients receiving ARIMIDEX (anastrozole) or anastrozole plus NOLVADEX (tamoxifen) compared to tamoxifen alone for the duration of trial therapy.*

*The secondary objectives of this sub-protocol were: 1) to compare BMD for patients who were recurrence-free and still receiving trial therapy at 2 years in all 3 treatment groups; 2) to summarise the changes in BMD in the treatment groups compared to an untreated, unrandomised 'control' group; and 3) to explore the relationship between changes in levels of biochemical markers with longer-term changes in BMD as measured by dual-energy X-ray absorptiometry (DEXA).*

Duration of treatment: The duration of the sub-study is planned for 24 months with a 60-month evaluation of patients who remain recurrence-free. To date, one-year data is available for this sub-study.

**Results:**

Patient Disposition: Of the 308 patients randomized, 249 contributed baseline and 1-year BMD data. Of the 46 control patients, 39 contributed baseline and 1-year BMD data. A summary of the patient disposition is in the following table:

**Table 14 Status of randomised patients as of the data cut-off (1-year visit)**

Patient status	Number (%) of patients			
	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole 1 mg plus tamoxifen 20 mg	Control
Randomised to treatment	94 (100.0)	109 (100.0)	105 (100.0)	46* (100.0)
Received trial treatment	92 (97.9)	105 (96.3)	103 (98.1)	NA
Withdrawn at baseline	14 (14.9)	22 (20.2)	23 (21.9)	7 (15.2)
Treatment not started	2 (2.1)	4 (3.7)	2 (1.9)	NA
Withdrawn from sub-protocol	10 (10.6)	17 (15.6)	17 (16.2)	1 (2.2)
Continuing sub-protocol	70 (74.5)	70 (64.2)	65 (61.9)	38 (82.6)

\* The control group consisted of patients with good prognoses; this group was not randomised.

NA Not applicable.

Data derived from Tables T1.1, T4.1, T4.2.1, and T4.2.2.

Consult

**Demographics:** In general, the basic demographics – age, race, and BMI (body mass index) were well balanced among the treatment groups and between studies. In the sub-study, there was no significant difference in lumbar or hip BMDs among the study groups. There was a slight imbalance in the control population compared to the treatment groups in that a greater proportion was < 60 years old, there were fewer smokers, and a lower proportion of patients who had received prior radiotherapy or chemotherapy.

**Safety Endpoints** (limited to those related to BMD):

**Bone Mineral Density:** The results for percent change in BMD, from baseline to endpoint, are represented in the following:

**Table 22 Percentage change in lumbar spine BMD from baseline to 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Anastrozole 1 mg (N = 80)	Tamoxifen 20 mg (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)	Control (N = 39)
n	73	71	64	38
Median	-2.27	1.06	0.09	-1.27
Range				
Estimated change*	-2.59	1.01	0.21	-0.36

\* Based upon the geometric mean of the 12-month to baseline ratio.

N Number of patients in the primary analysis population or number of eligible control patients;

n Number of patients with data at baseline and Month 12.

Data derived from Table T5.1.2.

**Table 29 Percentage change in total hip BMD from baseline to 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Anastrozole 1 mg (N = 80)	Tamoxifen 20 mg (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)	Control (N = 39)
n	73	71	62	39
Median	-1.50	0.85	1.16	0.21
Range				
Estimated change*	-1.68	0.48	0.78	-0.13

\* Based upon the geometric mean of the 12-month to baseline ratio.

N Number of patients in the primary analysis population or number of eligible control patients;

n Number of patients with data at baseline and Month 12.

Data derived from Table T5.2.2.

