

Best objective response for all randomized patients

(a) Intent-to-treat analysis

Table 26 summarizes the best objective response for all randomized patients.

Table 26 Best objective response for all randomized patients

| Objective response | Number (%) of patients | |
|--------------------------------|-------------------------------|------------------------------|
| | Anastrozole 1 mg (n = 171) | Tamoxifen 20 mg (n = 182) |
| Responders | 36 | 31 |
| Complete response | 5 | 5 |
| Partial response | 31 | 26 |
| Non-responders | 135 | 151 |
| Stable disease \geq 24 weeks | 65 | 52 |
| Stable disease <24 weeks | 7 | 4 |
| Progression | 63 | 95 |

The objective-response rate was defined as the proportion of patients showing a best objective response of complete response (CR) or partial response (PR). The best objective-response rate of CR or PR was slightly higher for patients who were randomized to anastrozole (21.1%) than for patients who were randomized to tamoxifen (17.0%). The proportion of patients who had a best response of stable disease \geq 24 weeks also appeared to be greater for patients who were randomized to anastrozole (38.0%), compared with patients who were randomized to tamoxifen (28.6%). Statistical testing of these data was not performed.

(b) Per-protocol analysis

The proportion of patients who had a best objective-response rate of CR or PR was greater for patients who were randomized to anastrozole (21.8%), compared with the rate for patients who were randomized to tamoxifen (18.0%). The proportion of patients who had a best response of stable disease $>$ 24 weeks also appeared to be greater for patients who were randomized to anastrozole (40.6%), compared with the proportion for patients who were randomized to tamoxifen (28.0%). The estimated differences in response rates were 4.64 and 3.80 from the adjusted and unadjusted analyses, respectively. Non-inferiority, which was demonstrated using the lower 1-sided 95% confidence limit for the difference in response rates, was greater than the statistical criterion of -10% for both the adjusted (-3.03%) and unadjusted analyses (-3.43%).

8.2.10.2 Time to treatment failure

Table 27 summarizes the reasons for treatment failure for all randomized patients as of 10 March 1999, the data cutoff date. Some patients had treatment failure resulting from objective progression before treatment was stopped.

Table 27 Reasons for treatment failure for all randomized patients

| Primary reason for treatment failure | Number (%) of patients | | | |
|---|-------------------------------|--------|------------------------------|--------|
| | Anastrozole 1 mg (n = 171) | | Tamoxifen 20 mg (n = 182) | |
| Disease progression (objective) | 100 | (58.5) | 121 | (66.5) |
| Disease-progression (investigator's opinion) | 13 | (7.6) | 13 | (7.1) |
| Adverse event | 8 | (4.7) | 6 | (3.3) |
| Unwilling to continue | 2 | (1.2) | 4 | (2.2) |
| Death without evidence of progression | 3 | (1.8) | 3 | (1.6) |
| Protocol non-compliance | 2 | (1.2) | 2 | (1.1) |
| Never started randomized treatment | 1 | (0.6) | 0 | (0.0) |
| Other reason | 6 | (3.5) | 3 | (1.6) |
| Total number of patients with treatment failure | 135 | (78.9) | 153 | (83.5) |

Of the 353 patients who were randomized to trial treatment, 247 (70.0%) patients had treatment failure resulting from disease progression (221 [62.6%] patients from the objective algorithm and 26 [7.4%] patients from the investigator's opinion). Thirty-four (9.6%) patients were withdrawn from trial treatment for reasons other than disease progression and 6 (1.7%) patients died before progression.

A total of 287 (81.3%) patients had treatment failure. A smaller proportion of patients who were randomized to anastrozole (78.9%) had treatment failure, compared with the proportion of patients who were randomized to tamoxifen (83.5%). Patients who were randomized to anastrozole also had a longer estimated median time to treatment failure (231 days), compared with the time for patients who were randomized to tamoxifen (163 days). Statistical testing of these data was not performed.

8.2.10.3 Duration of response

Duration of response was planned to be assessed in 2 ways:

- from the date of randomization to the date of first determined progression or death from any cause,
- from the date of first documentation of response to the date of first determined progression or death from any cause

Table 28 summarizes the duration of response for all randomized patients who had a best objective response of CR or PR.

Table 28 Duration of response for all randomized patients who had a best objective response of CR or PR

| Response data | Anastrozole 1 mg (n = 171) | Tamoxifen 20 mg (n = 182) |
|--|-------------------------------|------------------------------|
| Number (%) of patients with objective response | 36(21.1) | 31 (17.0) |
| Duration of response from randomization | | |
| Median (days) | 490 | 546 |
| Range (days) | | |
| Duration of response from first response | | |
| Median (days) | 376 | 332 |
| Range (days) | | |

Sixty-seven (19.0%) patients were responders (patients who had a best objective response of CR or PR). The estimated median duration of response from the time of randomization was lower for patients who were randomized to anastrozole (490 days) than for patients who were randomized to tamoxifen (546 days). However, the median duration of response from the first objective response was slightly higher for patients who were randomized to anastrozole (376 days), compared with the response for patients who were randomized to tamoxifen (332 days). These comparisons should be interpreted cautiously because they are based on small numbers of patients grouped by response to trial treatment. The reason for the difference between the 2 methods of defining duration of response is not clear. Statistical testing of these data was not planned.

Duration of Clinical Benefit

Table 29 Patients who had clinical benefit

| Objective response | Number of patients (%) | |
|--------------------------------|-------------------------------|------------------------------|
| | Anastrozole 1 mg (n = 340) | Tamoxifen 20 mg (n = 328) |
| Clinical benefit | | |
| Complete response | 5 (2.9) | 5 (2.7) |
| Partial response | 31 (18.1) | 26 (14.3) |
| Stable disease \geq 24 weeks | 65 (38.0) | 52 (28.6) |
| No clinical benefit | | |
| Stable disease <24 weeks | 7 (4.1) | 4 (2.2) |
| Progression | 63 (36.8) | 95 (52.2) |

The proportions of patients who had a clinical benefit appeared to be greater for patients who were randomized to anastrozole 101 (59.1%) compared with patients who were randomized to tamoxifen 83 (45.6%).

Table 30 summarizes the duration of clinical benefit for patients who had a response of CR, PR, or SD $>$ 24 weeks, from the date of randomization to the date of first determined progression or death from any cause.

Table 30 Duration of clinical benefit from the date of randomization to the date of first determined progression or death from any cause

| Duration of clinical benefit | Anastrozole 1 mg (n = 171) | Tamoxifen 20 mg (n = 182) |
|--|-------------------------------|------------------------------|
| Number (%) of patients with CR, PR or SD \geq 24 | 101 (59.1) | 83 (45.6) |
| Duration of clinical benefit, Median (days) | 503 | 442 |
| Range (days) | | |

One hundred eighty-four (52.1%) patients had clinical benefit. For these patients, the estimated median duration of response from the time of randomization to the date of first

determined progression appeared to be greater for patients who were randomized to anastrozole (503 days), than for patients who were randomized to tamoxifen (442 days). These comparisons should be interpreted cautiously because they are based on small numbers of patients grouped by response to trial treatment. Statistical testing of these data was not planned.

8.2.10.4 Survival

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

Intent-to-treat analysis

Table 31 shows survival status at the time of data cutoff (10 March 1999) for the intent-to-treat population.

| Survival status | Randomized treatment | | All patients (n = 353) |
|--------------------|-------------------------------|------------------------------|---------------------------|
| | Anastrozole 1 mg (n = 171) | Tamoxifen 20 mg (n = 182) | |
| Alive ^a | 124 (72.52) | 129 (70.9) | 253 (71.7) |
| Dead | 47 (27.5) | 53 (29.1) | 100 (28.3) |

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

The death rate was similar for the treatment groups (47 [27.5%] patients who were randomized to anastrozole and 53 [29.1%] patients who were randomized to tamoxifen had died at the time of data cutoff.

The proportion of patients who were alive longer than 2 years was 57.7% for patients who were randomized to anastrozole and 61.2% for patients who were randomized to tamoxifen. A statistical analysis of survival was not performed because only 100 (28.3%) patients in this trial had died at the time of data cutoff.

Per-protocol analysis

The results from the secondary (per-protocol) analysis are consistent with those from the intent-to-treat analysis, with a similar Kaplan-Meier curve. The death rate was similar between the 2 treatment groups (31 [23.3%] patients who were randomized to anastrozole and 41 [27.3%] patients who were randomized to tamoxifen had died at the time of data cutoff). The proportion of patients who were alive 2 years after trial treatment had ended was 63.8% for patients who were randomized to anastrozole and 64.4% for patients who were randomized to tamoxifen.

Table 31B Survival Status at February 23, 2000 cut-off date

| Survival status | Number (%) of patients | | All patients (n = 353) |
|--------------------|---|--|---------------------------|
| | Randomized treatment Anastrozole 1 mg (n = 171) | Randomized treatment Tamoxifen 20 mg (n = 182) | |
| Alive ^a | 108 (63.2%) | 107 (58.8%) | 253 (60.9%) |
| Dead | 63 (36.8%) | 75 (41.2%) | 138 (39.1%) |

^a Data for these patients were censored at the last known obser

Using the intent-to-treat population, the death rate, as indicated in Table 31B the death rate was lower for the Arimidex group (36.8% vs. 41.2%) at the second time of data cut-off (February 23, 2000). The sponsor did not perform a statistical analysis of survival at both times of data cut-off because the protocol specified that "if the median time to death cannot be estimated at the time of submission only Kaplan-Meier curves will be presented for each treatment group." (p. 210 in the sponsor's vol. 6.19).

Results from the per-protocol analysis were similar to those from the ITT analysis.

8.2.11. Quality of life

Quality of Life issues were determined in terms of analgesic use, WHO performance status and bone pain assessment.

Analgesic use:

Analgesic use during this trial was evaluated at Weeks 12 and 24. Approximately 49% of the patients who were randomized to anastrozole and 47% of the patients who were randomized to tamoxifen did not require the use of analgesics at Week 12. Similarly, approximately 52% of the patients who were randomized to anastrozole and 50% of the patients who were randomized to tamoxifen did not require the use of analgesics at Week 24. The percentages of patients who required nonnarcotic agents, oral narcotic agents, or injectable narcotics were similar between the 2 treatment groups at both timepoints. No statistically significant difference was found between the 2 treatment groups for analgesic use at Weeks 12 and 24.

For both treatment groups, the mean score was below 1 (nonnarcotic) from baseline to Week 132. This finding indicated that the majority of patients either had not required the use of analgesics (analgesic use = 0) or had taken nonnarcotic agents (analgesic use = 1). Analgesic use was similar between the treatment groups, especially for visits before Week 36. Increasing percentages of patients withdrew from the trial after Week 36; therefore, no data for analgesic use was collected from these patients.

WHO performance status

World Health Organization performance status was assessed at Weeks 12 and 24. Approximately 91% of the patients who were randomized to anastrozole and 82% of the patients who were randomized to tamoxifen were either fully active and able to carry on all

pre-disease activities without restriction (PS = 0) or restricted in physically strenuous activity but ambulatory and able to perform work of a light or sedentary nature (PS = 1) at Week 12. At Week 24, approximately 93% of the patients who were randomized to anastrozole and 87% of the patients who were randomized to tamoxifen had PS of 0 or 1. The percentages of patients who had WHO performance scores of 3 or 4 were generally similar between the 2 treatment groups at both time-points.

This indicated that the majority of patients were either fully active or able to carry on all pre-disease performance without restriction or restricted in physically strenuous activity but ambulatory and able to perform work of a light or sedentary nature.

Bone pain

Bone pain during this trial was assessed at Weeks 12 and 24. Approximately 82% of the patients who were randomized to anastrozole and 80% of the patients who were randomized to tamoxifen had no bone pain or mild bone pain at Week 12. Similarly, approximately 88% of the patients who were randomized to anastrozole and 85% of the patients who were randomized to tamoxifen had no bone pain or mild bone pain at Week 24. It should be noted that 65.5% of patients who were randomized to anastrozole had bone metastases, compared with only 53.8% of the patients who were randomized to tamoxifen. The percentages of patients who had moderate or severe pain was similar between the 2 treatment groups at both time-points. One patient who was randomized to anastrozole had intractable pain at Week 12 and was given injectable narcotics. This patient had a WHO performance score of 4 (completely disabled) at this time point. For each treatment group, the mean score was below 1 (mild) from baseline to Week 132. This finding indicated that the majority of patients had no bone pain. Among those who experienced bone pain, the distribution was similar between the 2 treatment groups..

8.2.12 Treatment received after study trial

Table 32 summarizes the number of patients who were given radiotherapy, chemotherapy, or hormonal therapy after withdrawal from trial treatment. This table presents treatment given for the 264 patients who withdrew from the trial.

Table 32 Therapy given after withdrawal from trial treatment

| Therapy | Therapy given after withdrawal from trial treatment | | | |
|------------------|---|--------|------------------------------|--------|
| | Anastrozole 1 mg (n = 235) | | Tamoxifen 20 mg (n = 241) | |
| Radiotherapy | 73 | (31.1) | 77 | (32.0) |
| Chemotherapy | 106 | (45.1) | 105 | (43.6) |
| Hormonal therapy | 117 | (49.8) | 142 | (58.9) |
| Other | 52 | (22.1) | 49 | (20.3) |

A greater proportion of patients who were given tamoxifen received hormonal therapy after withdrawal 142/241 (58.9%) compared with patients who were given anastrozole 117/235(49.8%). The proportions of patients who received non-hormonal therapies were similar between the 2 treatment groups.

8.2.13 Age and Ethnicity Analysis of Efficacy

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

8.2.14 Applicant's summary evaluation of efficacy results

The median duration of follow-up for Trial 0030 was 538 days, with 71.4% of patients having progressed at the time of data cutoff (10 March 1999). These results are adequate for obtaining clinically reliable data for the primary efficacy end points of time to progression and objective response. This trial encountered recruitment difficulties because most patients in North America who have advanced breast cancer had received previous adjuvant treatment with tamoxifen. Therefore, with permission from the FDA, recruitment into Trial 0030 was stopped when companion Trial 0027 had achieved a full recruitment of 660 patients. Intent-to-treat analyses of both primary end points found that anastrozole met the pre-specified criteria for non-inferiority, compared with tamoxifen. For time to progression, the adjusted analysis (designated as the primary analysis) yielded a hazard ratio of 1.44 favoring anastrozole and a lower 95% confidence limit of 1.16 (greater than the 0.8 confidence limit required for non-inferiority). The unadjusted analysis also demonstrated non-inferiority with a hazard ratio of 1.42 and a lower 95% confidence limit of 1.15. Although these trials were not set up to show a difference between anastrozole and tamoxifen, the lower 95% confidence limit is greater than 1, suggesting that anastrozole might actually be superior to tamoxifen for time to progression. Patients who were randomized to anastrozole appeared to have a lower progression rate and longer median time to progression (66.7% and 338 days, respectively) than did patients who were randomized to tamoxifen (75.8% and 170 days, respectively). The per-protocol analysis for time to progression yielded hazard ratios of 1.53 and 1.51 for the adjusted and unadjusted analyses, respectively, with lower 95% confidence limits of 1.21 and 1.19, which are above the 0.80 confidence limit required for non-inferiority. The consistent results for all analyses for time to progression affirmed the robustness of the clinical trial data and showed that anastrozole was at least as efficacious as tamoxifen, with a suggestion of numerical superiority for time to progression. For objective-response rate, the adjusted analysis yielded an odds ratio of 1.38 and a difference in response rate of 5.01 favoring anastrozole, with a lower 95% confidence limit of -1.90% (greater than the -10% confidence limit required for non-inferiority). The unadjusted analysis for objective-response rate yielded an odds ratio of 1.30 and a difference in response rate of 4.02, with lower 95% confidence limit of -2.47%. The per-

protocol analysis yielded estimated differences in response rates of 4.64 and 3.80 from the adjusted and unadjusted analyses, respectively, both favoring anastrozole. Criteria for non-inferiority were met according to the results of the per-protocol analysis (-3.03% and -3.43% for adjusted and unadjusted analysis, respectively). The consistent results for all analyses affirmed the robustness of the clinical trial data and showed anastrozole to be at least as efficacious as tamoxifen for objective-response rate. Thirty-six (21.1%) patients who were randomized to anastrozole and 31 (17.0%) who were randomized tamoxifen were considered to be responders (had a best objective response of complete response or partial response).

