Blood Chemistry[2]
Chest x-ray
Bone scan / Skeletal survey (Areas of uptake on the bone scan should be x-rayed)
Liver ultrasound or abdominal CT scan
FSH and LH levels if indicated
If indicated, thoracic CT, abdominal CT, brain CT, and NMR
Bidimensional measurements along the two longest axes
Color photographs of visible lesions
Endocrine profile including serum estrone, estradiol, estrone sulfate, cortisol, aldosterone, testosterone, FSH, LH, TSH, SHBG, T3, and T4 prior to initiation of drug therapy

On Study:

(At six months all patients will be restaged with same studies as required for entry.)

Chest x-ray (every three months)
Liver ultrasound or abdominal CT (if positive at entry or if abnormal liver function studies have developed) performed every three months
Bone scan / skeletal x-rays at six months on study:
Skeletal x-rays of involved areas every three months or of new areas of involvement on bone scan
Bidimensional measurements of any palpable lesions every three months
Color photographs of visible lesions every three months
Thoracic CT, Abdominal CT, Brain Scan, and / or NMR as indicated every three months
Subjective Response (Severity of Pain and Analgesic Use) every examination except two weeks
Toxicity assessments (using NIH Common Toxicity Criteria) at every examination
Vital signs including weight, blood pressure, and pulse rate at every examination
Hematology / blood chemistry at every exam except two weeks
EKG at examinations 1, 5, and 8
Endocrine parameters:
Estrone, estradiol, estrone sulfate, cortisol, aldosterone at visits 2, 3, 4, 5, 6, 7, and 8:
17a-hydroxyprogesterone, androstenedione, and testosterone at visits 2, 3, 4, and 5;
LH, FSH, TSH, SHBG, T3 and T4 at visits 1, 3, and 5
Synacthen Test at visits 1, 3, and 5 to determine adrenal reserve
Pharmacokinetic monitoring at visits 1, 2, 3, 4, 5, 6, 7, and 8.
Documentation on any adverse experiences with clinical judgement as to the relationship to study drug at every visit after visit one

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Sodium, potassium, total calcium, phosphate, creatinine, total protein, total bilirubin, GOT (AST), SGPT (ALT), gamma GT, alkaline phosphatase, fasting blood sugar

Evaluations for Efficacy

Main criterion for efficacy: Maintenance of suppression of estrone, estradiol, and estrone sulfate over the first three months of study. Inhibition of 50% of the pretreatment levels is considered effective.

Secondary criterion for efficacy: Evaluation of tumor response using the UICC criteria in patient who have been treated for at least three months with drug or in the case of progression for shorter periods. In patients on concurrent bisphosphonate therapy objective response (CR, PR) or stabilization (NC) in bone will not be included as part of the overall tumor response. Mixed blastic and lytic lesions will not be evaluated for response.

Tolerability will be assessed using the NIH Common Toxicity Criteria.

Reasons for Premature Discontinuation from Trial

Adverse experience
Abnormal laboratory value(s)
Abnormal test result(s)
Unsatisfactory therapeutic effect(s)
Cancer no longer requires trial treatment
Failure meet protocol criteria
Non-compliance
Withdrawal of consent
Lost to follow-up
Administrative Problems
Death

Statistical Considerations:

Sample size is based on the proportion of patients in each dose group with estrone (E1) levels below the limit of detection at one month. Data from AR/BC1 suggested that, after one month of treatment, estrone levels were suppressed to levels below the limit of detection in approximately 20% of patients on O.5 mg CGS 20267 and approximately 70% of the patients on 2.5 mg/d CGS 20267. In order to maintain a difference as statistically significant at the 5% level ($a = 0.5$) with an 80% power ($1 - B = 0.80$) eighteen patients in each group are required. Estimating a nonavailability rate of 10% at one month for the estrone measurements a sample size of forty (20 / arm) is needed..

For analysis of hormone data, only "endocrine evaluable" patients will be included. Patients who would not be evaluable would be patients with CGS 20267 detectable at baseline, inability to detect CGS 20267 on three or more occasions excluding baseline, or concurrent use of other glucocorticoid or endocrine medication while on study.

To determine if a difference exists in estrone suppression at one month between letrozole 0.5 mg and letrozole 2.5 mg Fisher's exact test will be used. To determine if the pattern of E1 suppression over the first three months of treatment is the same, a repeated measures analysis of variance will be used with the initial E1 value as the covariant. If multiple observations are missing, omission of that patient's data from the evaluation will occur. In order to determine if hormone suppression is maintained over three months, the regression slopes for each treatment arm will be calculated and tested against zero.

Other hormones including 17 *a*-hydroxyprogesterone, LH, FSH, TSH, androstenedione, testosterone, SHBG, T3, and T4 will analyzed using the same type of analysis as planned for estrogens. Changes in other hormone values during the Synacthen test (cortisol, 17 *a*-hydroxyprogesterone, aldosterone,) will be tested by using the T-test approach.

Plasma trough drug concentrations will be analyzed statistically in relation to the levels of plasma estrogens. Baseline drug concentrations will result in exclusion of hormone data from the analysis.