*Changes in lumbar spine BMD from baseline to 12 months showed a statistically<sup>2</sup> significant difference between the anastrozole 1-mg and tamoxifen 20-mg treatment groups, with lower values at 1 year in patients receiving anastrozole 1 mg. No statistically significant difference was evident between the anastrozole 1-mg plus tamoxifen 20-mg treatment group and the group receiving tamoxifen 20-mg monotherapy.*

*Patients receiving anastrozole 1 mg experienced an approximate 1.5% loss in total hip BMD between baseline and 12 months (based upon median values [to take account of a number of outliers]). The control group showed an unexpected marginal increase in BMD (based upon median values). Treatment with either tamoxifen 20 mg or the combination of anastrozole 1 mg plus tamoxifen 20 mg was associated with a small increase in total hip BMD.*

*Changes in total hip BMD from baseline to 12 months showed a statistically<sup>3</sup> significant difference between the anastrozole 1-mg and tamoxifen 20-mg treatment groups, with lower values at 1 year in patients receiving anastrozole 1 mg. No statistically significant difference was evident between the anastrozole 1-mg plus tamoxifen 20-mg treatment group and the group receiving tamoxifen 20-mg monotherapy.*

*Changes in total hip BMD between baseline and 12 months were not as marked as those in the lumbar spine. Patients receiving anastrozole 1 mg lost marginal amounts of bone from the total hip (an area consisting of measurements across the trochanteric, intertrochanteric, and femoral neck regions) whereas losses for the remaining active treatment groups and the control group were either minimal or slight gains were evident. The fact that BMD loss at this site was not as marked for the anastrozole 1-mg group as it was for the lumbar spine is important as hip fractures are associated with a greater degree of morbidity than all other osteoporotic fractures combined (Ref Nevitt 1994).*

**COMMENT:** The observed changes in BMD are consistent with the biological actions of the study drugs- tamoxifen, a SERM, increases BMD and anastrozole, an aromatase inhibitor that reduces estrogen levels, decreases BMD. The variations in individual BMD measurements, including increases in the placebo or control group, are consistent with results seen in other placebo controlled trials albeit to a somewhat greater extent. This increase in variation may be due to many factors including the relatively small sample size and failure to standardize BMD measurements across centers and between machine types. Other variables not accounted for include changes in baseline activity or diet. It is not known if patients were calcium and Vitamin D replete at the start of the study. Addition of calcium and or Vitamin D according to clinical practice guidelines could result in increased BMD in patients who were deficient<sup>4</sup>.

<sup>2</sup> p <0.0001 for anastrozole v tamoxifen; p = 0.2090 for anastrozole v combination; p values are for actual BMD measurements. Statistics for 'percent change' were not found.

<sup>3</sup> p = 0.0002 for anastrozole v tamoxifen; p = 0.3286 for anastrozole v combination; p values are for actual BMD measurements. Statistics for 'percent change' were not found.

<sup>4</sup> In contrast to osteoporosis clinical trials, calcium and vitamin D supplementation was not a part of the protocol. Assuming that the percentage of patients who were vitamin D deficient at baseline was similar across groups, vitamin D status would not have affected the relative changes in BMD across groups; absolute changes may have been larger, however, if subjects were made vitamin D replete during the study.

Consult

The Company suggests that the relatively smaller loss of hip BMD compared to lumbar spine BMD is reassuring. Although arguably hip fractures cause a more immediate loss of function and disability, vertebral fractures can cause considerable long-term morbidity and should not be discounted. Furthermore, it is far from clear that the difference in the median changes in BMD at the lumbar spine and hip observed with anastrozole treatment is clinically meaningful (i.e., would translate into a meaningful difference in fracture risk).

Markers of Bone Turnover– Tables summarizing percent change, from baseline to 3, 6, and 12 months, are summarized in Appendix C.

*Baseline levels of iFDPD were comparable for all groups. Treatment with anastrozole 1 mg monotherapy was associated with a constant iFDPD concentration over time. In comparison, a decrease in bone resorption was evident in the tamoxifen 20-mg group, the anastrozole 1-mg plus tamoxifen 20-mg group, and also the untreated control group (as determined by a reduction in iFDPD levels), although the decrease in the control group was not as marked.*

*NTX concentrations at baseline were comparable across all groups. At subsequent time points, the tamoxifen 20-mg group and the anastrozole 1-mg plus tamoxifen 20-mg group were associated with marked reductions in NTX concentrations (ie, marked reductions in the levels of bone resorption), with most of this decrease being evident within the first 3 months. In comparison, treatment with anastrozole 1 mg monotherapy was associated with a marginal increase in NTX concentration over time.*