The adjusted analysis of time to treatment failure yielded a hazard ratio of 1.35 with a lower 95% confidence limit of 1.11, while the unadjusted analysis yielded a hazard ratio of 1.33 with a lower 95% confidence limit of 1.10. This is consistent with the results for the primary end points in meeting the criteria for non-inferiority and shows that anastrozole is at least as efficacious as tamoxifen for time to treatment failure, with a suggestion of numerical superiority. Patients who were randomized to anastrozole had a lower rate of treatment failure and longer estimated median time to treatment failure (78.9% and 231 days, respectively), compared with the time for patients who were randomized to tamoxifen (83.5% and 163 days, respectively).

Statistical analyses were not planned for duration of response or duration of clinical benefit. Duration of clinical benefit was 503 days for anastrozole and 442 days for tamoxifen. Duration of response from randomization was 490 days for anastrozole and 546 days for tamoxifen, while duration of response from first response was 376 days for anastrozole and 332 days for tamoxifen. These comparisons must be interpreted cautiously because they are based on small numbers of patients grouped by response to trial therapy. The reason for the difference between the 2 methods for defining response is not clear. Two-year survival was similar for anastrozole (57.7%) and tamoxifen (61.2%); however, because only 28.3% of the patients in the trial died at the time of data cutoff (10 March 1999), there were too few patients to allow meaningful statistical analysis. The death rate was 27.5% for anastrozole and 29.1% for tamoxifen.

Significant protocol violations occurred for 2.5% of the patients and significant protocol deviations for 18.4% of the patients. The most common deviation was use of disallowed concomitant therapy (10.2% of patients). The most common non-permitted medication was a course of a glucocorticoid, which was given to treat exacerbation of chronic obstructive pulmonary disease or in conjunction with radiation therapy to spinal lesions. Because the per-protocol analyses and intent-to-treat analyses of the efficacy end points provided consistent results, the impact of these violations and deviations was small. For both treatment groups, response rates for patients who had measurable disease were higher than the response rates for all randomized patients (32.5% and 21.1% for patients who were given anastrozole and 22.1% and 17.0% for patients who were given tamoxifen). Patients who had only soft tissue or lung disease had higher response rates than patients who had all other disease combinations. Thirty-eight percent of the patients who were given anastrozole and 29% of the patients who were given tamoxifen achieved stable disease for more than 24 weeks. Such patients also benefit from treatment and indeed many such patients would probably have been included as responders in trials using less rigorous criteria. Analyses of analgesic use, bone pain scores, and performance

scores found no significant differences between the 2 treatments, but overall, most patients had performance scores less than 1. In general, data for these parameters fluctuate after Week 36 because of withdrawals. This trial demonstrates criteria for equivalence for both primary end points of time to progression and objective response rate. In addition, there was evidence of numerical superiority for time to progression. These findings suggest that anastrozole was at least as efficacious as tamoxifen for the treatment postmenopausal women with advanced breast cancer.

8.3 SAFETY RESULTS

All 352 treated patients were included in the safety evaluations according to actual treatment given. All adverse events that occurred during treatment or within 14 days after treatment was stopped for any reason were recorded.

Exposure

Trial treatment

Of the 352 patients who were included in the safety analyses, 170 patients were given anastrozole and 182 patients were given tamoxifen. Table 34. summarizes the extent of exposure to trial treatment and the duration of treatment (defined as the number of days from the date of the first dose until the date of the last dose by treatment group.

Table 33 Extent of exposure to trial treatment and duration of treatment

| Parameter | Duration of treatment | | | | Median (days) | Range (days) | |
|-----------------------------|------------------------|-----------|-----------|-----------|---------------|--------------|-----------|
| | Number (%) of patients | | | | | | |
| | 0 to 12 | >12 to 24 | >24 to 48 | >48 to 96 | | | |
| Anastrozole 1 mg (n=170) | 25 (14.7) | 28 (16.5) | 41 (24.1) | 61 (35.9) | 15 (8.8) | 263 | 18 to 932 |
| Tamoxifen 20 mg (n=182) | 35 (19.2) | 48 (26.4) | 45 (24.7) | 43 (23.6) | 11 (6.0) | 182 | 12 to 933 |

In general, more patients who were given tamoxifen had shorter periods of treatment, and more patients who were given anastrozole had longer periods of treatment. The median duration of treatment was longer for patients who were given anastrozole (263 days), compared with patients who were given tamoxifen (182 days). This finding correlates with the longer time to progression found for patients who were given anastrozole.

Concomitant treatment

No patient was made to withdraw from the trial because of concomitant treatment.

8.3.1 Overview of adverse events

Events that occurred during treatment or within 14 days after treatment was stopped were recorded as adverse events and are discussed in this section. Events determined by the investigator to be clearly related to progression of metastatic breast cancer were not recorded as adverse events.

Table 34 summarizes the number of patients with adverse events and the principal categories of adverse events. These categories are not mutually exclusive and patients may be included in more than 1 category. Data for patients with adverse events are included in this table, irrespective of the investigator's opinion of the causality of the event.

Table 34 Overview of adverse events

| Category ^a | Number (%) of patients | |
|--|-----------------------------|----------------------------|
| | Anastrozole 1 mg (n=170) | Tamoxifen 20 mg (n=182) |
| Patients who had 1 or more adverse events | 166 (97.6) | 171 (94.0) |
| Patients who had serious adverse events | 37 (21.8) | 42 (23.1) |
| Patients who had adverse events leading to withdrawal | 9 (5.3) | 8 (4.4) |
| Patients who had adverse events leading to death | 3 (1.8) | 2 (1.1) |
| Patients who had drug-related adverse events followed by death | 1 (0.6) | 0 |

^aPatients may be counted in more than 1 category.

All adverse events

Overall, 97.6% of the patients who were given anastrozole and 94.0% of the patients who were given tamoxifen had adverse events during the trial. Adverse events that occurred in more than 5% of patients in either treatment group are summarized by body system in Table 35. The 5% cutoff rate was selected to highlight the most frequently reported adverse events. All adverse events that occurred during the trial (including the 14-day follow-up period) at a rate of $\geq 5\%$ are summarized in Table 36

Table 35 Adverse events reported for more than 5% of patients in either treatment group during treatment, by body system

| Body system and adverse event by | Number (%) of patients | | | |
|----------------------------------|-----------------------------|--------|----------------------------|--------|
| | Anastrozole 1 mg (n=170) | | Tamoxifen 20 mg (n=182) | |
| Whole body | 127 | (74.7) | 126 | (69.2) |
| Asthenia | 54 | (31.8) | 65 | (35.7) |
| Pain | 43 | (25.3) | 48 | (26.4) |
| Back pain | 41 | (24.1) | 43 | (23.6) |
| Headache | 29 | (17.1) | 27 | (14.8) |
| Chest pain | 27 | (15.9) | 24 | (13.2) |
| Abdominal pain | 24 | (14.1) | 23 | (12.6) |
| Pelvic pain | 16 | (9.4) | 22 | (12.1) |
| Flu syndrome | 15 | (8.8) | 11 | (6.0) |
| Neck pain | 10 | (5.9) | 10 | (5.5) |
| Fever | 7 | (4.1) | 10 | (5.5) |
| Cardiovascular | 79 | (46.5) | 68 | (37.4) |
| Vasodilatation | 62 | (36.5) | 44 | (24.2) |
| Digestive | 103 | (60.6) | 111 | (61.0) |

| | | | | |
|---------------------------|----|--------|----|--------|
| Nausea | 52 | (30.6) | 62 | (34.1) |
| Diarrhea | 29 | (17.1) | 23 | (12.6) |
| Constipation | 26 | (15.3) | 38 | (20.9) |
| Vomiting | 25 | (14.7) | 22 | (12.1) |
| Anorexia | 19 | (11.2) | 29 | (15.9) |
| Dyspepsia | 11 | (6.5) | 10 | (5.5) |
| Metabolic and nutritional | 41 | (24.1) | 51 | (28.0) |
| Peripheral edema | 30 | (17.6) | 23 | (12.6) |
| Weight loss | 5 | (2.9) | 12 | (6.6) |
| Dehydration | 2 | (1.2) | 10 | (5.5) |
| Musculoskeletal | 59 | (34.7) | 49 | (26.9) |
| Bone pain | 33 | (19.4) | 32 | (17.6) |
| Arthritis | 14 | (8.2) | 2 | (1.1) |

Table 35 Adverse events reported for more than 5% of patients in either treatment group during treatment, by body system (continued)

| Body system and adverse event by | Number (%) of patients | | | |
|----------------------------------|-----------------------------|--------|----------------------------|--------|
| | Anastrozole 1 mg (n=170) | | Tamoxifen 20 mg (n=182) | |
| Nervous | 71 | (41.8) | 77 | (42.3) |
| Dizziness | 18 | (10.6) | 15 | (8.2) |
| Insomnia | 16 | (9.4) | 14 | (7.7) |
| Hypertonia | 13 | (7.6) | 20 | (11.0) |
| Anxiety | 12 | (7.1) | 11 | (6.0) |
| Paresthesia | 11 | (6.5) | 14 | (7.7) |
| Depression | 9 | (5.3) | 14 | (7.7) |
| Respiratory | 89 | (52.4) | 84 | (46.2) |
| Cough increased | 36 | (21.2) | 29 | (15.9) |
| Pharyngitis | 34 | (20.0) | 38 | (20.9) |
| Dyspnea | 33 | (19.4) | 29 | (15.9) |
| Sinusitis | 11 | (6.5) | 7 | (3.8) |
| Rhinitis | 6 | (3.5) | 11 | (6.0) |
| Skin and appendages | 55 | (32.4) | 44 | (24.2) |
| Rash | 27 | (15.9) | 19 | (10.4) |
| Pruritus | 11 | (6.5) | 8 | (4.4) |
| Sweating | 6 | (3.5) | 11 | (6.0) |
| Urogenital | 47 | (27.6) | 57 | (31.3) |
| Urinary tract infection | 9 | (5.3) | 12 | (6.6) |
| Breast pain | 7 | (4.1) | 16 | (8.8) |
| Leukorrhea | 5 | (2.9) | 18 | (9.9) |

^a A patient may have had more than 1 adverse event.

A wide variety of adverse events were reported for patients in both treatment groups. Some of these adverse events occurred frequently in both treatment groups (ie, asthenia, and various types of pain) and are common events in patients with advanced breast cancer. The most frequently reported adverse event was asthenia, which occurred in 54 (31.8%) patients who were given anastrozole and 65 (35.7%) patients who were given tamoxifen. Other commonly reported adverse events were nausea (52 [30.6%] patients who were given anastrozole and 62 [34.1%] patients who were given tamoxifen), vasodilatation (62 [36.5%] patients who were given anastrozole and 44 [24.2%] patients who were given tamoxifen), pain (43 [25.3%] patients who were given anastrozole and 48 [26.4%] patients who were given tamoxifen), back pain (41 [24.1%] patients who were given anastrozole and 43 [23.6%] patients who were given tamoxifen), bone pain (33 [19.4%] patients who were given anastrozole and 32 [17.6%] patients who were given tamoxifen), and constipation (26 [15.3%] patients who were given anastrozole and 38 [20.9%] patients who were given tamoxifen). Arthritis was more common among patients who were given anastrozole (14 [8.2%] patients) than those who were given tamoxifen (2 [1.1%] patients). On the basis of the anticipated pharmacological profiles of anastrozole and tamoxifen, certain adverse events were grouped into the following prespecified adverse event categories: depression, tumor flare, thromboembolic disease (includes both venous and arterial events), gastrointestinal disturbance, hot flushes (includes vasomotor menopause-like symptoms), vaginal dryness, lethargy, vaginal bleeding, and weight gain. Table 36 presents the number and percentage of patients who reported these pre-specified adverse events categories during this trial.

Table 36 Pre-specified adverse events categories reported during the trial

| Adverse event by | Number (%) of patients | |
|------------------------------|-----------------------------|----------------------------|
| | Anastrozole 1 mg (n=170) | Tamoxifen 20 mg (n=182) |
| Depression | 9 (5.3) | 14 (7.7) |
| Tumor flare | 7 (4.1) | 10 (5.5) |
| Thromboembolic disease | 7 (4.1) | 15 (8.2) |
| Gastrointestinal disturbance | 91 (53.5) | 104 (57.1) |
| Hot flushes | 65 (38.2) | 50 (27.5) |
| Vaginal dryness | 8 (4.7) | 7 (3.8) |
| Lethargy | 2 (1.2) | 6 (3.3) |
| Vaginal bleeding | 2 (1.2) | 7 (3.8) |
| Weight gain | 5 (2.9) | 2 (1.1) |

^a A patient may have had more than 1 event.

The most frequently reported pre-specified adverse events categories were gastrointestinal disturbance and hot flushes. The proportions of patients who had gastrointestinal disturbance and hot flushes were 53.5% and 38.2%, respectively, for patients who were given anastrozole and 57.1% and 27.5%, respectively, for patients who were given tamoxifen. A higher incidence of thromboembolic disease was reported in patients who were given tamoxifen (8.2%) than in patients who were given anastrozole (4.1%). The

proportions of patients who had vaginal dryness and weight gain were higher in the group who were given anastrozole (4.7% and 2.9%, respectively), compared with the group who were given tamoxifen (3.8% and 1.1%, respectively). Fewer patients who were given anastrozole reported depression, tumor flare, gastrointestinal disturbance, lethargy, and vaginal bleeding than patients who were given tamoxifen.

