Letrozole in the Extended Adjuvant Treatment of Postmenopausal Women with History of Early-Stage Breast Cancer Who Have Completed 5 Years of Adjuvant Tamoxifen

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Abstract

Purpose: To present the basis of the decision of the Food and Drug Administration to grant accelerated approval for letrozole for extended adjuvant treatment of early-stage breast cancer in postmenopausal women after completion of adjuvant tamoxifen.

Experimental Design: The Food and Drug Administration reviewed the data from the MA17 trial, a single, multinational, randomized, double-blind, and placebo-controlled trial, submitted by the applicant to support the proposed new indication.

Results: MA17 consisted of a core study and Lipid and Bone Mineral Density safety substudies. It enrolled 5,187 patients. In the core study, median treatment duration was 24 months and median follow-up duration was 27.4 months. Using a conventional definition of disease-free survival, 122 events on letrozole and 193 events on placebo were observed (hazard ratio, 0.62; 95% confidence interval, 0.49-0.78; $P = 0.00003$). Distant disease-free survival also improved with letrozole, 55 versus 92 events (hazard ratio, 0.61; 95% confidence interval, 0.44-0.84; $P = 0.003$). No statistically significant improvement in overall survival was observed. Hot flushes, arthralgia/arthritis, myalgia, and new diagnosis of osteoporosis were more common on letrozole. Frequency of fractures and cardiovascular ischemic events was not significantly different. A statistically significant mean decrease in bone mineral density in the hip occurred at 24 months on letrozole.

Conclusions: Letrozole administration led to a statistically significant prolongation in disease-free survival. Fractures and cardiovascular events were similar to placebo; however, new diagnoses of osteoporosis were more frequent. Short duration of treatment and follow-up precluded assessment of long-term safety and efficacy. Thus, accelerated approval was granted instead of regular approval.

Letrozole: mechanism of action. Letrozole (Femara, Novartis Pharmaceuticals, East Hanover, NJ) is a nonsteroidal inhibitor of the enzyme aromatase. Aromatase catalyses conversion of adrenal androgens to estrogens in the peripheral tissue. Letrozole administration to postmenopausal women causes a profound decrease in the levels of systemic estrogens. This inhibits growth of the hormone-dependent breast cancer; however, prolonged estrogen depletion adversely affects the bones and serum lipids (1, 2).

Letrozole: regulatory history. Letrozole is sold under the trade name Femara, as 2.5 mg oral tablets, administered once daily. In July 1997, it was approved for treatment of postmenopausal women with hormone receptor–positive or unknown advanced breast cancer that was progressing after antiestrogen therapy. In January 2001, it was granted approval for the first-line treatment of postmenopausal women with hormone receptor–positive or unknown locally advanced or metastatic breast cancer (3).

Letrozole: proposed new indication. In April 2004, the applicant (Novartis Pharmaceuticals) submitted a supplementary new drug application for letrozole with a proposed new indication: extended adjuvant treatment of early breast cancer in postmenopausal women after completion of 5 years of standard adjuvant tamoxifen. The standard of care for these women has been expectant follow-up, and a clinical benefit from continuation of tamoxifen beyond 5 years has not been shown (4); however, they remain at risk of breast cancer recurrence at an annual rate of 2% to 3% and a mortality rate of 1% to 2% (5). Unavailability of a beneficial treatment, after completion of 5 years of adjuvant tamoxifen, justified conducting a placebo controlled trial in this patient population.

Materials and Methods

Review process. The Food and Drug Administration (FDA) Division of Oncology Drug Products and the Division of Biometrics 1 reviewed the data from the pivotal MA17 trial submitted by the applicant to support the supplementary new drug application. The submission included the data analyzed at the first planned interim analysis of

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efficacy that was presented to the MA17 Data Safety and Monitoring Committee in August 2003. The Data Safety and Monitoring Committee had recommended early unblinding of the trial and disclosure and publication of its results (6). Additional data, collected until October 9, 2003, before online publication of the trial were also reviewed by the FDA. Additionally, a safety update of MA17, submitted by the applicant to the FDA in August 2004, was reviewed. Information from several other sources was reviewed: the applicant's oral presentation of the MA17 results to the FDA in June 2004; pertinent peer-reviewed literature (7–16); and publicly available information on other adjuvant and extended adjuvant trials of aromatase inhibitors—the International Breast Cancer Study Group trial BIG 18-98 and the National Surgical Adjuvant Breast and Bowel Project trial B-33. The FDA Division of Scientific Investigations provided on-site clinical inspection of selected study sites; the FDA Division of Metabolism and Endocrinology Drug Products provided a review of bone safety data from the Bone Mineral Density substudy; and the FDA Study Endpoints and Label Development Team reviewed the Quality of Life data.