*Baseline concentrations of i Bone ALP were comparable across all treatment groups. While tamoxifen 20 mg and the combination of anastrozole 1 mg plus tamoxifen 20 mg were associated with marginal reductions in bone formation, as determined by i Bone ALP, treatment with anastrozole 1 mg monotherapy resulted in an increase in i Bone ALP concentrations, ie, an increase in bone formation.*

**COMMENT: Changes in markers of bone turnover were consistent with the observed changes in BMD.**

Adverse Events– Adverse events from both the main trial have been summarized in the following tables from the submission to include only those adverse events that may be related to bone mineral density. There were limited bone related adverse events in the sub-study – 5 patients reported fracture: tamoxifen, 2 patients – 1 hip and 1 ankle; anastrozole: 2 patients – 1 rib and 1 radius; and control: 1 patient – distal forearm (anastrozole: none).

Note: BMD measurements were only obtained as a part of the sub-study. BMD was not routinely measured in patients enrolled in the main clinical trial and is not provided.

Bone Specific Adverse Events from Main Clinical Trial (from Table 49*)	Anastrozole 1 mg n = 3092		Tamoxifen 20 mg n = 3094		Combination n = 3097	
	n	%	n	%	n	%
Musculoskeletal						
Arthritis	380	12.3	296	9.6	312	10.1
Arthralgia	386	12.5	252	8.1	262	8.5
Osteoporosis <sup>1</sup>	192	6.2	134	4.3	152	4.9
Fracture	183	5.9	115	3.7	142	4.6
Bone pain	158	5.1	139	4.5	127	4.1
Arthrosis	161	5.2	112	3.6	103	3.3

\*Table 49: Adverse events occurring with an incidence of at least 5% in any treatment group during or within 14 days of the end of treatment. (Body system and adverse event by COSTART-preferred term)

<sup>1</sup>Osteoporosis is the term used by the Company. The criteria for defining osteoporosis in this trial was not specified.

Pre-Specified Bone Specific Adverse Events from Main Clinical Trial (from Table 41*)	Anastrozole 1 mg n = 3092		Tamoxifen 20 mg n = 3094		Combination n = 3097	
	n	%	n	%	n	%
Musculo-skeletal disorders <sup>1,a</sup>	860	27.8	660	21.3	685	22.1
Fractures <sup>2,a</sup>	183	5.9	115	3.7	142	4.6
Fractures of Spine, Hip, Wrist <sup>b</sup>	68	2.2	45	1.5	50	1.6

\*Table 42: Pre-specified adverse events occurring in any treatment group during or within 14 days of the end of treatment:

<sup>1</sup>Refers to joint symptoms, including arthritis, arthrosis, and arthralgia.

<sup>a</sup>p < 0.0001; <sup>b</sup>p = 0.0299 for anastrozole v tamoxifen. No significant difference for tamoxifen v combination. Analysis for anastrozole v combination was not provided. (From Table 42.)

<sup>2</sup>Fractures are presumed to be clinical. Assessments for radiographic, but not clinical, fracture did not appear in the protocol.

Site of Fracture from Main Clinical Trial (from Table 44)	Anastrozole 1 mg n = 3092		Tamoxifen 20 mg n = 3094		Combination n = 3097	
	n	%	n	%	n	%
All Fractures	183	5.9	115	3.7	142	4.6
Hip	11	0.4	13	0.4	10	0.3
Vertebral <sup>1</sup>	23	0.7	10	0.3	14	0.5
Wrist/Colles	36	1.2	25	0.8	27	0.9

For events occurring during or within 14 days of the end of treatment.

Patients may fall into more than one category.

<sup>1</sup>Fractures are presumed to be clinical. Assessments for radiographic, but not clinical, fracture did not appear in the protocol.