Drug Related Adverse Events

One hundred sixty-six (47.2%) patients had drug-related adverse events (87 [51.2%] patients who were given anastrozole and 79 [43.4%] who were given tamoxifen). The most commonly reported drug-related adverse events were vasodilatation (52 [30.6%] patients who were given anastrozole and 36 [19.8%] who were given tamoxifen), nausea (17 [10.0%] patients who were given anastrozole and 25 [13.7%] who were given tamoxifen), and asthenia (13 [7.6%] patients who were given anastrozole and 9 [4.9%] who were given tamoxifen). Most adverse events were mild or moderate in intensity.

8.3.2 Deaths

Table 37 shows the number of patients who died from breast cancer alone or other causes at any time during or after treatment. If a patient had multiple causes of death, only the primary cause of death from the survival CRF was presented here.

Table 37. Deaths

| Category | Number (%) of patients | |
|--|------------------------|-----------------|
| | Anastrozole 1 mg | Tamoxifen 20 mg |
| Number of patients treated | 170 | 182 |
| Number of patients who died | 48 (28.2) | 52 (28.6) |
| Deaths | | |
| During treatment ^a | 8 (4.7) | 6 (3.3) |
| Related to breast cancer | 5 (2.9) | 5 (2.7) |
| Due to adverse event ^b | 3 (1.8) | 1 (0.5) |
| Due to adverse event related to trial treatment ^c | 0 | 0 |
| After treatment | 40 (23.5) | 46 (25.3) |
| Related to breast cancer | 36 (21.2) | 44 (24.2) |
| Other causes | 3 (1.8) | 2 (1.1) |
| Unknown ^d | 1 (0.6) | 0 |

^a Death during treatment includes all deaths occurring within 14 days of treatment cessation and any death due to an adverse event that had an onset within 14 days of treatment cessation.

A total of 100 deaths were reported at the time of data cutoff (10 March 1999):

- 90 deaths from causes related to breast cancer
- 10 deaths from other causes

Most patients (41 [24.1%] patients who were given anastrozole and 49 [26.9%] patients were given tamoxifen) died from causes related to breast cancer during treatment (including the 14-day follow-up period). The numbers of deaths resulting from adverse events as a primary cause are listed in table 38.

Table 38. Primary causes of deaths during treatment resulting from adverse events

| Primary cause of death by body system and COSTART-preferred term | Number (%) of patients | |
|---|-----------------------------|----------------------------|
| | Anastrozole 1 mg (n=170) | Tamoxifen 20 mg (n=182) |
| Number of patients who died from adverse events | 3 (1.8) | 1 (0.5) |
| Reason for death | | |
| Suicide attempt | 1 (0.6) | 0 |
| Gastrointestinal hemorrhage | 1 (0.6) | 0 |
| Dyspnea | 1 (0.6) | 0 |
| Angioedema | 0 | 1 (0.5) |

Withdrawals from treatment due to adverse events

The number of patients withdrawn from trial treatment because of adverse events and the adverse events leading to withdrawal from trial treatment are presented in Table 39

Table 39. Patients with adverse events leading to withdrawal from treatment

| Body system and adverse event ^a | Number (%) of patients | |
|--|--------------------------|-------------------------|
| | Anastrozole 1 mg (n=170) | Tamoxifen 20 mg (n=182) |
| Number of patients with adverse events that led to withdrawal | 9 (5.3) | 8 (4.4) |
| Drug-related adverse events | 3 (1.8) | 5 (2.7) |
| Serious drug-related adverse events | 1 (0.6) | 1 (0.5) |
| Cardiovascular | 2 (1.2) | 2 (1.1) |
| Cerebrovascular accident | 1 (0.6) | 0 |
| Pulmonary embolus | 1 (0.6) | 1 (0.5) |
| Thrombophlebitis | 0 | 2 (1.1) |
| Digestive | 3 (1.8) | 1 (0.5) |
| Diarrhea | 1 (0.6) | 0 |
| Gastrointestinal hemorrhage | 1 (0.6) | 0 |
| Gastrointestinal neoplasia | 1 (0.6) | 0 |
| Nausea | 0 | 1 (0.5) |
| Respiratory | 1 (0.6) | 0 |
| Dyspnea | 1 (0.6) | 0 |
| Skin and appendages | 2 (1.2) | 1 (0.5) |
| Pruritus | 1 (0.6) | 0 |
| Rash | 1 (0.6) | 1 (0.5) |
| Urogenital | 1 (0.6) | 0 |
| Kidney function abnormal | 1 (0.6) | 0 |
| Metabolic and nutritional | 0 | 3 (1.6) |
| Dehydration | 0 | 1 (0.5) |
| Peripheral edema | 0 | 1 (0.5) |
| Weight gain | 0 | 1 (0.5) |
| Nervous | 0 | 1 (0.5) |
| Amnesia | 0 | 1 (0.5) |

^a A patient may have been withdrawn because of more than 1 adverse event.

Nine (5.3%) patients who were given anastrozole and 8 (4.4%) patients who were given tamoxifen withdrew from treatment because of adverse events. The incidence of withdrawal from trial treatment because of an adverse event was similar between the 2 treatment groups. Three (1.8%) patients who were given anastrozole (Patients 0013/0002, 0032/0001, and 0084/0011) had drug-related adverse events that led to withdrawal. One (0.6%) of these patients had a serious drug-related event: Patient 0013/0002 was found to have a serum creatinine of 2.4 mg/dL after 12 months of trial treatment and underwent renal biopsy, which revealed crescentic glomerulonephritis.

8.3.4 Serious adverse events

Serious adverse events were defined according to the criteria given in Section 8.1.1 of the protocol. A total of 79 (22.4%) patients had 1 or more serious adverse events; 37 (21.8%) of patients who were given anastrozole and 42 (23.1%) patients who were given tamoxifen. The incidences of serious adverse events were similar between the 2 treatment groups. More patients 8 (4.4%) patients who were given tamoxifen had serious drug-related adverse events, compared with patients who were given anastrozole 3 (1.8%) patients. The proportion of patients who had serious adverse events that led to death or withdrawal was similar between the 2 treatment groups.

Serious adverse events that were reported for at least 1% of patients in either treatment group are presented in Table 40, by body system.

Table 40 Serious adverse events reported for at least 1% of patients in either treatment group during treatment, by body system

| Body system and adverse event | Number (%) of patients | |
|---|-----------------------------|----------------------------|
| | Anastrozole 1 mg (n=170) | Tamoxifen 20 mg (n=182) |
| Number of subjects who had serious adverse events | 37 (21.8) | 42 (23.1) |
| Serious adverse events leading to death | 3 (1.8) | 2 ^a (1.1) |
| Serious adverse events leading to withdrawal | 5 (2.9) | 3 (1.6) |
| Drug-related serious adverse events | 3 (1.8) | 8 (4.4) |
| Whole body | 13 (7.6) | 17 (9.3) |
| Back pain | 3 (1.8) | 0 |
| Abdominal pain | 2 (1.2) | 2 (1.1) |
| Chest pain | 2 (1.2) | 2 (1.1) |
| Asthenia | 1 (0.6) | 6 (3.3) |
| Cellulitis | 1 (0.6) | 2 (1.1) |
| Pelvic pain | 1 (0.6) | 2 (1.1) |
| Cardiovascular | 8 (4.7) | 9 (4.9) |
| Syncope | 3 (1.8) | 1 (0.5) |
| Pulmonary embolus | 2 (1.2) | 1 (0.5) |
| Thrombophlebitis | 1 (0.6) | 2 (1.1) |
| Myocardial infarction | 0 | 2 (1.1) |
| Digestive | 12 (7.1) | 11 (6.0) |
| Nausea | 4 (2.4) | 5 (2.7) |

| | | |
|---------------------------|----------|---------|
| Dysphagia | 2 (1.2) | 0 |
| Melena | 2 (1.2) | 1 (0.5) |
| Vomiting | 1 (0.6) | 6 (3.3) |
| Metabolic and nutritional | 2 (1.2) | 8 (4.4) |
| Dehydration | 1 (0.6) | 7 (3.8) |
| Musculoskeletal | 3 (1.8) | 7 (3.8) |
| Pathological fracture | 2 (1.2) | 5 (2.7) |
| Nervous | 5 (2.9) | 6 (3.3) |
| Neuropathy | 0 | 2 (1.1) |
| Respiratory | 12 (7.1) | 5 (2.7) |
| Dyspnea | 7 (4.1) | 1 (0.5) |
| Pneumonia | 3 (1.8) | 2 (1.1) |
| Asthma | 2 (1.2) | 0 |
| Pleural effusion | 1 (0.6) | 2 (1.1) |
| Urogenital | 2 (1.2) | 3 (1.6) |
| Breast neoplasm | 0 | 2 (1.1) |

^a A patient may have had more than 1 serious adverse event.

The most commonly reported serious adverse events were nausea 4 (2.4%) patients who were given anastrozole and 5 (2.7%) who were given tamoxifen, dyspnea 7 (4.1%) patients who were given anastrozole and 1 (0.5%) who were given tamoxifen, dehydration 1 (0.6%) patients who were given anastrozole and 7 (3.8%) who were given tamoxifen, pathological fracture 2 (1.2%) patients who were given anastrozole and 5 (2.7%) who were given tamoxifen, vomiting 1 (0.6%) patients who were given anastrozole and 6 (3.3%) who were given tamoxifen, and asthenia 1 (0.6%) patients who were given anastrozole and 6 (3.3%) who were given tamoxifen. The incidence of the remaining serious adverse events was similar between the 2 treatment groups.

8.3.5 Clinical laboratory data

Hematology

Few patients developed laboratory abnormalities in hematology during treatment.

Hepatic biochemistry

Mean alkaline phosphatase, AST, and ALT levels in both treatment groups tended to decrease for the first year, possibly reflecting efficacy of treatment. Mean cholesterol levels decreased slightly in patients who were given tamoxifen and increase slightly in patients who were given anastrozole. Triglyceride levels increased in both treatment groups.

Laboratory abnormalities in alkaline phosphatase and total cholesterol were more common in patients who were given anastrozole than in patients who were given tamoxifen. Of the 16 patients who had abnormalities in serum cholesterol, 11 patients had peak serum cholesterol levels less than 300 mg/dl, 4 patients had peak levels between 300 and 400 mg/dl, and 1 patient had a peak level at 427 mg/dl.

Other biochemistry

Mean values for creatinine, sodium, potassium, and calcium were similar between the 2 treatment groups, and there were few laboratory abnormalities related to these parameters.

Body weight

From baseline to Week 96, mean weight was slightly greater in patients who were given anastrozole, compared with patients who were given tamoxifen.

Vital signs

Intermittent variability in vital signs measurements during the trial was considered clinically insignificant. Overall, mean blood pressure and pulse were similar between the 2 treatment groups throughout the trial.

8.3.6 Age and Ethnicity Analysis of Safety

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

8.3.7 Applicant's evaluation of safety results

In general, the numbers of adverse events, serious adverse events, events leading to withdrawal, and events leading to death were similar between the 2 treatment groups. Within the pre-specified adverse event categories, thromboembolic disease was more common in patients who were given tamoxifen, compared with patients who were given anastrozole (8.2% and 4.1%, respectively). A greater number of patients who were given tamoxifen withdrew from trial treatment because of thromboembolic events, compared with patients who were given anastrozole (3 patients and 1 patient, respectively). Three thromboembolic events in patients who were given tamoxifen were judged by the investigator to be drug related; none of the patients who were given anastrozole had thromboembolic events judged to be drug related.

Tumor flare was slightly more common in patients who were given tamoxifen; the 2 patients who were withdrawn from the trial because of tumor flare (both had hypercalcemia) had been given tamoxifen. Hot flushes, vaginal dryness, and weight gain were more common in patients who were given anastrozole, while gastrointestinal disturbances, vaginal bleeding, lethargy, and depression were more common in patients who were given tamoxifen. The somewhat higher frequency of hot flushes and vaginal dryness reported by patients who were given anastrozole might be due to anastrozole's ability to lower serum estradiol to level of detection, whereas tamoxifen has some recognized estrogen-agonist activity in postmenopausal women.

Most deaths (90%) were related to breast cancer. Four patients died because of adverse events: 3 patients who had been given anastrozole (suicide, gastrointestinal bleeding, respiratory failure) and 1 patient who had been given tamoxifen (angioedema). In cases where adverse events led to death, none of the primary causes of death were drug related..

Similar proportions of patients withdrew from treatment because of adverse events (5.3% of patients who were given anastrozole and 4.4% of patients who were given tamoxifen) or had drug-related adverse events leading to withdrawal (1.8% of patients who were given anastrozole and 2.7% of patients who were given tamoxifen). There was 1 serious drug-related adverse event that led to withdrawal in both the anastrozole group (renal insufficiency) and the tamoxifen group (pulmonary embolus). The overall incidence of serious adverse events was also similar between the treatment groups (21.8% of the patients who were given anastrozole and 23.1% of the patients who were given tamoxifen). More patients who were given anastrozole had serious adverse events related to the respiratory system (7.1% of patients who were given anastrozole and 2.7% of patients who were given tamoxifen), while serious adverse events related to the musculoskeletal system and metabolic and nutritional system were more common in patients who were given tamoxifen (1.8% and 1.2%, respectively, for patients who were given anastrozole and 3.8% and 4.4%, respectively, for patients who were given tamoxifen). Due to the small numbers, the clinical significance of these data is uncertain. Despite concerns about anastrozole's effect on bone mineral density, fractures were slightly more common in patients who were given tamoxifen during this trial. An increase in joint symptoms (arthritis, arthrosis, and arthralgia) was found in patients who were given anastrozole, but a causal relationship and physiologic mechanism is uncertain. Hematological parameters changed very little during the trial for either treatment group. Mean serum alkaline phosphatase, AST, ALT, GGT, and lactate dehydrogenase levels in both treatment groups tended to decrease for the first year, possibly reflecting efficacy in treatment. Mean serum cholesterol levels tended to increase slightly for patients who were given anastrozole and decreased slightly for patients who were given tamoxifen. The clinical correlate of this finding is uncertain; the 2 patients in this trial who experienced a myocardial infarction during treatment had been given tamoxifen. More patients who were given anastrozole developed laboratory abnormalities in serum alkaline phosphatase and total bilirubin. Review of these cases showed that these abnormalities could be directly related to breast cancer progression. There was little change in pulse, blood pressure, or weight in either treatment group. Overall, both anastrozole and tamoxifen were well tolerated.

8.3.8 APPLICANT'S OVERALL CONCLUSIONS

Trial 1033IL/0030 was designed to evaluate the efficacy and tolerability of anastrozole versus tamoxifen as a first-line therapy in the treatment of advanced breast cancer in postmenopausal women. Anastrozole satisfied the predefined criteria of equivalence to tamoxifen for the 2 primary end points of time to disease progression and objective response for both the intention-to-treat and per-protocol analyses. In addition, there was numerical superiority of anastrozole for time to progression. Supporting results were observed from the secondary end points. There were too few deaths to allow statistical comparisons. Therefore, one may conclude that anastrozole is at least as effective as tamoxifen in the first-line treatment of advanced breast cancer in postmenopausal women.