Tumor response will be analyzed using non-parameter procedures taking into account the ordered categorical nature of the data. Influence of baseline characteristics on prognosis or response will no be analyzed..

Time to progression is defined as the interval in days between the date of first intake of CGS 20267 and documented date of disease progression. Patients who have not progressed at the time of analysis will have right censored observation times (TTP+). Deaths due to cancer or cause unknown will be regarded as progressive disease. Time to treatment failure is defined as the interval in days between the date of first intake of CGS 20267 and the earliest occurring date of progression or withdrawal from the trial for any treatment related reason. Patients still on trial without evidence of progressive disease at the time of analysis or withdrawal for the trial for reasons unrelated to the trial treatment will have right censored observation times. Time to progression in days and time to treatment failure in days will be estimated in each dose group using the Kaplan-Meier product-limit method.

Tolerability data will be tabulated according to dose group. Laboratory data will be tabulated and graded using the NIH Common Toxicity Criteria. For adverse experience data, summaries using the COSTART terms will be provided if appropriate. Summary descriptive statistics will be presented for body weight and blood pressure data.

Study Report:

Disposition of Patients:

AR/ES1 was conducted between June 6, 1993 and January 10, 1995 at two sites: Milan, Italy and Bobigny, France. The total study enrollment was forty-six with thirty-eight Italians and eight

French women. Distribution of patients by trial group is shown in the following table.

Table AR/ES-1: Distribution of Patients and Exposure Times by Arm

Parameter	Letrozole 0.5 mg	Letrozole 2.5 mg
Number Randomized	22	24
Number Discontinued	13	16
Reason:		
For Adverse Experiences	--	1
For Unsatisfactory Therapeutic Response	12	14
For Other Reasons	1	1
Efficacy Analyses		
Endocrine Endpoints	22	22
Tumor Response	20	20
Pharmacokinetics	22	24
Safety Analysis		
Hormonal Laboratory Tests	22	24
Adverse Reactions	22	24
Routine Laboratory Testing	22	24
Duration of Exposure to Study Drug		
Mean	177.5 days	124.5 days
Range	days	days

Reasons for trial discontinuation will be discussed in a later section. With regard to objective tumor response evaluation three patients did not have measurable / evaluable disease at entry onto the trial. For one patient histologic / cytologic proof of breast cancer was missing and estrone and estradiol values were premenopausal. Two addition patients are not evaluable for tumor response (not explained)

Demographic Data:

In this study all patient were white. The mean age in the L-0.5 arm reported as 62.5 years (range: and in the L-2.5 arm 64.9 years (range: Weights were well matched between arms with the mean weight on the L-0.5 arm equal to 66.3 kg (range: kg) and on the L-2.5 arm (range: kg). Median duration of disease on the L-0.5 arm was 3.5 years (range , on the L-2.5 arm the median was 4.0 years (range: . Median time interval from first metastases or local recurrence was 5.0 months with a range of months in the L-0.5 arm and 0 - 124 months in the L-2.5 arm. The interval from the most recent progression to entry onto the trial was one month in each arm with a range from months. In five patients on the L-0.5 arm and in five patients on the L-2.5 arm the receptor status was unknown. In

seventeen patient on the L-0.5 arm and in 19 patients on the L-2.5 arm the receptor status was positive for primary or recurrent tumor. Progesterone receptors were positive in 23 patients on both arms, negative in nine, and unknown in four patients. The dominant site of disease was bone in twenty-one patients, soft tissue in six patients, and visceral in nineteen patients.

With regard to primary therapy for breast cancer forty-five of forty-six patients had some form of breast surgery: some type of mastectomy in thirty-three patients; mammectomy with axillary disease in one patient; lumpectomy only in seven patients; and biopsy in four patients. Twenty-nine patients had received radiotherapy prior to trial entry of whom twenty-three had loco or locoregional therapy and eleven had radiotherapy for metastatic disease. While on study eight patients received radiotherapy for palliation. Eighteen patients had received chemotherapy: adjuvant or neoadjuvant in ten patients; therapeutic in six patients; and, adjuvant plus therapeutic in two patients. Twenty-two of the study participants had received adjuvant tamoxifen, twenty-two had received therapeutic tamoxifen, and two had received tamoxifen in both settings.

Patient distribution on each arm by number of sites of disease, by severity of pain at study entry, and by performance status are shown in the following table.

Table AR/ES -2: Distribution of Patients by Disease Sites, Pain Severity, and Performance Status

Parameter	Letrozole 0.5 mg	Letrozole 2.5 mg
Site(s) of Involvement		
Soft Tissue	3	3
Soft Tissue + Bone	4	3
Soft Tissue + Bone + Viscera	2	3
Bone	6	8
Bone + Viscera	1	3
Viscera	6	4
Severity of Pain		
None	15	13
Mild	4	6
Moderate	2	4
Severe	1	1
Karnofsky Performance Status		
Grade 0 (90 - 100)	11	9
Grade 1 (70 - 80)	9	13
Grade 2 (50 - 60)	1	2
Grade 3 (30 - 40)	1	0

Determination of menopausal status is not well documented in the demographic data, however all patients had hormone determinations pre-study which confirmed the menopausal status in all but one patient enrolled on this trial. Common medical problems in this population group included terial hypertension in forty patients and diabetes mellitus[3] in five patients (well controlled).