**COMMENT:** There is a statistically significantly higher incidence of fracture in the anastrozole treated patients compared to tamoxifen treatment. (Statistical comparisons of anastrozole to combination treatment were not made.) Direct comparisons to the results in the sub-study are limited because of the dissimilarities among the study groups. The main study did not exclude patients based on history of fracture, BMD, or use of medications that could affect BMD. In fact, BMD measurements were not routinely obtained in this population. The sub-study specifically excluded patients at higher risk of fracture. The main study required that patients were willing to stop the use of drugs affecting hormone status (including HRT) and did not exclude the use of bisphosphonates, whereas the sub-study required that patients had discontinued use of such drugs  $\geq 12$  months before enrollment. The duration of treatment in the main study was planned for 60

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months with an average exposure of 30 months; the sub-study has only completed 12 months. The size of the main study, over 9000 patients, suggests that there should be balance among the randomization groups, including baseline BMD, risk for fracture, and time since estrogen use. However, this can not be assumed. (Comments for future studies are found later in this consult.)

Despite these limitations, some observations can be made. The changes observed in BMD measurements and markers of bone turnover are consistent with the known biological activity of the drugs used in the study. Patients taking anastrozole are subject to increases in bone turnover and lowered BMD secondary to the decrease in circulating estrogen levels. Lowered BMD is associated with increased risk of fracture. Therefore, it is plausible that the increased fracture incidence in the anastrozole vs. tamoxifen group is drug-related.

This reviewer does not believe that the negative effects of anastrozole on BMD and fracture risk should necessarily preclude the approval of a highly effective treatment for patients with breast cancer. There are several approved anti-resorptive agents that could be used to address the BMD concerns. For example, bisphosphonates are well studied and are effective for the treatment of postmenopausal osteoporosis and decreased risk of fracture. One caveat is the possibility of an unknown direct effect of anastrozole on bone quality or structure (i.e., strength and demineralization) independent of its action to reduce circulating estrogen levels. The preclinical data should be carefully examined for evidence of osteomalacia in bone samples from animal models. If this data is not available then bone quality studies could be performed as part of a Phase IV commitment and DMEDP would be happy to discuss the design of preclinical bone studies with the sponsor. Although the likelihood of an independent effect is remote, as the indication for this drug becomes broader and the population less at risk, for example, prevention rather than treatment, it is important to address the possibility of poor bone quality. Again, this should not preclude approval for the currently proposed indication.

**Label**

Please review the label and make any recommendations concerning the bone information that should be communicated.

Proposed labeling:

**COMMENT:** This section should be expanded to include, in tabular form, information on fractures and BMD from the main study and sub-study. Recommendations for patient treatment should include baseline BMD and fracture risk assessment and appropriate treatment with a non-hormonal anti-resorptive

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agent according to standard clinical practice. Follow up BMD assessments with changes in therapy as indicated should be proposed. Patients should also be advised to take calcium and Vitamin D according to current recommendations unless otherwise contraindicated.

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**Cholesterol concerns**

The sNDA event rate for hypercholesterolemia for anastrozole was 6 % compared with 2.2% for tamoxifen. The information on hypercholesterolemia was just that the investigator noted that the patient had developed hypercholesterolemia. No laboratory data was provided or control for fasting state was provided. No analysis of the hypercholesterolemia event was performed other than a comparison of event rates. The sponsor had planned to perform a substudy to assess lipid profiles during the trial but stopped. Per the sponsor the trial was stopped because 1) laboratory results from Arimidex patients in a first-line hormone treatment Arimidex trial in advanced breast cancer patients demonstrated an increase in cholesterol 2) difficulty accruing to the ATAC trial because the cholesterol substudy required patients to have blood samples for lipids taken prior to breast cancer surgery (presumably so samples would not be influenced by stress hormones) and prior to enrollment in the main ATAC trial.

I am concerned that we have two trials where Arimidex use is associated with an increase in cholesterol; however, Arimidex does not appear conclusively associated with increased cardiovascular events. Tamoxifen is associated with lower cholesterol but this has not shown to be correlated with lower cardiovascular events. So comparisons with tamoxifen may overestimate the risk of increased cholesterol.