Similar rates of adverse events, serious adverse events, adverse events leading to withdrawal, and adverse events leading to death were reported for both treatment groups. Both anastrozole and tamoxifen were well tolerated. Among the prespecified adverse event categories, depression, tumor flare, thromboembolism, gastrointestinal disturbances, lethargy, and vaginal bleeding were less common in patients who were given anastrozole, while hot flushes, vaginal dryness and weight gain were more common. The greater frequency of hot flushes and vaginal dryness, together with the reduced frequency of vaginal bleeding and the adverse event vaginal discharge (leukorrhea), is consistent with the known pharmacology of anastrozole and the fact that anastrozole would be predicted to lack estrogenic activity and estrogenic effects on the endometrium. The incidence of thromboembolic events with anastrozole was low.

9.0 FDA ASSESSMENT OF RESULTS:

9.1 PROTOCOL 0027

9.1.1 DEMOGRAPHICS

A total of 668 patients were enrolled in this study at 83 sites in several countries outside North America. 340 patients (50.9%) were randomized to trial treatment, anastrozole and 328 (49.1%) were randomized to tamoxifen. The distribution of patients in terms of age, body mass and ethnic origin is as indicated in Table 2.

Patient characteristics are as indicated in Tables 3 and 4 obtained from the sponsor's submission. The majority of patients 368 (55.1%) had ER/PR Unknown versus 298 (44.6%) who had ER+/PR+ status. Patients in the tamoxifen group had more advanced disease and more sites of metastatic disease than in the anastrozole group. The difference is most striking among patients with pulmonary metastases. If metastatic diseases are grouped into bony and soft tissue distributions, patients in the tamoxifen group appear to have more extensive disease in more critical soft tissue organs than in the anastrozole group.

All other characteristics however showed no glaring disparities.

Overall there was a satisfactory balance in the distribution of demographic characteristics between the two treatment groups.

9.1.2 Protocol Violation and Deviations

A protocol violation was defined as any infringement of the protocol selection criteria. A protocol violation was defined as any departure from the protocol design or procedures after the patient had entered the trial.

9.1.2.1 Postmenopausal Status.

The inclusion criteria required enrolled patients to be post menopausal. Post menopausal status was defined as:

(i) women aged 50 years or over who have not menstruated during the preceding 12 months or who have follicle stimulating hormone (FSH) levels within the post-menopausal range;

(ii) women under the age of 50 years who have FSH levels within the post-menopausal range

43 patients in this study were under the age of 50. 3 of these patients had FSH in the post menopausal range

Other reasons provided by the sponsor were:

- Post-menopausal due to surgery 4 patients
- Patient's physicians claim prior amenorrhea clinically 11 patients
- Prior systemic Chemotherapy, thus presumption of amenorrhea 22 patients
- No information 3 patients

9.1.2.2 Protocol Deviations

The most frequent deviations were:

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

9.1.2.3 Summary of effect of Violations and deviations: A review of data on individual patients involved in various protocol violations and deviations reveal no material effect or influence on the outcome of the studies.

9.1.3 Withdrawals:

A total of 476 (71.6%) patients who started trial treatment withdrew from the trial. 235 (69.9%) patients who were given anastrozole and 241 (73.3%) patients who were given tamoxifen. The majority of all patients 390/665 (58.6%) withdrew because of disease progression; 193/336 (57.4%) patients on arimidex and 197/329 (59.9) patients on tamoxifen.

A total of 24 (3.6%) patients died while on study drug or within 14 days; 11/336 (3.2%) on Arimidex 13/329 (3.9%) on tamoxifen. The majority of the deaths were due to progressive disease.

Overall, the withdrawal rates and reasons for withdrawal were similar between the 2 treatment groups.

The patients who had withdrawn from the trial were given radiotherapy, chemotherapy, hormonal therapy and other clinically appropriate treatment regimen.

9.1.4 Disposition of Patients.

668 patients were randomized and were all included in the primary ITT efficacy end point analysis. 665 patients actually received trial treatment and were included in the safety analysis.

9.1.2 EFFICACY RESULTS

9.1.2.1 Primary Efficacy Endpoints:

Populations analyzed

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

9.1.2.1.1 Time to Progression: Time to progression was evaluated for each patient on the study. Using the ITT approach, a total of 495 (78.2%) patients had progressive disease at the time of data cut-off.

Of these, 250 patients were randomized to Arimidex and 245 patients to tamoxifen. The estimated median time to progression was 249 days for patients randomized to Arimidex and 246 days for patients randomized to tamoxifen. The results of statistical analysis were very similar to those based on the sponsor's data. Using the PP population (secondary approach), 581 patients were included in this population. Of these, 290 (49.9%) patients were randomized to Arimidex and 291 (50.1%) patients to tamoxifen. A total of 434 (74.7%) patients had disease progression. Of these, 218 patients were randomized to Arimidex and 216 patients to tamoxifen. The estimated median time to progression was 249 days for patients randomized to Arimidex and 246 days for patients randomized to tamoxifen. Results from the per-protocol analysis were consistent with those from the ITT analysis

See the Statistician's report for the Kaplan-Meier probability plot of time to progression using both types of analyses.

9.1.2.1.2 Objective response

Table 43 summarizes the medical reviewer's results along with the sponsor's results of objective-response rate using the intent-to-treat population. The reviewer's objective-response rate of CR or PR for all randomized patients was identical with the sponsor's. The results were very similar for patients randomized to receive Arimidex and patients randomized to receive tamoxifen (32.9% vs. 32.6%). With the exception of 1 patient (001/0107), the results for patients classified as non-responders were similar as well. This patient had stable disease that was less than 24 weeks.

Results of the adjusted analysis (using the ITT population) showed that the estimated difference in response rate (-1.01%) favored tamoxifen. The lower 1-sided 95% confidence limit for the difference rate (Arimidex - tamoxifen) was -6.74. The unadjusted analysis gave an estimated difference in response rate of 0.32% and a lower 95% confidence limit of -5.37%. The reviewer agrees with the sponsors conclusion that Arimidex was equivalent to tamoxifen in terms of objective-response rate.

The results from the per-protocol analysis were consistent with those from the ITT analysis.

TABLE 41 Objective Response for all Randomized patients

| | SPONSOR | | MEDICAL REVIEWER | |
|----------------------|-----------------|-------------------|------------------|-------------------|
| | ARIMIDEX 1mg | TAMOXIFEN 20mg | ARIMIDEX 1mg | TAMOXIFEN 20mg |
| #Pts Enrolled | 340 | 328 | 340 | 328 |
| Responders | 112 (32.9) | 107 (32.6) | 112 (32.9) | 107 (32.6) |
| CR | 19 (5.6) | 16 (4.9) | 19 (5.6) | 15 (4.9) |
| PR | 93 (27.4) | 91 (27.7) | 93 (27.4) | 91 (27.7) |
| Non-Responders | 228 (67.1) | 221 (67.4) | 228 (67.1) | 221 (67.4) |
| SD>24wks | 79 (23.2) | 75 (22.9) | 79 (23.2) | 74 (22.6) |
| Progression | 149 (43.8) | 146 (44.5) | 149 (43.8) | 147 (44.8) |

9.1.2 Secondary Endpoints

9.1.2.1 Time to Death (Survival)

The survival data comprised three dates; the initial cut-off date of March 10, 1999, the 4 month safety update of September 9 1999 and an updated cut off date of February 23, 2000.

Using the intent-to-treat population, at the second time of data cut-off, the Kaplan-Meier estimate for the median time were 1145 days for the Arimidex group and 1246 days for the tamoxifen group. The adjusted analysis (the protocol specified primary analysis) resulted in an estimated hazard ratio (tamoxifen:Arimidex) of 0.87 with a p-value of 0.29 at the second time of data cut-off, as compared to a hazard ratio of 0.76 and p-value of 0.09 at the first time of data cut-off. This suggested that tamoxifen was associated with a reduction (compared with Arimidex) in the “instantaneous” risk of death by 24% before survival data was updated, but by only 13% after survival data was updated. Since the p-value for the updated survival data was 0.29, there was no evidence of difference in survival using the adjusted analysis. The results for the unadjusted analysis were similar to those for the adjusted analysis.

Please see the Statistician's Kaplan-Meier survival curves for both original and updated data

9.1.2.2 Time to treatment failure

Treatment failure was defined as the earliest occurrence of disease progression or withdrawal of trial treatment for any reason including death from any cause. Time to treatment failure was calculated by the medical reviewer as the number of days from the date of randomization to the date of treatment failure. Any patient who had not reached

treatment failure or disease progression at the time of data cut-off, or who had been lost to follow-up, was right-censored at the date of their last disease assessment.

Of the 353 patients who were randomized to trial treatment, 247 (70.0%) patients had treatment failure resulting from disease progression. 34 (9.6%) patients were withdrawn from the trial for reasons other than disease progression and 6 (1.7%) patients died before progression. This resulted in a total of 287 (81.3%) patients who had treatment failure. A smaller proportion of patients who were randomized to Arimidex (78.9%) had treatment failure, compared with the proportion of patients who were randomized to tamoxifen (83.5%). Patients who were randomized to Arimidex also had a longer estimated median time to treatment failure (231 days), compared with the time for patients who were randomized to tamoxifen (163 days).

The hazard ratio from the adjusted analysis was very close to 1 and the lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen:Arimidex) was 0.89 which was greater than the minimum value (0.8) required to demonstrate non-inferiority. Similar results were observed from the unadjusted analysis, with a hazard ratio of 1.04 and a lower 1-sided 95% confidence limit of 0.90. *See Statistician's report for a more detailed analysis.*

9.1.2.3 Duration of response

Duration of response for all randomized patients who had a best objective response of CR or PR. 67 (19.0%) patients were responders. The estimated median duration of response from the time of randomization was lower for patients who were randomized to Arimidex (490 days) than for patients who were randomized to tamoxifen (546 days). However, the median duration of response from the first objective response was slightly higher for patients who were randomized to Arimidex (376 days), compared with the response for patients who were randomized to tamoxifen (332 days).

Please see the Statistician's Kaplan-Meier survival curves for duration of response and time to treatment failure

SUMMARY OF EFFICACY.

The medical reviewer agrees with the sponsor's claim of non-inferiority in both primary endpoints: time to progression and objective response rate. There was also no evidence of difference in the secondary end-point of survival

9.1.3.SAFETY

9.1.3.1 DEATHS

A total of 247/668 (37.0%) deaths had occurred at the time of second data cut-off on February 23 2000. 128/340 (37.6%) patients who were given arimidex compared with patients who were given tamoxifen 119/328 (36.3%), had died by the time of data cut-off. All patient deaths were from causes related to breast cancer either during treatment (including the 14-day follow-up period) or after treatment had been withdrawn.

As discussed in Section 9.1.2.1, the data reveal no significant difference in death rates among patients who were randomized to receive Arimidex, compared with patients who were randomized to receive tamoxifen.

9.1.3.2 Adverse Events.

All 665 treated patients were included in the safety evaluation according to actual treatment received. 338 patients were randomized to receive arimidex and 327 to Tamoxifen. All adverse events that occurred during treatment or within 14 days after stopping treatment for any reason (2week follow-up period) were recorded by the sponsor and reviewed by the medical reviewer.

A wide variety of adverse events were reported for patients in both treatment groups by the investigators as possibly treatment related. Table 42 lists the distribution of most common adverse events. The most frequently reported pre-specified adverse events were, gastrointestinal disturbances and , hot flushes, vaginal complaints. Other less frequent complaints were respiratory complaints, bone pains, weight gain, edema. Thromboembolic complaints while present, were fewer in both treatment groups than would have been anticipated.

TABLE 42 Distribution of Most Common Adverse Events

| | ARIMIDEX | TAMOXIFEN | TOTAL |
|---------------------|----------|-----------|-------|
| Hot Flashes | 69 | 68 | 137 |
| Gastro intestinal | | | |
| Constipation | 21 | 28 | 49 |
| Diarrhea | 29 | 23 | 52 |
|Nausea/Vomiting | 42 | 44 | 86 |
| Vaginal | | | |
| Discharge | 2 | 8 | 10 |
| Bleeding/spotting | 3 | 11 | 14 |
| Dryness | 7 | 6 | 13 |
| Respiratory | | | |
| Cough increased | 19 | 23 | 42 |
| Bronchitis | 6 | 17 | 23 |
| Dyspnea | 18 | 18 | 36 |
| Pharyngitis | 15 | 18 | 33 |

Vaginal complaints, especially bleeding, as well as respiratory complaints appear more common in the group randomized to tamoxifen. There was no difference between the two treatment groups in episodes of hot flushes and gastrointestinal complaints.

9.1.3.3 Weight Gain

4 patients in each treatment group had recordings of significant weight gain.

9.1.3.4 Serious Adverse Events.

There were relatively few serious adverse events in this study. The episodes of these events when present was equally distributed between the two treatment groups.

The database reveal 2 episodes of acute myocardial infarction, with 1 episode in a patient in the arimidex group (0076/0003) which resulted in death, and 1 non-fatal but serious event in a patient in the tamoxifen group (0045/0004). 1 patient on Arimidex had seizures (0034/0101), while 1 other patient in the Tamoxifen group died from a cerebrovascular accident (0030/0002). Pathologic fractures were reported, but case were very few in either group.

9.1.3.5 Clinical Laboratory Data

While there were modest abnormalities in cholesterol and triglycerides, in both treatment groups, there were no striking laboratory abnormalities attributable to either drug. An occasional patient had hypercalcemia as part of the tumor flare syndrome.

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ON ORIGINAL

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ON ORIGINAL

9.2 PROTOCOL 0030

9.2.1 DEMOGRAPHICS

A total of 353 patients were enrolled in this study at 97 sites in North America. 171 patients (48.4%) were randomized to trial treatment, arimidex and 182 (51.6%) were randomized to tamoxifen. The distribution of patients in terms of age, body mass and ethnic origin is as indicated in Table 2. Patient characteristics are as indicated in Tables 3 and 4 obtained from the sponsor's submission. The majority of patients 313/353 (88.7) in this study had known ER+ and /or PR+ status. Overall there was a satisfactory balance in the distribution of demographic and metastatic disease distribution characteristics between the two treatment groups.

9.2.2 Protocol Violation and Deviations

A protocol violation was defined as any infringement of the protocol selection criteria. A protocol violation was defined as any departure from the protocol design or procedures after the patient had entered the trial.

9.2.2.1 Post-menopausal Status.

The inclusion criteria required enrolled patients to be post- menopausal. Post-menopausal status was defined as:

- (i) women aged 50 years or over who have not menstruated during the preceding 12 months or who have follicle stimulating hormone (FSH) levels within the post-menopausal range;
- (ii) women under the age of 50 years who have FSH levels within the post-menopausal range

24 patients in this study were under the age of 50. 17 of these patients had FSH in the post menopausal range (>40IU/L)

Table 43 provides the list of the remaining 7 patients grouped according to the sponsor's explanation.