Study design. MA17, a randomized, double-blind, placebo-controlled, parallel group, multicenter trial, sponsored by Novartis Pharmaceuticals, was conducted by the National Cancer Institute of Canada Clinical Trialists Group. The trial consisted of a core study for safety and efficacy, and Lipid and Bone safety substudies to focus on the effects of letrozole on serum lipids and bones. Details of the core study have previously been published (6).

Patient selection. Postmenopausal women with history of hormone receptor–positive or unknown early-stage breast cancer that had been surgically removed, who had completed 5 years of adjuvant tamoxifen within 3 months before randomization, and who were free of breast cancer recurrence were eligible to enter the study. Other eligibility criteria included an informed consent, Eastern Cooperative Oncology Group performance status of $\leq$2, life expectancy of $\geq$5 years, and adequate bone marrow and liver functions. Patients with known hormone receptor–negative primary tumors were excluded.

Study treatment. Study treatment was letrozole (2.5 mg) or placebo, once daily for 5 years, or until documentation of a recurrence, a second malignancy, or other protocol-specified events leading to treatment discontinuation. The core study allowed concomitant use of thyroid medications, calcium, vitamin D, bisphosphonates, and intermittent use of vaginal estrogens.

Treatment assignment and stratification factors. Treatment assignment was balanced within each cooperative group using three stratification factors: tumor hormone receptor status (positive or unknown), regional lymph node status (positive or negative or unknown), and prior adjuvant chemotherapy (received or not).

Study objectives and end points. The primary objective of the MA17 trial was demonstration of a statistically significant prolongation of disease-free survival with use of letrozole compared with placebo. For efficacy analysis and trial monitoring, the investigators had defined disease-free survival as the time from randomization to the first confirmation of a locoregional recurrence, distant relapse, or contralateral breast cancer; deaths without a recurrence or without contralateral breast cancer were not counted as events. Secondary objectives were determination of the overall survival, defined as the time from randomization to the time of death from any cause; evaluation of the incidence of contralateral breast cancer; and determination of the long-term clinical and laboratory safety of letrozole with focus on cardiovascular morbidity and mortality, incidence of all bone fractures, incidence of new osteoporosis diagnosis, common toxicities, and evaluation of overall quality of life.

Follow-up. Follow-up visits were scheduled every 6 months in the first year and every 12 months thereafter. Data on patient reported symptoms and toxicities were collected. Specific questions evaluated symptoms of estrogen withdrawal (e.g., hot flashes). New diagnoses of hypercholesterolemia, bone fractures, osteoporosis, or new cardiovascular events were also ascertained. Patients had a physical examination and blood tests for standard hematology and chemistry. At selected centers, serum lipid profile, bone turnover markers, and bone mineral density were assessed. No imaging studies, except for mammograms, were obtained unless clinically indicated. Patients in selected centers participated in quality of life assessments using the SF-36 Health Survey and Menopause-Specific Quality of Life questionnaires.

Statistical design. Sample size calculations were based on disease-free survival estimates. The original estimate of 80% disease-free survival at 4 years for patients in the placebo arm was revised to 88% after the Early Breast Cancer Trialists' Collaborative Group publication (5). Accordingly, the estimated sample size was increased to 4,800 patients to be accrued over 4 years; with at least 2 years of further follow-up, this sample size would detect an absolute improvement of 2.5% in disease-free survival (from 88% to 90.5%). A total of 515 events were expected in the 6 years after study initiation.

Twice-a-year monitoring of the accumulating data by the independent Data Safety and Monitoring Committee was a part of the protocol. Interim analyses were planned at one third (171) and two thirds (342) of the total expected number of events (515). Applying O'Brien-Fleming boundaries and a Lan-DeMets α spending function to allow for the two interim analyses (while maintaining the overall two-sided significance level at 5% in the final analysis), the nominal significance level for early termination or unblinding of the study at the first interim analysis was 0.00079, based on the stratified log-rank test statistic for disease-free survival.