**COMMENT:** It is difficult to draw conclusions from spontaneously reported data. However, as with the BMD and bone marker effects, alterations in lipid values with decreases in circulating estrogen is biologically plausible. The results of the recent Women's Health Initiative trial have shown that the improved lipid profile observed with estrogen treatment is not associated with a positive cardiovascular effect.

In the absence of clinical event data (i.e., MI, CVA), the possible adverse effects on lipid profiles should be discussed in the label. A recommendation should be made for baseline lipid evaluation with treatment with cholesterol lowering drugs as indicated by current clinical practice. Follow up lipid profiles should be performed to monitor for change in status after the initiation of aromatase inhibitor treatment.

Note: The DMEDP will be happy to assist DODP with labeling discussions related to the bone and lipid concerns.

We anticipate that the sponsor will \_\_\_\_\_ another high risk population and treat for a prolonged period of time. Do you have any recommendations for future study or collection of additional information (medical prophylaxis against bone events, medical treatment of hypercholesterolemia while on Arimidex (Anastrozole))?

**COMMENT:** Future studies should address the effectiveness of currently available non-hormonal anti-resorptive agents and cholesterol lowering agents to mitigate the effect of lowered estrogen levels in this patients population. In general, patients would need to be stratified according to the presence of absence of osteoporosis, and possibly osteopenia, and hypercholesterolemia. Patients with preexisting conditions

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should be treated according to currently accepted practices. All patients should be followed and treatment modified according to a pre-specified protocol. Initiation or alteration of treatment for osteoporosis, osteopenia, or hypercholesterolemia would then be scored as events. Strict safety monitoring and dropout plans should be in place. Detailed study design is beyond the scope of this consult. However, DMEDP would be available for comment and further discussion of proposed trials.

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## APPENDIX A: Inclusion and Exclusion Criteria, ATAC trial.

### 2.2.2 Inclusion criteria

For inclusion into the trial, patients were required to fulfil all of the following criteria:

- histologically proven operable invasive breast cancer
- completed all primary surgery and chemotherapy (if given), and were candidates to receive hormonal adjuvant therapy
- women defined as postmenopausal according to one or more of the following:
  - aged 60 years or more
  - aged 45 to 59 years and satisfying one or more of the following criteria:
    - amenorrhoea for at least 12 months and intact uterus
    - amenorrhoea for less than 12 months and follicle stimulating hormone (FSH) concentrations within the postmenopausal range including:
      - patients who have had a hysterectomy
      - patients who have received hormone replacement therapy (HRT)
      - patients rendered amenorrhoeic by adjuvant chemotherapy (NB such patients must have FSH measured at least 6 weeks after stopping chemotherapy)
    - bilateral oophorectomy
- documented informed consent to participate

Protocol Amendment 3 introduced a lower age limit of 45 years to ensure that premenopausal women were not inadvertently enrolled into this trial [see Section 2.1.3]. There was therefore a period from the initiation of the trial up until 01 September 1997 [date of implementation of this amendment] where patients less than 45 years of age were recruited.

### 2.2.3 Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the trial:

- clinical evidence of metastatic disease
- patients who, for whatever reason (eg, confusion, infirmity, alcoholism), were unlikely to comply with trial requirements
- patients whose chemotherapy was started more than 8 weeks (ie, 56 days) after completion of primary surgery or whose chemotherapy was completed more than 8 weeks before starting randomised treatment. Chemotherapy, if given, should have been given post-operatively, ie, patients who received neoadjuvant chemotherapy were ineligible.
- patients who had not received chemotherapy and whose primary surgery was completed more than 8 weeks (ie, 56 days) before starting randomised treatment
- previous hormonal therapy as adjuvant treatment for breast cancer, unless:
  - this was tamoxifen started prior to first surgical procedure and received for less than 29 days
  - or
  - this was hormonal therapy received pre-surgery in the context of a formal trial, approved by the Steering Committee
- patients who had received tamoxifen as part of any breast cancer prevention trials, eg, the International Breast Cancer Intervention Study
- patients unwilling to stop taking any drug known to affect sex hormonal status (including HRT), or in whom it would be inappropriate to stop
- previous history of invasive breast cancer at any time or other invasive malignancy within the last 10 years, other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied
- any severe concomitant disease which would place the patient at unusual risk or confound the results of the trial, eg, strong family history of osteoporosis, severe renal or hepatic impairment (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] concentrations more than 3 times the upper limit of the reference range)
- treatment with a non-approved or experimental drug during the 3 months before randomisation
- considered by the investigator to be at risk of transmitting any infection through blood or other body fluids