TABLE 43 Violation of Postmenopausal status requirement

| Patient ID | Age | Treatment | Sponsor's Comments |
|------------|-----|-----------|--|
| 0001/0012 | 31 | | Post-menopausal due to surgery |
| 0054/0004 | 44 | | Post-menopausal due to surgery |
| 0080/0034 | 48 | | Post-menopausal due to surgery |
| 0085/0003 | 45 | | Post-menopausal due to surgery |
| 0001/0015 | 48 | | MD claims amenorrhea pre-trial |
| 0071/0002 | 49 | | Would be 50 yrs 1 wk after entry |
| 0072/0008 | 48 | | Received prior chemotherapy.MD believes pt to be amenorrheic |

9.2.2.2 Protocol Deviations

The most frequent protocol deviations were: Use of disallowed concurrent therapy, especially glucocorticoids in both groups of patients.

"Significant interruption of trial therapy" which also occurred with similar frequency in both treatment groups.

9.2.2.3 Summary of effect of Violations and deviation: A review of data on individual patients involved in various protocol violations reveals no material effect or influence on the outcome of the studies.

9.2.3 Withdrawals:

A total of 264/353 patients who started trial treatment withdrew from the trial 122/171 (71.3%) patients were given anastrozole and 142/182 (78.0%) patients who were given tamoxifen. The majority of all patients withdrew because of disease progression. A total of 24 (3.6%) patients died while on study drug; 11/336 (3.2%) on Arimidex 13/329 (3.9%) on tamoxifen. The majority of the deaths were due to progressive disease. Overall, the withdrawal rates and reasons for withdrawal were similar between the 2 treatment groups.

The patients who had withdrawn from the trial and were still alive, were given radiotherapy, chemotherapy, hormonal therapy and other clinically appropriate treatment regimen.

9.2.4 Disposition of Patients.

353 patients were randomized and were all included in the primary ITT efficacy end point analysis. 352 patients actually received trial treatment and were included in the safety analysis.

9.2.2 EFFICACY RESULTS

9.2.2.1 Primary Efficacy Endpoints:

Populations analyzed

The primary efficacy analyses of all the end points included all randomized patients and compared the treatment groups based on randomized treatment, regardless of whether this treatment was actually received (ITT approach). In addition, the secondary efficacy analyses, excluding 70 (19.8%) patients with significant protocol violations and deviations. These analyses, were performed on 283 (80.2%) patients for time to progression and objective-response rate to assess whether the conclusions from the primary efficacy analyses were robust ('per-protocol' approach).

9.2.2.1.1 Time to Progression:

Time to progression was evaluated for each patient on the study. Using the ITT approach, a total of 252 (71.4%) patients had progressive disease at the time of data cut-off. Of these, 114 patients were randomized to Arimidex and 138 patients to tamoxifen. The estimated median time to progression was 338 days for patients randomized to Arimidex and 170 days for patients randomized to tamoxifen. The results of statistical analysis were very similar to those based on the sponsor's data.

Using the PP population (secondary approach), 283 patients were included in this population. Of these, 133 (47.0%) patients were randomized Arimidex and 150 (53.0%) patients to tamoxifen. A total of 198 (70.0%) patients had disease progression. Of these, 85 patients were randomized Arimidex and 113 patients to tamoxifen. The estimated median time to progression was 407 days for patients who received Arimidex and 170 days for patients who received tamoxifen. Results from the per-protocol analysis were consistent with those from the ITT analysis. Both sets of data showed the superiority of Arimidex over tamoxifen

See the Statistician's report for the Kaplan-Meier probability plot of time to progression using both types of analyses.

9.2.2.1.2 Objective response

Table 44 summarizes the medical reviewer's results along with the sponsor's results of objective-response rate using the intent-to-treat population. The reviewer's objective-response rates of CR or PR for all randomized patients were identical to the sponsor's. The results were very similar for patients randomized to receive Arimidex and patients randomized to receive tamoxifen (21.0% vs. 17.0%).

Results of the adjusted analysis showed that the estimated difference in response rates (1.38%) favored Arimidex. The lower 1-sided 95% confidence limit for the difference rate (Arimidex – tamoxifen) was -1.90%, which was greater than the statistical criterion of -10% to declare non-inferiority. Consistent results were observed from the unadjusted analysis, with an estimated difference in response rates of 4.02% and a lower 95% confidence limit of -2.47%

The results from the per-protocol analysis were consistent with those from the ITT analysis. *See the Statistician's report for detailed analyses using both types of analyses*

TABLE 44 Objective Response for all Randomized patients

| | SPONSOR | | MEDICAL REVIEWER | |
|----------------|-----------------|-------------------|------------------|-------------------|
| | ARIMIDEX 1mg | TAMOXIFEN 20mg | ARIMIDEX 1mg | TAMOXIFEN 20mg |
| #Pts Enrolled | 171 | 182 | 171 | 182 |
| Responders | 36 (21.0) | 31 (17.0) | 36 (21.0) | 31 (17.0) |
| CR | 5 (2.9) | 5 (2.7) | 5 (2.9) | 5 (2.7) |
| PR | 31 (18.1) | 26(14.3) | 31 (18.1) | 26(14.3) |
| Non-Responders | 135 (78.9) | 151 (73.0) | 135 (78.9) | 151 (73.0) |
| SD>24wks | 65(38.0) | 52 (28.6) | 65(38.0) | 52 (28.6) |
| Progression | 70(40.9) | 99(54.4) | 70(40.9) | 99(54.4) |

9.2.2.1.3 Duration of response

Duration of response is as shown in Table 45 and was measured for responding patients (CR and PR)..

Table 45: Duration of response for responding patients

| Response data | Arimidex 1 mg [n = 171] | Tamoxifen 20 mg [n = 182] |
|---|----------------------------|------------------------------|
| Number (%) of responders ((CR,PR), | 36 (21.1%) | 31 (17.0%) |
| Duration of response from randomization median (days) | 490 | 546 |
| Range | | |
| Duration of response from first response median (days) | 376 | 332 |
| Range | | |

9.2.2 Secondary Endpoints

9.2.2.1 Time to Death (Survival)

The survival data comprised three dates; the initial cut-off date of March 10, 1999, the 4 month safety update of September 9 1999 and an updated cut off date of February 23, 2000.

Using the intent-to-treat population, the death rate was slightly higher in patients who were randomized to receive Arimidex (26.8%), compared with patients who were randomized to receive tamoxifen (22.6%) at the first time of data cut-off (March 10, 1999). However, the death rate was lower for the Arimidex group (36.8% vs. 41.2%) at the second time of data cut-off (February 23, 2000). The additional information provides information on deaths occurring since the initial cut-off date of March 10 1999, and thus alleviates the concern about worse survival results of Arimidex when compared to Tamoxifen. Survival data are immature because 61% of patients are still censored for death. A phase 4 commitment by the sponsor to submit an updated survival data will be necessary.

. Please see the Statistician's Kaplan-Meier survival curves for both original and updated data

9.2.2.2 Time to treatment failure.

Treatment failure was defined as the earliest occurrence of disease progression or withdrawal of trial treatment for any reason including death from any cause. Time to treatment failure was calculated by the medical reviewer as the number of days from the date of randomization to the date of treatment failure. Any patient who had not reached treatment failure or disease progression at the time of data cut-off, or who had been lost to follow-up, was right-censored at the date of their last disease assessment.

Of the 353 patients who were randomized to trial treatment, 247(70.0%) patients had treatment failure resulting from disease progression. 34 (9.6%) patients were withdrawn from the trial for reasons other than disease progression and 6 (1.7%) patients died before progression. This resulted in a total of 287 (81.3%) patients who had treatment failure. A slightly smaller proportion of patients who were randomized to Arimidex (78.9%) had treatment failure, compared with the proportion of patients who were randomized to tamoxifen (83.5%). Patients who were randomized to Arimidex also had a longer estimated median time to treatment failure (231 days), compared with the time for patients who were randomized to tamoxifen (163 days).

The hazard ratio for time to treatment failure from the adjusted analysis was very close to 1 and the lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen:Arimidex) was 0.89. Similar results were observed from the unadjusted analysis, with a hazard ratio of 1.04 and a lower 1-sided 95% confidence limit of 0.90.

See Statistician's report for a more detailed analysis.

9.2.3.SAFETY

9.2.3.1 DEATHS

A total of 138/353 (38.5%) deaths had occurred at the time of second data cut-off on February 23 2000. 63/171 (36.8) patients who were given arimidex compared with patients who were given tamoxifen 75/182 (41.2%), had died by the time of data cut-off. All patient deaths were from causes related to breast cancer either during treatment (including the 14-day follow-up period) or after treatment had been withdrawn. As discussed in Section 9.2.2.1, the data reveal no significant difference in death rates among patients who were randomized to receive Arimidex, compared with patients who were randomized to receive tamoxifen.

9.2.3.2 Adverse Events.

All 353 treated patients were included in the safety evaluation according to actual treatment received. 171 patients were randomized to receive arimidex and 182 to Tamoxifen. All adverse events that occurred during treatment or within 14 days after stopping treatment for any reason (2week follow-up period) were recorded by the sponsor and reviewed by the medical reviewer.

A wide variety of adverse events were reported for patients in both treatment groups by the investigators as possibly treatment related. Table 46 lists the distribution of most common adverse events. The most frequently reported pre-specified adverse events were, gastrointestinal disturbances, hot flushes, vaginal complaints. Other less frequent complaints were respiratory complaints, bone pains, weight gain, edema, hypercalcemia, cataracts and other visual problems. Thromboembolic complaints while present, were fewer in both treatment groups than would have been anticipated.

TABLE 46 Distribution of Most Common Adverse Events

| | ARIMIDEX | TAMOXIFEN | TOTAL |
|-----------------------|----------|-----------|-------|
| Hot Flashes | 65 | 50 | 115 |
| Gastro intestinal | | | |
| Constipation | 30 | 38 | 68 |
| Diarrhea/Loose stools | 29 | 23 | 52 |
| Nausea/Vomiting | 52 | 62 | 114 |
| Vaginal | | | |
| Discharge | 5 | 18 | 23 |
| Bleeding/spotting | 2 | 11 | 13 |
| Dryness | 8 | 7 | 15 |
| Respiratory | | | |
| Cough | 36 | 29 | 65 |
| Pharyngitis | 34 | 38 | 72 |
| Dyspnea | 33 | 29 | 62 |
| Upper Resp. Inf. | 9 | 9 | 18 |

Vaginal complaints, especially bleeding, and gastrointestinal complaints appear more common in the group randomized to tamoxifen. Episodes of hot flushes were more common in the group randomized to arimidex. There was no difference between the two treatment groups in episodes of respiratory complaints.

9.2.3.3 Weight Gain

4 patients in the arimidex group and 2 patients in the tamoxifen treatment group had recordings of significant weight gain.

9.2.3.4 Serious Adverse Events.

There were relatively few serious adverse events in this study. The episodes of these events when present were equally distributed between the two treatment groups. The database reveals 2 patients with acute myocardial infarction in the tamoxifen group (0068/0002, and 0105/0001). Pulmonary embolus was reported in 2 patients on Arimidex (0030/0001, and 0080/001). 1 patient on Arimidex had seizures (0001/0013), while cerebrovascular accident was observed in 1 patient on Arimidex (0080/0039) and 1 other patient in the Tamoxifen group ((0116/0001). This reviewer doubts the relationship of the neurologic episodes to drug therapy. For example, patient 0080/0039 in the arimidex group had a history of CVA prior to study entry, and had another episode that led to withdrawal from further treatment in the course of the trial. Pathologic fractures were reported in 2 patients on Arimidex (0027/0001, 0121/0012) and 5 patients on tamoxifen (0035.0002, 0063/0002, 0105/0001, 0119/0001, 0145/0002). There were 8 episodes of hip pain, all in tamoxifen patients

9.2.3.5 Clinical Laboratory Data

While there were modest abnormalities in cholesterol and triglycerides, in both treatment groups, there were no striking laboratory abnormalities attributable to either drug. An occasional patient had hypercalcemia as part of the tumor flare syndrome.

10.0 REVIEWER'S COMMENTS AND CONCLUSIONS OF STUDY RESULTS

The two pivotal trials, Protocol #0027 and Protocol # 0030 were very well conducted and the data were presented in a manner that is readily reviewable. Credible conclusions can therefore be drawn from results of the studies.

The population of patients studied adequately represented the post-menopausal patients that were the primary focus of the trial.

The size of the patient population in both trials was large enough for a meaningful conclusion to be drawn from the results.

There was satisfactory balance of patient distribution, by demographic and disease factors, between both treatment groups.

The results of the studies confirm the sponsor's claim that Arimidex is non-inferior to Tamoxifen as first line treatment of post-menopausal women with advanced breast cancer.

On safety issues, and within the context of these studies, both drugs appear equally safe, with one having no overt safety advantage over the other.

Tamoxifen however appears to have more episodes of vaginal bleeding than arimidex as determined by events in both studies. Arimidex appears to have more episodes of gastrointestinal complaints. It may also be associated with greater episodes of hot flushes

In the opinion of this reviewer, arimidex has no advantage over tamoxifen in terms of thromboembolic complications or cardiovascular events, nor does tamoxifen have an advantage over arimidex in terms of musculoskeletal events.

11.0 ONCOLOGY DRUG ADVISORY COMMITTEE (ODAC)

This SNDA was not presented to the Advisory committee.

12.0 120 DAY SAFETY UPDATE

This 4-month safety update (4MSU) provides additional safety data from the first-line clinical trial program for anastrozole. The purpose of this document was to further characterize the safety profile of anastrozole based on additional data obtained since the data cutoff date for the Integrated Summary of Safety which was submitted to the Food and Drug Administration (FDA) on 1 November 1999 with a cut-off date of March 1999. This 4MSU covers the period 11 March 1999 to 9 September 1999.

No new data regarding adverse events, deaths, or withdrawals were obtained from the "additional" trials. The 4MSU includes additional safety data for the 2 core controlled trials (Trials 0030 and 0027). These 2 trials are completed and follow-up continues.

12.1 Baseline characteristics and extent of exposure

At the time of data cutoff for this 4MSU (9 September 1999), a total of 1017 postmenopausal women with advanced breast cancer in the core controlled clinical trials (506 subjects who were given anastrozole and 511 subjects who were given tamoxifen) were given trial treatment. Subjects in the core controlled trials were exposed to anastrozole at the therapeutic dose of 1 mg daily for up to 1344 days. The duration of exposure and duration of follow-up were similar between the 2 treatment groups. Both treatment groups were well matched in terms of demographic characteristics and pre-existing conditions and abnormalities. Baseline clinical and laboratory abnormalities were common, but were consistent with the population being analyzed.

12.2 Safety

A total of 415 (82.0%) subjects who were given anastrozole and 429 (84.0%) subjects who were given tamoxifen reported at least 1 adverse event. This represents an increase of 7 subjects who were given anastrozole and 3 subjects who were given tamoxifen from the time of the ISS data cutoff (10 March 1999) to the time of the 4MSU data cutoff. The incidence of most adverse events that occurred in >5% of subjects increased by at least 1 occurrence, with the exception of leukorrhea.