Lipid substudy. The objective of the Lipid safety substudy was to evaluate the effect of letrozole on serum lipids. The end points were changes from baseline in cholesterol, triglycerides, lipoprotein A concentrations, and low-density lipoprotein/high-density lipoprotein ratio, incidence of new prescriptions for lipid lowering drugs, and/or dietary changes. Patients were eligible if they were not hyperlipidemic and not taking any lipid lowering drugs. Follow-up measurements were at 6 months, 1 year, and yearly thereafter until 1 year off the study treatment. Changes in the lipids from the baseline were to be reported at 2 and 5 years after the end of enrollment.

Bone Mineral Density substudy. The objectives of the Bone Mineral Density substudy were to evaluate the effect of letrozole on bone mineral density, on development of osteoporosis, and on bone metabolism. End points were the percent change in bone mineral density from the baseline at yearly intervals (in L2-L4 region of the spine and hip), proportion of women developing bone mineral density below the threshold value for osteoporosis, and changes in the markers of bone turnover in each group. Bone mineral density and bone turnover markers were recorded at the baseline and eligible patients were enrolled. Women with bone mineral density below the threshold value for osteoporosis were excluded. Bone mineral density of the lumbar spine and hip (by dual X-ray absorptiometry scans) was to be followed up annually for 5 years and standardized T scores and percent changes in bone mineral density were to be plotted over time. Changes in bone mineral density and bone markers were to be reported at 2 and 5 years after the end of enrollment in the core protocol.

Mandatory supplements in the Bone Mineral Density safety substudy. Calcium (500 mg/d) and vitamin D (400 IU/d) supplements, provided by the applicant, were mandatory for all the patients in the Bone Mineral Density substudy.

Results

Patient enrollment. A total of 5,187 patients were enrolled in the core study between August 1998 and September 2002. Although enrollment of 4,800 patients was completed in May 2002, additional patients were allowed to be enrolled for the Bone Mineral Density substudy. Data from one site with 17 patients were excluded from all analyses because of Good Clinical Practice irregularities. Data on two patients with recurrent disease at enrollment were excluded from all efficacy analyses. Safety was evaluated in patients who received any

letrozole or placebo. Thus 5,168 patients were evaluable for efficacy (letrozole: 2,582; placebo: 2,586), and 5,136 patients were evaluable for safety (letrozole: 2,563; placebo: 2,573) in the core study. The Lipid substudy enrolled 347 patients; 310 were evaluable (letrozole: 169; placebo: 141). The Bone Mineral Density substudy enrolled 226 patients; 222 were evaluable (letrozole: 119; placebo: 103).

Patient and disease characteristics. Characteristics of the patients and of the disease in the MA17 trial have been previously published and the FDA review confirmed the comparability of the two study arms (6). Notably, 98% of the tumors were hormone receptor positive; median time from the end of adjuvant tamoxifen to randomization was 0.7 months; 97.5% of the patients were randomized within 3 months of completing adjuvant tamoxifen; and more than 99% of the patients had received tamoxifen for longer than 4.5 years.

Conduct of the trial: results of the first interim analysis. The minimum number of events required for the first interim analysis (171) had occurred by March 2003. Efficacy results based on the data collected until August 19, 2003 were presented to the Data Safety and Monitoring Committee that recommended unblinding of the study and disclosure of the results to the patients, offering the patients in the placebo arm the chance of crossover to active treatment with letrozole (6).

Treatment and follow-up durations. The respective start and data cutoff dates (for the data submitted to the FDA) were August 27, 1998 and October 9, 2003 for the core study; November 24, 1999 and November 30, 2003 for the Lipid substudy; and August 25, 2000 and November 30, 2003 for the Bone Mineral Density substudy.

The median duration of treatment in the core study was 24 months (range: ≤1 to ≥60 months; 2.3% and 0.2% of the patients, respectively); <1% of the patients had completed the planned 60 months of treatment and ~24% of the patients had completed ≥36 months of treatment (Table 1). The median duration of treatment in the Bone Mineral Density substudy was 18 months, and in the Lipid substudy it was 25 months.

The median duration of follow-up in the core study was 28 months, ranging from 1.1 to 61.2 months (Table 1). The median duration of follow-up in the Bone Mineral Density substudy was 20 months, and in the Lipid substudy it was 28 months.

Patient disposition. Table 2 shows the disposition of the patients at the time of data cutoff (October 2003). The number of patients who had received the assigned treatment for 5 years at the time of data cutoff was <1%. Treatment was ongoing for most patients (letrozole arm: 74.9%; placebo arm: 72.8%). It had been discontinued for 24.3% of patients in the letrozole arm and for 26.2% of patients in the placebo arm; reasons for treatment discontinuation are shown in Table 2.