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#### 2.2.4 Withdrawal criteria

Patients were withdrawn from trial therapy if any of the following circumstances occurred:

- disease recurrence was confirmed
  - the patient refused to continue
  - the investigator recommended cessation of treatment because of concomitant disease/medication
- Trial therapy could also be stopped if a patient experienced an adverse event.

The reason for, and date of, trial treatment withdrawal were fully documented on the case report form (CRF) provided. At the time of stopping trial treatment, the following assessments were to be made: breast cancer status, body weight, concurrent medication, and adverse events.

After stopping trial treatment, all patients were followed for: the resolution of adverse events (if present), further adverse events for the initial 14 days and subsequently any serious adverse events, first loco-regional recurrence and first distant recurrence (unless already recorded), and survival.

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## **APPENDIX B: Additional exclusion criteria for sub-study.**

The following additional exclusion criteria applied to all patients, ie, those recruited from the ATAC main trial and those recruited into the control group:

- patients who had received HRT within the 12 months prior to randomisation
- patients who had received bisphosphonate therapy within the 12 months prior to randomisation
- patients who had a bone fracture within the 6 months prior to randomisation
- patients who had chronic renal/liver impairment
- patients with malabsorption syndrome
- patients with any of the following endocrine disorders: hyperparathyroidism, untreated thyroid disease, Cushing's syndrome, pituitary disease
- patients who took anti-convulsant therapy
- patients who took corticosteroids

### **2.2.4 Withdrawal criteria**

Patients were withdrawn from this sub-protocol if any of the following circumstances occurred

- patients developed osteoporosis, defined as a reduction in BMD over a 2-year period of either  $\geq 10\%$  in the lumbar spine and/or  $\geq 15\%$  in total hip: this included patients who had this reduction after the 1-year scan
- patients were confirmed as having severe osteoporosis at baseline, 1 year, or 2 years as defined in the criteria for the diagnosis of osteoporosis (see Commentaries on Terms). However, if a patient had a T-score of -2.5, that patient was considered to be borderline and the presence of associated fragility fractures was to be ruled out. If the presence of fragility fractures was confirmed, the patient was to be withdrawn. However, patients who had a T-score of -2.5 without associated fragility fractures were permitted to continue in the sub-protocol. (T-scores were calculated based upon BMD assessments of a 30-year-old healthy woman at the time of her peak bone mass.)
- patients commenced any of the prohibited concomitant treatments as defined in the protocol (Appendix B) and Section 2.4 of this report
- patients wished to withdraw at any time (NB: this did not prejudice patients from remaining in the ATAC main trial)
- patients developed skeletal metastases in any part of the L1 to L4 lumbar spine or total hip region
- patients received bisphosphonate therapy
- patients did not receive randomised treatment (for patients from the ATAC main trial only)
- death

Recurrence of breast cancer per se was not a reason for withdrawal of patients from this sub-protocol.

Cessation of randomised treatment was also not a reason for withdrawal from this sub-protocol.

Withdrawal from this sub-protocol did not necessarily mandate withdrawal from the ATAC main trial.

Untreated patients recruited to the control group were also withdrawn from this sub-protocol if:

- they had recurrence of their breast cancer
- they received any hormonal therapy for their breast cancer

Trial participation could also be stopped if a patient had an adverse event. The reason for, and date of, trial treatment withdrawal were fully documented on the CRF provided. At the time treatment was stopped, the following assessments were made: breast cancer status, body weight, concurrent medication, and adverse events. All patients were followed for the resolution of the adverse events (if present), any further serious adverse events, first loco-regional recurrence and first distant recurrence (unless already recorded), and survival.