The most frequently reported adverse event was vasodilatation, which occurred in 131 (25.9%) subjects who were given anastrozole and 110 (21.5%) subjects who were given tamoxifen in the core controlled trials (an increase of 3 subjects who were given anastrozole and 4 subjects who were given tamoxifen from the time of the ISS data cutoff). Other commonly reported adverse events were nausea (an increase of 3 subjects who were given anastrozole and 2 subjects who were given tamoxifen), asthenia (an increase of 7 subjects who were given anastrozole and 2 subjects who were given tamoxifen), pain (an increase of 5 subjects who were given anastrozole and 6 subjects who were given tamoxifen), back pain (an increase of 3 subjects who were given anastrozole and 3 subjects who were given tamoxifen), bone pain (an increase of 5 subjects who were given anastrozole and 3 subjects who were given tamoxifen), and pharyngitis (an increase of 1 subject who was given anastrozole and 3 subjects who were given tamoxifen).

A total of 416 subjects were considered by the investigator to have had drug-related adverse events at the time of data cutoff for the 4MSU: 209 (41.3%) of subjects who were given anastrozole and 207 (40.5%) of subjects who were given tamoxifen. From the time of the ISS data cutoff to the time of the 4MSU data cutoff, there was an increase of 3 subjects who were given anastrozole and 3 subjects who were given

tamoxifen who had drug-related adverse events. Overall, the most commonly reported drug-related adverse events were vasodilatation, nausea, and asthenia.

The total number of subjects who reported at least 1 joint-related symptom was higher in the group of subjects who were given anastrozole, which is consistent with that observed in the ISS. Events that were mapped to the COSTART terms 'arthritis,' 'arthralgia,' and 'arthrosis' in the core controlled trials were seen more frequently in subjects who were given anastrozole, compared with subjects who were given tamoxifen. The incidences of these events increased slightly from the time of the ISS data cutoff. Overall, the incidence of events that were mapped to the COSTART terms 'joint disorder' and 'myalgia' were unchanged from the time of the ISS data cutoff to the time of the 4MSU data cutoff; these events occurred more frequently in subjects who were given tamoxifen.

The incidence of thromboembolic disease in subjects who were given tamoxifen was numerically greater than for those who were given anastrozole, and the incidence of this event increased by 2 subjects for each treatment from the time of the ISS data cutoff. The events categorized as gastrointestinal disturbances occurred more frequently in the tamoxifen group and increased by an additional 6 subjects who were given anastrozole and 2 subjects who were given tamoxifen. The events of depression, tumor flare, lethargy, and vaginal bleeding were the other events that were reported by a greater proportion of subjects who were given tamoxifen, compared with those who were given anastrozole; the incidences of these events were small (0 to 2 subjects each). Hot flushes occurred more frequently in the anastrozole group and increased by an additional 3 subjects who were given anastrozole and 4 subjects who were given tamoxifen. Vaginal dryness and weight gain were the other categories of pre-specified adverse events that were reported by a greater proportion of subjects who were given anastrozole, compared with those who were given tamoxifen; the incidences of these events increased minimally or not at all.

A total of 316 deaths were reported at the time of data cutoff for this 4MSU. This represents an increase of 51 deaths since the time of the ISS data cutoff. As was shown in the ISS, most deaths (82.6%) in the core controlled trials were related to breast cancer (an increase of 42 deaths since the time of the ISS data cutoff). No change was observed for the number of subjects who died from adverse events: 17 subjects in the core controlled trials died from adverse events (10 [2.0%] subjects who were given anastrozole and 7 [1.4%] who were given tamoxifen). In cases where adverse events led to death, none of the primary causes of death were attributable to anastrozole or tamoxifen in the core controlled trials.

The incidences of adverse events that led to withdrawal (4.7% of subjects who were given anastrozole and 5.5% of subjects who were given tamoxifen) and drug-related adverse events that led to withdrawal (2.0% of subjects who were given anastrozole and 2.5% of subjects who were given tamoxifen) were low and similar between the 2 treatment groups. The only change to this information after the ISS data cutoff was the

addition of 1 subject (Subject 0027/0103/0102) who was given tamoxifen and had a serious event of vomiting that led to withdrawal from treatment.

A total of 207 subjects had serious adverse events, which represents an increase of 21 subjects from the time of the ISS data cutoff. The overall incidence of serious adverse events in the core controlled trials was similar between the treatment groups (19.0% of subjects who were given anastrozole and 21.7% of subjects who were given tamoxifen). Most serious adverse events were not related to trial treatment. The only serious drug related adverse event that was reported by more than 1 additional subject since the time of the ISS data cutoff was vaginal hemorrhage (3 [0.6%] subjects total, all of whom were given tamoxifen).

12.3 Conclusion of 120 day safety update

On the basis of the data presented in the ISS and this 4MSU, the sponsor recommends that the following additions be made to the prescribing information for Arimidex.

Possible adverse reactions: "ARIMIDEX may be associated with joint pain/stiffness."

13.0 FINANCIAL DISCLOSURE

Protocol 0027 was conducted outside North America. There were 83 centers and a total number of 101 investigators at those centers. 48 investigators responded to the sponsor's inquiry concerning Financial Disclosure. All 48 investigators indicated no existing financial arrangement with the sponsor. 53 investigators have failed to report to requests from the sponsor for financial disclosure. The sponsor however claims no payment is identified in corporate accounting records concerning payment by sponsors to these investigators.

Protocol 0030 was conducted at 97 centers in North America. There was a total of 26 Principal investigators and 727 sub-investigators at those centers. All 26 Principal investigators and 105 sub-investigators responded to the sponsor's inquiry concerning Financial Disclosure, and all but two indicate no existing financial arrangement with the sponsor. 621 sub-investigators have failed to respond to requests from the sponsor for financial disclosure. The sponsor however claims no payment to these sub-investigators is identified in corporate accounting records.

For protocol 0030 one investigator reported a financial interest, but only 9 patients were entered at that center. One sub-investigator reported a financial interest, but no patients were entered at that center.

14.0 LABELING

The labeling proposed by the applicant has been revised by the review team. See separate Labeling document.

15.0 RECOMMENDATION

This SNDA is approvable with labeling revisions (See attached labeling with FDA revisions). The applicant must also commit to submit annual safety and survival updates for studies 0027 and 0030 until 75% of patients are dead in each study.

TS/

OLUWOLE O. ODUJINRIN MD
Medical Reviewer
August 29, 2000

/S/

JOHN JOHNSON MD
Medical Team Leader
August 29, 2000

*See also my Team Leader
Review. GRJ*

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HFD-710/Dr. P. Yang
HFD-710/Dr. G. Chen

MEDICAL OFFICER REVIEW OF NEW PROTOCOL

IND **Serial No. 108**
Drug: **Arimidex™ (Anastrozole)**
Sponsor: **Zeneca Pharmaceuticals**
Date of Submission: **January 16, 1997**

Protocol Number: 1033IL/0029

Protocol Title: A Randomized, Double-Blind Trial Comparing Arimidex Alone with Nolvadex Alone with Arimidex and Nolvadex in Combination, as Adjuvant Treatment in Post-Menopausal Women with Breast Cancer

Principal Investigator: Aman Buzdar, MD, M.D. Anderson Cancer Center

Date of Activation: January 1997 (in US) with six patients accrued as of 2/11/97; July 1996 in the UK and at other sites

Background:

This is a phase 3, multicenter, double-blind, placebo-controlled trial to compare the equivalence of Nolvadex (20 mg qd) and Arimidex (1 mg qd) and to compare the difference between Nolvadex (20 mg qd) and the combination of Nolvadex (20 mg qd) plus Arimidex (1 mg qd) as adjuvant treatment for post-menopausal women with Stage I or II breast cancer.

Primary efficacy endpoints will be time to disease recurrence and safety. Secondary efficacy endpoints will be time to distant recurrence, survival, and incidence of new breast primaries. In addition, some patients will also be included in one or more sub-protocols at selected centers evaluating pharmacodynamic/ pharmacokinetic parameters, modulation of lipoprotein profiles, endometrial status, bone mineral metabolism, and quality of life.

Approximately 6000 patients will be recruited from at least 150 centers worldwide over a 3 year period. One interim analysis of time to disease recurrence and time to death will be conducted when approximately half the expected number of events has occurred in any one arm (estimated to take place at 3.5 years after the start of accrual). The major trial analysis will be performed when approximately 450 disease events have occurred in any one treatment arm (estimated to take place at 5 years after the start of accrual).

Please convey the following to the sponsor:

The study may proceed, however, the sponsor should address the following deficiencies as soon as possible.

Deficiencies:

- 1) Please justify the use of single agent Arimidex as adjuvant treatment of post-menopausal women with early stage breast cancer. In particular, what information is available on the efficacy of Arimidex as first-line therapy of metastatic breast cancer?
- 2) Please justify the use of the combination of Arimidex plus Tamoxifen as adjuvant treatment of post-menopausal women with early stage breast cancer. Is there data available regarding the efficacy of this combination in breast cancer patients?
- 3) Please justify the inclusion of post-menopausal women with ER- tumors on this trial. In particular, what information is available on the efficacy of Arimidex in this patient population?
- 4) Please justify the inclusion of patients with prior chemotherapy on this trial. If such patients must be enrolled, it is recommended that the choice of chemotherapy given be specified, at least by center (rather than leaving the choice of chemotherapy up to the individual investigator).
- 5) Please justify the proposed definition of equivalence between Arimidex vs Tamoxifen. Since the effect of Tamoxifen on time to recurrence is small, especially Stage I breast cancer patients, there is concern that the proposed equivalence definition may allow for overlap (in terms of hazard ratio and its associated confidence interval) with the comparison of Tamoxifen vs no Tamoxifen. Please use the results presented in the publication by the Early Breast Cancer Trialists' Collaborative Group (*Lancet*, 339:1-15, 1992) as a basis for your estimation of the benefit of Tamoxifen vs no Tamoxifen.
- 6) Patients should be stratified prospectively at the time of randomization for baseline estrogen receptor status, nodal status, primary tumor size, previous chemotherapy, and age.
- 7) The primary analysis should be via logrank and stratified logrank tests. Cox modeling should also be provided, but as a supportive analysis.
- 8) Careful attention should be paid to assure accrual of equal numbers of Stage I and II breast cancer patients on this trial. This can be achieved via unblinded monitoring of proportions of each disease stage during the course of the trial.

Comment:

The proposed single pivotal study in 6000 patients will support the indication of Arimidex either alone or in combination with Tamoxifen as adjuvant treatment of post-menopausal women with early stage breast cancer. The proposed indication for node-negative and node-positive breast cancer is too broad, given that only patients with Stages I and II breast cancer will be enrolled.

/S/

..... 2/11/97
Julie Beitz, MD Date

/S/

..... 2/2/97
Robert Justice, MD Date

cc:
IND
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ M. Brower
HFD-150/ L. Vaccari

Zeneca ZD1033 (anastrozole, ARIMIDEX™)

**ZENECA'S RESPONSIBLE MEDICAL OFFICER
APPROVAL**

Integrated Summary of Effectiveness Data

This document falls within the goals of the International Clinical Plan, meets Zeneca standard practices, and is suitable for inclusion in the regulatory submission.

Mark Steinberg MD
Zeneca's Responsible Medical Officer
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Signature *Mark Steinberg*.....

Date *Sept 21, 1999*.....

ARIMIDEX is a trademark, the property of Zeneca Limited.

Zeneca ZD1033 (anastrozole, ARIMIDEX™)

**CLINICAL STRATEGY LEADER
APPROVAL**

Integrated Summary of Effectiveness Data

This document falls within the goals of the International Clinical Plan, meets Zeneca standard practices, and is suitable for inclusion in the regulatory submission.

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Date 27/9/99

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Zeneca ZD1033 (anastrozole, ARIMIDEX™)

**GLOBAL PROJECT STATISTICIAN
APPROVAL**

Integrated Summary of Effectiveness Data

This document falls within the goals of the International Clinical Plan, meets Zeneca standard practices, and is suitable for inclusion in the regulatory submission.

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Zeneca ZD1033 (anastrozole, ARIMIDEX™)

Supplemental New Drug Application

Integrated Summary of Effectiveness Data

27 September 1999

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SUMMARY

Anastrozole (ZENECA ZD1033, ARIMIDEX™), a potent and selective aromatase inhibitor, is currently approved for the treatment of advanced breast cancer in postmenopausal women who have failed treatment with tamoxifen. The current clinical program assessed the efficacy of anastrozole as first-line therapy for advanced breast cancer in postmenopausal women in comparison with tamoxifen.

To support this supplemental indication, 2 Phase IIIb trials (1033IL/0030 and 1033IL/0027) were conducted to compare anastrozole with tamoxifen as first-line therapy for advanced breast cancer. The primary end points for both trials were time to progression and objective response rate. Since both Phase IIIb trials were similar in design, an analysis of the combined efficacy data was planned, thus strengthening interpretation of the results from the individual trials.

The consistent results from all analyses indicate that anastrozole is at least as efficacious as tamoxifen for the primary end points of time to progression and objective response rate. In addition there was a numerical superiority for anastrozole in time to progression in Trial 0030 and the combined trials. These results were supported by the secondary end points, especially time to treatment failure and duration of clinical benefit.

These results support the claim that anastrozole is indicated for first-line treatment of advanced breast cancer in postmenopausal women.

Table A summarizes, by treatment arm, the combined results of the primary efficacy end points (time to progression and objective response rate), as well as time to death (survival) and time to treatment failure.

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Table A Combined results of selected efficacy end points

| End point | Treatment arm | | Analysis Estimated hazard ratio ^a (T:A) or estimated difference in response rate ^b (A-T) and associated lower 95% CL |
|---------------------------------------|--------------------------------|-------------------------------|---|
| | Anastrozole 1 mg (n=511) | Tamoxifen 20 mg (n=510) | |
| Time to progression (TTP) | | | |
| Median TTP (days) | 259 | 212 | 1.13 (1.00) |
| Number (%) of subjects who progressed | 363 (71.0) | 385 (75.5) | |
| Best objective response rate | | | |
| Number (%) of subjects with CR + PR | 148 (29.0) | 138 (27.1) | 1.08 (-3.49) |
| Time to death (survival) | | | |
| Percentage of subjects alive ≥2 years | 65.2 | 69.4 | NA |
| Number (%) subjects who died | 138 (27.0) | 127 (24.9) | |
| Time to treatment failure (TTF) | | | |
| Median TTF (days) | 208 | 176 | 1.13 (1.01) |
| Number (%) subjects who failed | 402 (78.7) | 418 (82.0) | |

^a Hazard ratio of tamoxifen:anastrozole was generated using a Cox regression model including factors of treatment, extent of disease at entry, previous hormonal therapy, estrogen/progesterone receptor status, and age using trial as a stratification factor. Hazard ratio >1.00 indicates that anastrozole is associated with longer time to event than is the tamoxifen.