Disposition of the patients in the placebo arm of the trial (after unblinding and disclosure of the early results). Of the 2,570 patients originally randomized to receive placebo, 1,903 (74%) were still on treatment and 667 (26%) had discontinued at the time of unblinding. Of the 1,903 patients still receiving placebo, the status of 168 was reported unknown, 1,735 could be contacted, and 1,406 (81%) of these switched to letrozole.

Analysis of efficacy: disease-free survival. Letrozole showed a statistically significant prolongation of disease-free survival. Table 3 shows the number of events, the corresponding hazard ratios, and the *P* values in the two study arms using different disease-free survival definitions. Using the protocol-specific definition of disease-free survival, 92 events in the letrozole arm and 155 events in the placebo arm were observed [hazard ratio, 0.58; 95% confidence interval (95% CI), 0.45-0.75; $P = 0.00003$]. The O'Brien-Fleming boundary for early termination of the trial was 0.00079. Thus, the statistical test for early trial termination was met.

When a definition of disease-free survival that counted all deaths as events was used, 122 events in the letrozole arm and 193 events in the placebo arm were observed (hazard ratio, 0.62; 95% CI, 0.49-0.78; $P = 0.00003$). Disease-free survival counting all deaths as events is shown in Fig. 1. The risk of distant metastases was also significantly lower with letrozole than with placebo. There were 55 distant recurrences in the letrozole arm and 92 in the placebo arm (hazard ratio, 0.61; 95% CI, 0.44-0.84; $P = 0.003$).

Analysis of efficacy: overall survival. No statistically significant difference in the overall survival between the two study arms was observed. There were 51 (2.0%) deaths in the letrozole arm and 62 (2.4%) in the placebo arm (hazard ratio, 0.80; 95% CI, 0.55-1.16). The most frequent cause of death was breast cancer; however, non–breast cancer deaths were more frequent (Table 4). An update of the data (cutoff date: March 31, 2004) also did not show a significant difference in overall survival; there were 68 and 78 deaths in the letrozole and the placebo arms, respectively (hazard ratio, 0.87; 95% CI, 0.63-1.21).

Table 1. Duration of exposure to study treatment and duration of follow-up in the core study

Duration	Exposure to study treatment		Follow-up	
	Letrozole, *n* = 2,563	Placebo, *n* = 2,573	Letrozole, *n* = 2,582	Placebo, *n* = 2,586
Median	24	24	28	27
Estimated percentage of patients at	On the study treatment (%)		Followed up (%)	
1 y	82	82	95	95
2 y	50	50	62	61
3 y	24	23	31	30
4 y	8	8	10	10
5 y	0.2	0.2	0.2	0.3

Table 2. Patient disposition at the time of data cutoff

	Letrozole, *n* = 2,583	Placebo, *n* = 2,587	Total, *n* = 5,170
	n (%)	*n* (%)	*n* (%)
No. patients treated	2,567 (99.4)	2,569 (99.3)	5,136 (99.3)
Treatment completed	6 (0.2)	8 (0.3)	14 (0.3)
Ongoing at time of data cutoff	1,934 (74.9)	1,884 (72.8)	3,818 (73.8)
Discontinued	627 (24.3)	677 (26.2)	1,304 (25.2)
Reasons for treatment discontinuation			
Patient refusal	303 (11.7)	293 (11.3)	596 (11.5)
Toxicity of therapy	127 (4.9)	95 (3.7)	222 (4.3)
Other	101 (3.9)	136 (5.3)	237 (4.6)
Recurrent disease	58 (2.2)	109 (4.2)	167 (3.2)
Intercurrent illness	22 (0.9)	24 (0.9)	46 (0.9)
Death	16 (0.6)	18 (0.7)	34 (0.7)
Protocol violation	0 (0.0)	1 (0.0)	1 (0.0)
Unknown	0 (0.0)	1 (0.0)	1 (0.0)

Based on an earlier exploratory subgroup analysis, the sponsor had suggested that there was a survival advantage in the subset of women who had lymph node involvement with breast cancer at diagnosis. However, in the updated data (cutoff date: March 31, 2004), this post hoc analysis finding was not confirmed (hazard ratio, 0.67; 95% CI, 0.44-1.02).