Patients ceased participation in this sub-protocol if any of the following occurred:

- withdrawal of consent from the ATAC trial
- if disease recurrence occurred after the 24-month DEXA scan
- otherwise, after the completion of the 60-month DEXA scan

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#### 2.4 Concomitant treatment

With the exception of the trial treatments, no drugs that affected sex hormone status or prevented recurrence of disease were to be used after randomisation until confirmation of disease recurrence. These drugs included:

- cytotoxic chemotherapy
- oral administration of ketoconazole (antifungal) or related compounds; topical applications were acceptable
- other hormonal treatments for breast cancer

In addition to the concomitant medication excluded from use during the ATAC main trial, the concomitant use of bone resorption inhibitors, HRT, and corticosteroids were excluded from use by patients in this sub-protocol.

Administration of any of these treatments, and of treatments taken for adverse events, were documented on the CRF.

If a patient experienced serious menopausal symptoms, eg, vaginal dryness or bleeding, hot flushes, abdominal cramps, or dyspareunia, the following actions were to be taken:

- (1) the symptom was reported as an adverse event
- (2) the patient continued to receive randomised treatment if she was still willing to participate in the trial
- (3) treatment with progestins for a 3- to 6-month period was available, if necessary

If up to 6 months of treatment with progestins failed to control any menopausal symptoms, HRT and/or oestrogen creams could be prescribed and randomised treatment continued.

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APPENDIX C: Summary of bone turnover markers (Tables 36, 39, and 42).

**Table 36** Percentage change in iFDPD levels from baseline to 3, 6, and 12 months: primary analysis population and eligible controls with data at both time points

Percentage change from baseline	Anastrozole 1 mg (N = 80)	Tamoxifen 20 mg (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)	Control (N = 39)
<b>3 months</b>				
n	69	70	68	31
Median	3.30	-22.4	-14.9	-9.92
Range				
<b>6 months</b>				
n	66	68	64	30
Median	-1.06	-27.8	-17.8	-9.70
Range				
<b>12 months</b>				
n	60	63	59	31
Median	1.51	-34.2	-26.4	-9.38
Range				

iFDPD Free urinary deoxypyridoline crosslinks; N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients with data at both time points.  
Data derived from Table T6.1.2.

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**Table 39 Percentage change in NTX levels from baseline to 3, 6, and 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Anastrozole 1 mg (N = 80)	Tamoxifen 20 mg (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)	Control (N = 39)
<b>3 months</b>				
n	71	71	68	34
Median	11.1	-28.0	-26.7	-3.99
Range				
<b>6 months</b>				
n	69	68	66	31
Median	11.9	-32.1	-35.0	-9.51
Range				
<b>12 months</b>				
n	63	66	61	35
Median	14.6	-40.0	-33.2	-12.7
Range				

N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients with data at both time points; NTX Urinary crosslinked N-telopeptides.  
Data derived from Table T6.2.2.

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**Table 42 Percentage change in i Bone ALP levels from baseline to 3, 6, and 12 months: primary analysis population and eligible controls with data at both time points**

Percentage change from baseline	Anastrozole 1 mg (N = 80)	Tamoxifen 20 mg (N = 87)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 82)	Control (N = 39)
<b>3 months</b>				
n	72	74	68	32
Median	6.91	-5.38	-3.85	7.90
Range				
<b>6 months</b>				
n	69	69	67	30
Median	14.0	-9.74	-9.75	3.91
Range				
<b>12 months</b>				
n	67	65	62	31
Median	21.8	-14.7	-8.01	2.24
Range				

N Number of patients in the primary analysis population or number of eligible control patients; n Number of patients with data at both time points; i Bone ALP Serum bone isoform of alkaline phosphatase. Data derived from Table T6.3.2.

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/s/

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