^b Difference in response rate (anastrozole-tamoxifen) was calculated from odds ratio using the formula stated in Section 2.7.4.1. A difference >0 indicates that anastrozole is associated with a higher response rate than is tamoxifen. The odds ratio of anastrozole:tamoxifen was generated using a logistic regression model including factors of treatment, extent of disease at entry, previous hormonal therapy, estrogen/progesterone receptor status, and age using trial as an additional covariate.

CR Complete response.

PR Partial response.

CL Confidence limit.

NA Not applicable.

1 INTRODUCTION

1.1 Structure of the Integrated Summary of Effectiveness Data

This Integrated Summary of Effectiveness Data (ISE) provides an overview of efficacy data from the core trials (Trials 1033IL/0030 and 1033IL/0027) that support the use of the nonsteroidal aromatase inhibitor, anastrozole (ZENECA ZD1033, ARIMIDEX) 1 mg daily, for the first-line treatment of postmenopausal women with advanced breast cancer.

This ISE and the 2 clinical trial reports for the Phase IIIb trials present the data available up to a cutoff date of 10 March 1999. Sections 2, 3, and 4 describe the 2 Phase IIIb controlled trials that demonstrated the efficacy of anastrozole; Sections 3 and 4 present the integrated analyses of the demography and efficacy data from these Phase IIIb trials. Accrual to both trials is complete, and follow-up continues. The conclusions are presented in Section 5.

In this document, trial numbers have been shortened for ease of review. Trial numbers, which are generally prefixed "1033IL/", are abbreviated to the last 4 digits. For example, Trial 1033IL/0030 is referred to in this summary as Trial 0030. In addition, subjects are referred to by center and subject number.

1.2 The anastrozole clinical program

The current clinical trial program evaluates the efficacy and tolerability of anastrozole as first-line therapy in subjects who have not received any therapy for advanced disease. Tamoxifen, an antiestrogen, is widely used in the management of breast cancer as both adjuvant treatment and treatment of advanced disease. Its antitumor effects are related to its ability to compete with estrogens for binding sites in target tissues such as breast. However, depending on tissue, species, and menopausal status, tamoxifen can also act as a partial estrogen agonist.

After the menopause, the predominant source of estrogen is the conversion of adrenal androgens by the aromatase enzyme (Reed et al 1983). Aromatase inhibitors are therefore an effective means of reducing estrogen production in post-menopausal women. Previous trials have shown anastrozole to be well-tolerated and efficacious in the treatment of post-menopausal women with advanced breast cancer whose tumors had become refractory to tamoxifen (Buzdar et al 1998, Buzdar et al 1997, Jonat et al 1996). Furthermore, anastrozole has no intrinsic estrogenic activity. It therefore was biologically plausible that anastrozole would be well-tolerated and efficacious in the first-line treatment of advanced breast cancer as well. This provided the scientific foundation for the current Clinical Trial Program.

Trials 0030 and 0027 were similar in design. Each trial was a randomized, double-blind, multicenter trial that compared anastrozole (1 mg once daily) with tamoxifen (20 mg once daily) in the treatment of postmenopausal women with advanced breast cancer. A combined total of 1021 subjects from 97 centers in the US and Canada (Trial 0030) and 83 centers in Europe, South America, Australia, and South Africa (Trial 0027) were randomized. Each trial recruited postmenopausal women with advanced breast cancer (metastatic, locally advanced disease, or both) who were eligible for first-line hormonal therapy.

1.3 Summary of trials relating to efficacy in the clinical program

A summary of the trials that contributed to the evaluation of the efficacy of anastrozole as first-line therapy (Trials 0030 and 0027) is presented in Table 1a. Other additional trials in the current program are presented in Tables 1b through 1e. As agreed with the Food and Drug Administration (FDA) on 28 April 1999, these additional trials are not discussed in the ISE.

Each table is presented in 2 parts, Part 1 contains a summary of the trial information and the location within the application of the clinical trial report, case report forms, and tabulations; Part 2 of each table provides drug formulation information.

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Table 1a (Part 1) Summary of controlled trials presented in the ISE for the anastrozole first-line clinical trial program

| Trial ID | Design and objectives | Subjects | | | Treatment | Results and conclusions | Location (volume/ page and/or pdf file) Report Tabulation Case report Forms |
|---|--|--|---|---|--|---|---|
| | | Ethnic origin W/B/H/ AO/OT | Sex (M/F) Type of patient | Number entered in each treatment group (total enrolled) | Dosage ^a (duration) | | |
| 10331L/0030 97 US, Canada Buzdar None 26 Feb 96 Recruitment completed | Randomized, double-blind, double-dummy, placebo-controlled trial to compare the efficacy and safety of anastrozole with tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women | 312/19/ 13/2/7 67 (30-92) | 0/353 Postmenopausal women with advanced breast cancer | Anastrozole 171 Tamoxifen 182 (353) | Anastrozole 1 mg daily Tamoxifen 20 mg daily (Until disease progression or withdrawal) | Anastrozole met the prespecified criteria for equivalence (noninferiority), compared with tamoxifen. In this trial, 88.7% of patients were known to be estrogen- and/or progesterone-receptor positive. The proportion of patients who had progressed and median time to progression for anastrozole were 66.7% and 338 days, respectively, and for tamoxifen were 75.8% and 170 days, respectively. Thirty-six (21.1%) patients randomized to anastrozole and 31 (17.0%) patient randomized to tamoxifen were considered to be responders. Supporting results were observed from the secondary end points. At the time of data cutoff (10 March 1999), 47 (27.5%) patients randomized to anastrozole and 53 (29.1%) patients randomized to tamoxifen had died. The proportions of patients who were alive longer than 2 years were 57.7% for anastrozole and 61.2% for tamoxifen. Data were not sufficiently mature to allow reliable inferences for overall survival. The majority of patients (97.6% anastrozole, 94.0% tamoxifen) had adverse events and 79 (22.4%; 21.8% anastrozole, 23.1% tamoxifen) patients reported serious adverse events. A total of 17 (4.8%; 5.3% anastrozole, 4.4% tamoxifen) patients had adverse events that led to withdrawal. Three patients who were given anastrozole and 5 patients who were given tamoxifen had drug-related adverse events that led to withdrawal. Of the 100 deaths reported at the time of data cutoff, 4 deaths resulted from an adverse event (the primary causes of the deaths were not drug related). Similar rates of adverse events, serious adverse events, adverse events that led to withdrawal, and adverse events that led to death were reported for both treatment groups. No significant laboratory assessments or clinical findings were observed. Both anastrozole and tamoxifen were well tolerated. | clinstat/ cntrld/ ii0030/ ii0030.pdf crt/ datasets/ ii0030/ define.pdf crt/ crftoc.pdf |

Table 1a (Part 1) Summary of controlled trials presented in the ISE for the anastrozole first-line clinical trial program (continued)

| Trial ID | Design and objectives | Subjects | | | Treatment Dosage* (duration) | Results and conclusions | Location (volume/ page and/or pdf file) Report Tabulation Case report forms |
|---|---|-------------------------------------|---|---|---|--|--|
| | | Ethnic origin W/B/H/ AO/OT | Sex (M/F) Type of patient | Number entered in each treatment group (total enrolled) | | | |
| 10331L/0027 83 | Randomized, double-blind, double-dummy, placebo-controlled trial to compare the efficacy and safety of anastrozole with tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women | 610/4/ 18/2/34 | 0/668 | Anastrozole 340 | Anastrozole 1 mg daily | Anastrozole met the prespecified criteria for equivalence (noninferiority), compared with tamoxifen. In this trial, 44.6% of patients were known to be estrogen- and/or progesterone-receptor positive. The proportion of patients who had progressed and median time to progression for anastrozole were 73.2% and 251 days, respectively, and for tamoxifen were 75.3% and 252 days, respectively. Similarly, the proportions of patients who were considered to be responders was similar for anastrozole (32.9%) and tamoxifen (32.6%). Supporting results were observed from the secondary end points. At the time of data cutoff (10 March 1999), 91 [26.8%] patients randomized to anastrozole and 74 [22.6%] patients randomized to tamoxifen had died. The proportions of patients who were alive longer than 2 years were 67.9% for anastrozole and 73.3% for tamoxifen. Data were not sufficiently mature to allow reliable inferences for overall survival. The majority of patients (72.0% anastrozole, 77.5% tamoxifen) had adverse events and 107 (16.1%; 14.9% anastrozole and 17.3% tamoxifen) patients reported serious adverse events. A total of 34 (5.1%; 4.5% anastrozole, 5.8% tamoxifen) patients had adverse events that led to withdrawal. Seven patients who were given anastrozole and 8 patients who were given tamoxifen had drug-related adverse events that led to withdrawal. Of the 165 deaths reported at the time of data cutoff, 13 deaths resulted from an adverse event unrelated to trial treatment. Similar rates of adverse events, serious adverse events, adverse events that led to withdrawal, and adverse events that led to death were reported for both treatment groups. No significant laboratory assessments or clinical findings were observed. Both anastrozole and tamoxifen were well tolerated. | clinstat/ cntrld/ il0027.pdf |
| Europe, South America, Australia, South Africa Bonnetere None 30 Aug 95 Recruitment completed | | 66 (34-92) | Postmenopausal women with advanced breast cancer | Tamoxifen 328 (668) | Tamoxifen 20 mg daily (Until disease progression or withdrawal) | | |

* Drug formulation information can be found in Part 2 of this table.
W White; B Black, H Hispanic; AO Asian/Oriental; OT Other.

Table 1a (Part 2) Drug formulation information

| Trial ID | Tablet strength (Formulation no.) | Tablet lot no. | Batch no. | Date of manufacture | Site of manufacture |
|-------------|--------------------------------------|----------------|-----------------|---------------------|---------------------|
| 1033IL/0030 | Anastrozole 1 mg (F11292) | T9111NA | ST2009-001-PA02 | 4 January 1994 | |
| | | N63100A | 9026W | 20 May 1996 | |
| | | N63100C | 9026W | 20 May 1996 | |
| | | N63108A | 9027W | 20 May 1996 | |
| | | N63100 | 9026W | 20 May 1996 | |
| | | N73192 | 0729Y | 22 April 1997 | |
| | | N83091B | 9026A | 27 March 1998 | |
| | Anastrozole placebo (F11314) | N53197A | ADM28075/95 | 1 August 1995 | Zeneca UK |
| | | N63054A | ADM28075/95 | 1 August 1995 | Zeneca UK |
| | | N63135B | ADM37519G96 | 3 June 1996 | Zeneca UK |
| | | N73085A | ADM40074K96 | 10 February 1997 | Zeneca UK |
| | | N73248 | ADM40071I96 | 6 February 1997 | Zeneca UK |
| | | N73085 | ADM40074K96 | 10 February 1997 | Zeneca UK |
| | | N83014B | ADM38330F97 | 24 November 1997 | Zeneca UK |
| | Tamoxifen 20 mg (F12061) | N63003A | 9072T | 23 October 1995 | |
| | | N63118A | 9043W | 26 June 1996 | |
| | | N63120A | 9045W | 26 June 1996 | |
| | | N73101 | 9039Y | 6 May 1997 | |
| | | N73180 | 9061Y | 21 July 1997 | |
| | | N83046A | 9008A | 29 January 1998 | |
| | | N83057A | 9010A | 29 January 1998 | |
| | Tamoxifen placebo (F12062) | N53181A | T9003 | 13 November 1995 | |
| | | N63047A | W9008 | 21 May 1996 | |
| N73103 | | 8021Y | 13 March 1997 | | |
| N83080A | | 9038A | 20 May 1998 | | |

Table 1a (Part 2) Drug formulation information (continued)

| Trial ID | Tablet strength (Formulation no.) | Tablet lot no. | Batch no. | Date of manufacture | Site of manufacture |
|-------------|--------------------------------------|----------------|------------------|---------------------|---------------------|
| 10331L/0027 | Anastrozole 1 mg (F11292) | P/0114/20 | ADM 28054/95 | 9 June 1995 | Irl UK |
| | | 9111N | ADM 27037/95 | 12 January 1994 | |
| | | 4227W | ADM 39146J96 | 20 May 1996 | |
| | | 9020Y | ADM 36266F97 | 20 December 1996 | |
| | | 3816Y | ADM 37713C97 | 23 April 1997 | |
| | | 9024A | ADM 02216E98 | 27 March 1998 | |
| | Anastrozole placebo 1 mg (F11314) | P/0114/03 | ADM 28025/95 | 20 April 1995 | |
| | | P/1204/18 | ADM 37519G96 | 03 June 1999 | |
| | | P/1204/20 | ADM 37521E96 | 05 June 1996 | |
| | | P/1301/36 | ADM 38330F97 | 24 November 1997 | |
| | | P/1301/10 | ADM 40073C96 | 10 February 1997 | |
| | Tamoxifen 20 mg (F6293) | NP288 | ADM NP 288 | 08 July 1994 | |
| | | HH254 | ADM HH254 | 16 May 1995 | |
| | | HH256 | ADM HH256 | 18 May 1995 | |
| | | PO208/1 | ADM 37363D96 | 11 April 1996 | |
| | Tamoxifen placebo 20 mg (F11003) | OP383X | ADM 34549/94 | 21 June 1994 | |
| | | P/1301/21 | ADM 37422F97 | 25 June 1997 | |
| DN354X | | ADM 39153C97 | 13 November 1997 | | |

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This submission includes additional trials of anastrozole as outlined below; however, because these trials were done in different subject populations with different end points, they do not contribute to the evaluation of efficacy of anastrozole as first-line therapy for postmenopausal women with advanced breast cancer. Safety results of these trials will be discussed in the Integrated Summary of Safety (ISS), but tables of data will not be provided in the ISE.

- **Core controlled trials**
 - Trials 1033IL/0030 and 1033IL/0027 are completed, core controlled trials.
- **Additional trials**
 -
 -
 - Trials 1033IL/0033, A-15-12, 1033IL/0035 (A-15-13) are completed clinical pharmacology trials.
 - Trial 1033IL/0032 is a completed pharmacodynamic trial designed to evaluate the effect of anastrozole on peripheral and tumor aromatase activity in early stage breast cancer.

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2 CONTROLLED TRIALS: DESIGN AND METHODS FOR THE INTEGRATION OF EFFICACY DATA

This section summarizes the methods used for evaluating the efficacy of anastrozole in the core controlled trials (Trials 0030 and 0027). The 2 trials had similar objectives and design and were planned to allow analysis of the combined efficacy data. Follow-up is continuing in both trials.

2.1 Objectives

The primary objectives of Trials 0030 and 0027 were to compare the efficacy and safety of anastrozole (1 mg once daily) with tamoxifen (20 mg once daily) on the following parameters:

- time to progression of disease
- objective response rate
- safety (tolerability)

The secondary objectives were to compare the treatment groups with respect to the following variables:

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

Trial 0030 had the following additional variables (not discussed in this ISE) to compare treatment groups:

- WHO performance scores
- analgesic use
- bone pain

2.2 Trial design

Both trials were randomized, double-blind, double-dummy, and multicenter trials. Each trial compared the efficacy and safety of anastrozole with tamoxifen in the treatment of advanced breast cancer in postmenopausal women.