Analysis of safety. Data from 5,136 evaluable patients (letrozole: 2,563; placebo: 2,573) who took at least one dose of the study treatment were analyzed for evaluation of general safety (Table 5). Hot flushes, arthralgia/arthritis, and myalgia were significantly more common in the letrozole arm (50% versus 43%, 28% versus 22%, and 10% versus 7%, respectively; $P < 0.001$ for each comparison). Incidence of new diagnosis of osteoporosis reported by the patients was significantly higher in the letrozole arm, both while on treatment (6.4% versus 4.9%, $P = 0.02$) and at any time after randomization (6.9% versus 5.5%, $P = 0.042$). The frequency of fractures was not significantly different between the two groups (5.9% versus 5.5%, $P = 0.6196$). Approximately 21% of the patients in the letrozole arm and 18% of the patients in the placebo arm received bisphosphonates. Cardiovascular ischemic events were reported on the study treatment by 5.6% of patients on the letrozole arm and by 5.4% on the placebo arm. Second malignancies or marrow dysplasia were reported by 1.9% of the patients in the letrozole arm and by 1.9% in the placebo arm. Endometrial cancer was the most common second malignancy with 4 cases (0.2%) in the letrozole arm and 11 (0.4%) in the placebo arm.

In the Bone Mineral Density safety substudy, 119 patients were allocated to letrozole and 103 to placebo. At the time of analysis, no patient had completed the assigned treatment. A greater mean decrease in bone mineral density at hip was detected at 24 months (−3% versus −0.4%, $P = 0.048$) in the letrozole arm compared with the placebo. A similar but statistically nonsignificant trend of mean decrease in bone mineral density in the lumbar spine was also observed (−4.6% versus −2.2%, $P = 0.069$).

Table 3. Comparative results using different disease-free survival definitions

Definition of disease-free survival	Letrozole, *n* = 2,582	Placebo, *n* = 2,586
Protocol definition (first event of locoregional recurrence, distant relapse, or CLBC)	92 (3.6%)	155 (6.0%)
Hazard ratio (95% CI), *P*	0.58 (0.45-0.76), 0.00003	
First event of locoregional recurrence or distant relapse excluding CLBC	75 (2.9%)	127 (4.9%)
Hazard ratio (95% CI), *P*	0.58 (0.44-0.77), 0.00015	
First event of locoregional recurrence, distant relapse, invasive CLBC (excluding DCIS/DCIS)	89 (3.5%)	146 (5.7%)
Hazard ratio (95% CI), *P*	0.60 (0.46-0.78), 0.00013	
First event of locoregional recurrence, distant relapse, or any second malignancy (including CLBC)	142 (5.5%)	198 (7.7%)
Hazard ratio (95% CI), *P*	0.71 (0.57-0.88), 0.00155	
First event of locoregional recurrence, distant relapse, or death from any cause	122 (4.7%)	193 (7.5%)
Hazard ratio (95% CI), *P*	0.62 (0.49-0.78), 0.00003	
First event of locoregional recurrence, distant relapse, any second malignancy, or death from any cause	161 (6.2%)	224 (8.7%)
Hazard ratio (95% CI), *P*	0.71 (0.58-0.87), 0.00080	

NOTE: CLBC, contralateral breast cancer; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*. Analyses stratified for receptor status, nodal status, and adjuvant chemotherapy are summarized.

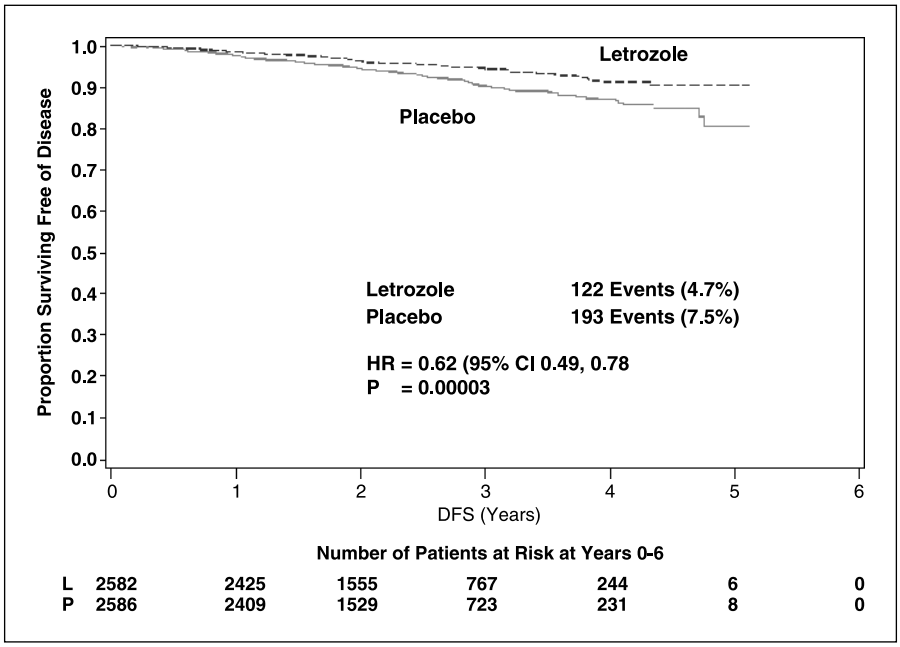

Fig. 1. Kaplan-Meier estimates of disease-free survival.

In the Lipid substudy, 169 patients were allocated to letrozole and 141 to placebo. At the time of analysis, no patient had completed the assigned treatment. Lipid levels were similar in both treatment arms.

Discussion

Data from the randomized, double-blind, placebo-controlled, multicenter MA17 trial was reviewed for the proposed new indication for letrozole: extended adjuvant treatment of early-stage hormone receptor–positive breast cancer in postmenopausal women who had completed 5 years of adjuvant tamoxifen. The planned duration of treatment in the pivotal trial was 5 years.

In this trial, two interim and one final analyses were planned. To control the overall type I error rate (from multiple interim analyses of disease-free survival) at the 0.05 level (two sided), O'Brien-Fleming boundaries with a Lan-DeMets α spending function were used. The nominal significance level for early termination of the study at the first interim analysis was 0.00079. The observed P value at the first interim analysis of disease-free survival was 0.00003. Thus, the statistical criterion for early termination of the trial was met.

When the trial was unblinded early and the majority of the patients crossed over from placebo to letrozole, the median duration of treatment was 24 months; <1% of the patients had actually received 5 years of letrozole. Therefore, information on the safety or efficacy of letrozole administered for 5 years is not available.

An improvement in disease-free survival from letrozole has been observed compared with placebo. Larger absolute differences over time between the two study arms, both in the disease-free survival and overall survival, have been reported (6). This has been attributed to longer treatment duration by some investigators (17). However, such observations are common in trials with short follow-up when the number of patients at risk diminishes rapidly over the follow-up period (18, 19). In the MA17 trial, the observed difference between the two study arms over the first year of follow-up will not change much because 95% of the patients have been actually followed up for at least a year. However, the currently observed projected differences between the two study arms over later years may change when more patients have been actually followed up through those years. The fractions of patients who had been followed up through years 2, 3, 4, and 5 were 60%, 30%, 10%, and <1%. Caution is warranted in overly optimistic interpretation of these early results and in attributing the observed widening differences between the two trial arms to longer treatment duration.

No difference in the overall survival was observed between the two study arms when the entire study population was analyzed. An exploratory subset analysis showed a statistically significant difference (using an unadjusted significance level) in the overall survival in the lymph node–positive subgroup. Such subset analysis is exploratory. Observed results can be misleading when follow-up duration is short and only a few of the expected events have occurred. FDA concluded that the follow-up period in the study was too short to provide reliable information on overall survival; therefore, this information was not included in the drug label.

Table 4. Overall survival

	Letrozole, n = 2,582	Placebo, n = 2,586
Number of patients who died	51 (2.0%)	62 (2.4%)
Hazard ratio (95% CI)	0.82 (0.56 to 1.19)	
P (stratified log-rank)	0.291	
Cause of death		
Breast cancer	17	23
Second malignancy	9	11
Cardiovascular death	9	12
Fatal stroke	2	4
Other, miscellaneous	13	12
Unknown cause	1	0