2.2.1 Selected doses of anastrozole for controlled efficacy trials

The doses of anastrozole investigated in the controlled efficacy trials were chosen on the basis of 2 Phase III trials conducted for the second-line therapy clinical program (NDA 20-541, approved December 1995). In those trials, daily doses of 1 mg anastrozole were shown to have efficacy similar to megestrol acetate (160 mg daily) as second-line therapy for advanced breast cancer in postmenopausal women. There was no difference in efficacy or tolerability between daily doses of 1 and 10 mg of anastrozole; therefore, a daily dose of 1 mg was chosen for the marketed dose and for the first-line clinical trial program.

2.2.2 Selection of comparison drug

Tamoxifen is considered to be the standard first-line therapy in most clinical situations requiring endocrine therapy to palliate advanced disease in postmenopausal women (Henderson and Harris 1991, Forbes 1997).

A dose of 20 mg was chosen because it is a widely used dose in medical practice, and no increase in effectiveness has been shown with higher doses (Mouridsen et al 1978). This dose maximally reliably lowers estradiol levels to the limits of detection.

2.2.3 Visit structure

Screening and efficacy assessments were to be performed within 4 weeks before randomization into the trial. However, assessments for which repetition would pose an undue hardship for subjects (eg, bone scan, CAT scan, chest or skeletal X-ray) were accepted if they had been done recently but not within 4 weeks. The eligibility of each subject was established before randomization to trial treatment.

After trial treatment began, subjects were seen every 4 weeks for the first 12 weeks (Trial 0030) or 24 weeks (Trial 0027) of trial treatment, every 12 weeks thereafter, and at the time of withdrawal for any reason. Blood samples for clinical laboratory tests were collected every 12 weeks until objective progression, and at the time of withdrawal from trial treatment; radiographic examination of confirmed metastatic lesions was repeated every 12 weeks during treatment and at withdrawal; bone scans were repeated every 24 weeks (every 48 weeks if negative at baseline) until disease progression or withdrawal. When trial treatment was withdrawn before progression had occurred, attempts were made to continue to follow the

subject for progression and time to death (survival). In addition, for subjects who were withdrawn from trial treatment because of an adverse event, every effort was made to conduct tumor assessments every 3 months until disease progression.

Monitoring for adverse events was continuous throughout the trial; however adverse events were recorded at the time of subject visits. All adverse events were documented and details of concomitant treatment recorded until 2 weeks after trial treatment was stopped. After withdrawal of trial treatment, subjects were followed, whenever possible, at 6-month intervals for survival.

2.3 Trial population

The basic entry criteria were the same for Trials 0030 and 0027; women were required to satisfy the following criteria:

- (1) be postmenopausal with locally advanced or metastatic disease
- (2) have measurable or evaluable disease
- (3) have hormone receptor status (estrogen receptor, progesterone receptor, or both) of positive or unknown
- (4) be suitable for first-line hormonal therapy
- (5) have informed consent

However, in order to conform to local medical practice, there were differences between the 2 protocols. A list of these differences is presented in Appendix A. These differences are not considered to impact the integration of the data from the 2 trials.

2.4 Withdrawal criteria

Reasons for withdrawal included: death, disease progression (at the discretion of the investigator), subject lost to follow-up, adverse event, noncompliance with protocol procedures, subject unwilling or unable to continue in the trial, or other specified reasons. All subjects were followed for survival, as possible, following withdrawal of active treatment.

2.5 Trial treatment

Subjects were randomly allocated on a 1:1 basis to either 1 mg of anastrozole once daily and tamoxifen placebo daily, or 20 mg of tamoxifen daily and anastrozole placebo daily. Subjects were instructed to take 2 tablets (1 active and 1 placebo tablet) daily at approximately the same time each day. Treatment continued until disease progression (as determined by the investigator), or until the subject withdrew from treatment for a reason other than progression.

2.6 Definition of efficacy end points

At each site of tumor involvement, it was recommended that at least 1 lesion was monitored; if any given site contained more than 1 lesion, the investigator decided how many lesions were monitored based on his or her clinical judgment. The selected lesion(s) were monitored throughout the trial until objective disease progression occurred.

2.6.1 Time to disease progression

Time to disease progression was defined as the number of days from the date of randomization to the date when objective disease progression was first documented by algorithm, or until death from any cause, whichever occurred first. Subjects who had not reached progression, had been lost to follow-up, or had not died by the time of data cutoff were right-censored in the analysis at the date of the last disease assessment.

2.6.2 Objective response

The assessment of tumor response included the evaluation of both measurable and nonmeasurable disease by assigning a response category (see Appendix B).

Measurable disease was defined as the presence of metastatic lesions measurable in 1 or 2 dimensions using physical or radiographic methods. Osteolytic bone lesions were considered to be measurable disease. For measurable lesions, the investigators recorded the physical or radiological measurements. To ensure consistency and objectivity in the assignment of response categories, an algorithm generated by ZENECA Pharmaceuticals, ZENECA Inc, used these measurements to assign response. The algorithm strictly applied the protocol definition of response which was based on UICC criteria (Hayward 1977).

Single metastatic lesions smaller than 0.5 cm, malignant pleural effusions or ascites, a positive bone scan, and osteoblastic or intratrabecular bone lesions were considered to be nonmeasurable. For nonmeasurable lesions, the investigators were asked to assign a response category, but were only permitted to assign complete response, stable disease, or progressive disease. The category

of partial response was not allowed to be assigned, because this category is difficult to objectively evaluate for nonmeasurable lesions.

The categories of response are defined in the following sections.

2.6.2.1 Complete response

A complete response was recorded if all of the following criteria were met: complete disappearance of all known disease, clear improvement of bone lesions on bone scan or skeletal radiographs, evidence of reossification of all lytic bone lesions, freedom from all cancer-related symptoms, and absence of new lesions. For subjects with evaluable disease of bone only, a complete response was recorded if all of the following criteria were met: remineralization of all lytic lesions, absence of bone pain (without analgesia), no new pathological fractures, evidence of remodeling of previously distorted bones, no new lesions, and normalization of the bone as visualized on the bone scan.

2.6.2.2 Partial response

A partial response was recorded if no new lesions appeared and either of the following criteria was met: for bidimensionally assessable lesions, a decrease of 50% or more from the pretreatment value in the sum of the products of the 2 perpendicular diameters measured; or for unidimensionally assessable lesions, a decrease of 30% or more from the pretreatment value in the sum of the longest diameters.

2.6.2.3 Stable disease

A response of stable disease was recorded if disease progression (defined below) did not occur, if there was insufficient evidence to record a complete or partial response, and if no significant change occurred (defined as a decrease in size less than 50% for bidimensional lesions and less than 30% for unidimensional lesions, or slight enlargement of lesions but less than 25% increase in size). Increased pain due to tumor flare was considered stable disease and was not considered indicative of objective progression.

If a subject had results for both measurable and nonmeasurable disease at entry, but subsequently only 1 of these was available for assessment, an overall visit response of stable disease was assigned unless there was evidence of progression.

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2.6.2.4 Disease progression

A response of disease progression was assigned if any of the following occurred: appearance of any new lesions; for bidimensionally assessable lesions, an increase of 25% or more from the smallest measurement recorded for the sum of the products of the 2 perpendicular diameters measured in existing lesions; late hypercalcemia; or progression in nonmeasurable disease.

2.6.2.5 Determining best overall response

For the objective response rate, responders were those subjects with a best objective response of CR or PR. Subjects with a best objective response which was not CR or PR were defined as non-responders. The best objective response for each subject was derived by the algorithm, using the response status across the set of visits for the subject. A best response of CR meant the subject has had 1 visit assessment of CR and a later (at least 28 days) visit assessment which confirmed the CR by assessing all known disease (not just monitored lesions). A best response of PR meant the subject had either: 1 visit assessment of PR and a later (at least 28 days) visit assessment which confirmed a PR; or 1 visit assessment of PR and a later (at least 28 days) visit assessment which assigned a CR.

2.6.3 Time to treatment failure

Time to treatment failure was defined as the number of days from randomization until the earliest occurrence of progression, death, or withdrawal of trial treatment. Subjects who had not experienced treatment failure at the time of data cutoff, or who were lost to follow-up, were right-censored in the analysis at the date of the last disease assessment. Subjects who had never received any trial treatment were assigned an uncensored time to treatment failure of zero days.

2.6.4 Time to death (survival)

Survival status of subjects was recorded every 6 months after disease progressed or after withdrawal for any reason, until death. Time to death was the number of days from randomization until death. Subjects who were still alive at the time of data cutoff, or who were lost to follow-up, were right-censored in the analysis at the latest date they were known to be alive.

2.6.5 Duration of response

Duration of response was measured for responding subjects (any subjects who had a best response of CR or PR). This was defined in the trial protocols in 2 ways: (1) from the date of randomization to the date of first determined progression or death from any cause and (2) from the date of first documentation of response to the date of first determined progression or death

from any cause. Any subject who had not progressed or died at the time of the data cutoff was right-censored in the analysis at the date of the last disease assessment.

2.6.6 Duration of clinical benefits

Duration of clinical benefit was measured for subjects with clinical benefit (any subjects who had a best response of CR, PR or SD \geq 24 weeks). This was defined from the date of randomization to the date of first determined progression or death from any cause. Any subject who had not progressed or died at the time of the data cutoff was right-censored in the analysis at the date of the last disease assessment.

2.6.7 Health outcomes

Health economics were evaluated by the number and proportion of subjects who received radiotherapy, chemotherapy, hormonal therapy, or other therapies for the treatment of breast cancer following the withdrawal of trial treatment until the date of data cutoff.

2.7 Statistical analysis

2.7.1 Power and general methods

2.7.1.1 Power

Initially, each trial was planned to include 426 subjects, but was later amended to include 660 subjects to meet noninferiority criteria.

The estimation of sample size was based on the primary end points of time to disease progression and objective-response rate. The trial was powered to demonstrate noninferiority, as defined by the confidence limit, for each of these end points. For time to progression, the lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen:anastrozole) had to be no less than 0.8 to assume noninferiority. For response rate, the lower 1-sided 95% confidence limit for the difference in response rates (anastrozole-tamoxifen) had to be no less than -10% to assume noninferiority.

The median time to progression, based on the literature (Muss et al 1988), was predicted to be 7.7 months for subjects with advanced breast cancer who were treated with tamoxifen as a first-line treatment. Based on this reference, the calculated sample size for Trials 0030 and 0027 indicated that 330 subjects in each treatment group (660 in total) recruited at a uniform rate over 24 months with a minimum follow-up of 6 months would give 80% power to rule out a median time to progression for anastrozole of less than 6.2 months (ie, median time to progression for anastrozole was 20% less than that for tamoxifen). This calculation was based on a 1-sided

5% significance level. A 1-sided approach was justified because it was of interest to demonstrate that median time to progression was at worst 20% less for anastrozole than for tamoxifen (ie, the trial demonstrated whether anastrozole was at least as effective as tamoxifen).

The response rate within the tamoxifen group was expected to be approximately 30% (Furr and Jordan 1984). To rule out a greater than 10% reduction in the anastrozole group with 80% power, the sample size would be 251 per group.

Since time to progression is more demanding in terms of sample size, the trial aimed to recruit 660 subjects. However, Trial 0030 encountered recruitment difficulties because of the strict entry criteria and the fact that many subjects in the United States with advanced breast cancer had already received adjuvant tamoxifen. In response to comments from the FDA, recruitment into Trial 0030 was stopped when companion Trial 0027 had accrued 660 subjects. At that point, 353 subjects had been enrolled into Trial 0030.

A 6-month minimum follow-up for both trials was planned, but lower than expected rates of disease progression were observed during a blind review of the Trial 0027 data (the data were not broken down by treatment). Therefore, the minimum follow-up time for both trials was extended to 8 months. The date for recruitment of the final subject in Trial 0030 was 9 July 1998 and for Trial 0027 was 01 July 1998. Thus, the data cutoff date (the date on which the final subject visit data was generated for the analysis) for both trials was moved to 10 March 1999. The database was locked 1 month after the data cutoff data and the treatment group was unblinded thereafter.

A total of 1021 subjects are included in the ISE, with 353 from Trial 0030 and 668 from Trial 0027.

2.7.1.2 General methods

This analysis included all randomized subjects and compared the treatment groups on the basis of randomized treatment, regardless of whether this treatment was actually received ('intention to treat' approach).

The hypothesis for these combined trials was tested at the 1-sided 5% significance level as follows:

H_0 : anastrozole (1 mg daily) was inferior to tamoxifen (20mg daily)

H_1 : anastrozole (1 mg daily) was non-inferior to tamoxifen (20mg daily)

The primary objective was declared to be achieved if the non-inferiority had been obtained on both time to progression and objective response rate.

The effects of center and treatment-by-center interaction were not investigated because recruitment at most centers was low, which could cause problems with computational convergence. No analysis was performed for individual centers or a subgroup of centers.

2.7.2 Covariate fitting approach for adjusted models

In both trials, the following 4 prespecified baseline prognostic covariates were fitted in the model in the same order of decreasing clinical relevance. These 4 covariates were included in the combined analysis in the same way as the individual trials.

- A) extent of disease at entry (soft tissue alone, or lung disease alone, or soft tissue and lung disease vs other)
- B) previous hormonal therapy (yes vs no)
- C) estrogen and progesterone receptor status at diagnosis (either ER+, PR+, or both ER+ and PR+ vs other)
- D) age ≤ 65 vs > 65 years)

The covariates have been identified in the literature as predictors of response rate to hormonal therapy (Muss 1992), prolonged time to progression, or survival (Dhodapkar 1996). Age and receptor status were ranked lower than they might otherwise have been because the trials only included postmenopausal women who were hormone receptor positive or unknown.

2.7.3 Time to progression, treatment failure and death

Time to event (disease progression, treatment failure, and death) were summarized by randomized trial treatment using Kaplan-Meier method. Kaplan-Meier plots and Kaplan-Meier estimates of median times to event were presented for each treatment.

Formal treatment comparison was analyzed for each time to event end point using a Cox regression model to assess that anastrozole was non-inferior to tamoxifen. Because the death rate was low (265 [26.0%] subjects died) at the time of submission, only Kaplan-Meier curves were presented for time to death by treatment group and no statistical analysis was performed. The SAS procedure was implemented using the exact method to control for tied data. The Cox regression model was used in 3 ways: (a) adjusted analysis with treatment factor and the baseline prognostic covariates using "trial" as a stratification factor; (b) adjusted analysis with treatment factor and the baseline prognostic covariates using "trial" as an additional covariate; and (c) unadjusted analysis with treatment factor only. The primary analysis is (a) and the other 2 analyses are considered as supportive. The baseline prognostic covariates were fitted into the model using the approach specified in Section 1.2. In analysis (b), trial-by-treatment interaction was assessed, and if there was evidence of significant trial-by-treatment interaction