Table 5. The most frequently reported adverse events during chronic therapy

	Number (%) of patients with grade 1-4 adverse event		Number (%) of patients with grade 3-4 adverse event	
	Letrozole, *n* = 2,563	Placebo, *n* = 2,573	Letrozole, *n* = 2,563	Placebo, *n* = 2,573
Any adverse event	2,232 (87.1)	2,174 (84.5)	419 (16.3)	389 (15.1)
Vascular disorders	1,375 (53.6)	1,230 (47.8)	59 (2.3)	74 (2.9)
Flushing	1,273 (49.7)	1,114 (43.3)	3 (0.1)	0
General disorders	1,154 (45.0)	1,090 (42.4)	30 (1.2)	28 (1.1)
Asthenia	862 (33.6)	826 (32.1)	16 (0.6)	7 (0.3)
Musculoskeletal disorders	978 (38.2)	836 (32.5)	71 (2.8)	50 (1.9)
Arthralgia	565 (22.0)	465 (18.1)	25 (1.0)	20 (0.8)
Nervous system disorders	863 (33.7)	819 (31.8)	65 (2.5)	58 (2.3)
Headache	516 (20.1)	508 (19.7)	18 (0.7)	17 (0.7)
Dizziness	363 (14.2)	342 (13.3)	9 (0.4)	6 (0.2)
Skin disorders	830 (32.4)	787 (30.6)	17 (0.7)	16 (0.6)
Sweating increased	619 (24.2)	577 (22.4)	1 (<0.1)	0
Gastrointestinal disorders	725 (28.3)	731 (28.4)	43 (1.7)	42 (1.6)
Constipation	290 (11.3)	304 (11.8)	6 (0.2)	2 (<0.1)
Nausea	221 (8.6)	212 (8.2)	3 (0.1)	10 (0.4)
Diarrhea not otherwise specific	128 (5.0)	143 (5.6)	12 (0.5)	8 (0.3)
Metabolic disorders	551 (21.5)	537 (20.9)	24 (0.9)	32 (1.2)
Hypercholesterolaemia	401 (15.6)	398 (15.5)	2 (<0.1)	5 (0.2)

NOTE: The reported adverse events were observed after the first month of treatment.

During the relatively short time on the study when a comparative group was available, letrozole administration was tolerated by the majority of the patients. However, due to the short follow-up period, the long-term effects of letrozole on bone mineral density and serum lipids remain unknown. Observed effects of letrozole on bones in the core study are confounded by administration of bisphosphonates in about one fifth of the patients.

Regulatory basis for accelerated approval. Under the Subpart H provisions (Code of Federal Regulations 21 314.500), accelerated approval can be granted to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses, and that provide meaningful therapeutic benefit to patients over existing treatments; approval may be granted based on a surrogate end point or an early outcome (20). Letrozole was considered for accelerated approval as no treatment of proven clinical benefit was available for the proposed new indication. Early evidence of clinical benefit for letrozole, prolongation of disease-free survival compared with placebo, was available from the pivotal trial. Prolongation of distant disease-free survival was an additional factor that was considered in granting this accelerated approval.

FDA has accepted a prolongation in disease-free survival as a demonstration of clinical benefit for regular approval of adjuvant therapies in breast cancer; however, the follow-up in this study was relatively short, and the ultimate outcome of both safety and efficacy is unknown. Thus, accelerated approval under Subpart H was granted instead of regular approval.

Under similar circumstances, anastrozole was granted an accelerated approval based on a prolongation in disease-free survival shown in the Arimidex, Tamoxifen, Alone or in Combination trial (21).

Approval under Subpart H is subject to the requirement that the applicant further study the drug to verify and describe its clinical benefit. As a condition of the letrozole accelerated approval, the applicant will provide follow-up data on the safety and efficacy of letrozole from the patients who were enrolled in the pivotal trial. Annual submissions of follow-up data to the agency are required. Each patient will be followed up until death or for at least 5 years, and a final study report will be submitted. The substudies on bone and lipid/cardiovascular effects will be completed per protocol with submission of annual reports and a final study report.

As a second Subpart H commitment, the applicant agreed to submit data from the now closed International Breast Cancer Study Group trial 18-98 (BIG 18-98). Further data on the safety of letrozole administered for 5 years will be available from this study.

In addition to agreeing on Subpart H commitments, the Agency and applicant must agree on drug labeling. The applicant proposed that labeling for this indication recommend 5 years of letrozole administration. However, the study results do not support this duration of administration because very few patients received letrozole for 5 years. Thus, the approved labeling sates, "The planned duration of treatment in the study was 5 years. However, at the time of the analysis, the median treatment duration was 24 months, 25% of patients were treated for at least 3 years, and <1% of patients were treated for the planned duration of 5 years. The median duration of follow-up was 28 months. Treatment should be discontinued at tumor relapse." Further studies will be needed to define an optimal duration of therapy.

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