[3]Diabetes mellitus was an exclusion criteria in this study. The applicant considers these minor protocol violations.

Efficacy Results:

Hormone Suppression:

Fourteen days after initiation of treatment E1 and E2 levels were markedly suppressed in both groups. At one month the level of suppression of E1 and E2 were significantly reduced from baseline ($p = 0.0001$). No difference in the level of detection between the L-0.5 and the L-2.5 group was observed (Fisher's exact, $p = 0.23$). Twenty-four percent of the patients in the L-0.5 group and twenty-eight percent of the patients in the L-2.5 group had E1 and E2 levels below the level of detection. No period effect was noted (Estrogen suppression remained the same from day 14 to three months. When the level of E1 and E2 were examined using analysis of covariance for possible site effect no difference in the level of suppression is noted in the low dose group (letrozole 0.5 mg). In the letrozole 2.5 mg group less estrogen suppression was observed in the French participants considered to be due to an outlier among the smaller number (8) of French participants as compared to the larger number (36) Italian patients enrolled in the study.

Tumor Efficacy Information:

Tumor Response Data

Table AR/ES-3 presents the tumor response data by arm. Verification of the response category is difficult at best due to: (1) the inclusion in the line listing of sites which are not involved as "not assessable" when the protocol required studies were done and (2) the failure to document changes in the soft tissue and visceral tests as reported in Listing 24 and then in Listing 19 reporting these lesions as areas of progression and (3) discontinuation of antiestrogen just prior to study enrollment so that antiestrogen withdrawal response may be a confounding factor.

Table AR/ES-3: Response Data as Determined by Ciba by Arm

Response (IUCC)	Letrozole 0.5 N = 22	Letrozole 2.5 N = 24
Complete Response	2 (9)	2 (8)
Partial Response	2 (9)	0 (0)
No Change (Stable Disease)	5 (23)	4 (17)
Progressive Disease	11 (50)	14 (58)
Non-Assessable	2 (9)	4 (17)

In reviewing all of the response data two patients on the L-2.5 arm and one patient on the L-0.5 arm considered non-evaluable by the applicant were determined to have the following responses: No. 13 - NC, No. 37 - PR, and No. 27 -NC. In addition one patient

on the L-0.5 arm) categorized as a PR by the applicant. On review the patient has evaluable disease only and is reclassified as stable disease.

Time to Event Information

Table AR/ES-3 contains the time to event information as determined by Ciba. The dates assigned by the applicant with regard to treatment failure and progression were reviewed. No discrepancy between the reviewer and the applicant time to event dates have been observed. Several patients were continued on trial despite progression . Hence the time to progression is inaccurate. Since treatment failure included progression, median time to treatment failure as reported by the applicant is the same as the median time to progression.

Table AR/ES-3: Time to Event Information

Event	Letrozole 0.5	Letrozole 2.5
Median Time to Progression (Range)	101 days days)	92 days
Time to Treatment Failure (Range)	101 days days)	92 days days)

Overall survival was not determined in this trial. The median duration of response could not be calculated because eleven of the fifteen responders remained on drug therapy at the conclusion of the trial. For the two responders on the L-0.5 arm the durations of response were 177 days and 494 days and in the L-2.5 arm the duration of response for the two responders was 170 days and 184 days.

Pain Severity and Performance Status Data:

The information of the changes in pain severity is presented in such a way that no conclusions can be drawn about improvement or worsening of the score. Similar information about changes in the pain score are difficult to interpret.

Endocrine Efficacy Data

Cortisol Levels

To determine if letrozole had any effect on synthesis of cortisol Synacthen™ testing was performed on all patients prestudy, at 14 days, one , two, and three months. Baseline cortisol levels at all time points in both treatment groups were not statistically significantly different from the prestudy value. After stimulation a statistically significant ($p = 0.015$) decrease in the peak values as compared to the baseline peak value was noted in both treatment groups with not difference in the amount of decrease detected between groups. No pattern of suppression was observed.

Aldosterone

Patients had serum aldosterone measured prestudy and at day 14, and months one, two, and three. Statistical analysis showed an increase the baseline value over the three months which is significant ($p = 0.025$). After Synacthen™ testing a slight increase in the peak aldosterone level in the L-0.5 group was observed while a decrease in the peak aldosterone level in the high dose group was noted, a difference which is clinically significant.

17*a*-Hydroxyprogesterone, Testosterone, and Androstenedione

No statistically significant difference was noted in the baseline or peak post stimulation 17*a*-hydroxyprogesterone values over time in either treatment group. Testosterone levels remained stable over the duration of the study. Androstenedione values increased over time from baseline (statistically significant, $p = 0.04$) in both treatment arms.

FSH, LH, SHBG, and Thyroid Function

Significant changes occurred over time in FSH ($p = 0.001$), LH ($p = 0.001$), and SHBG ($p = 0.0001$) in both arm with no difference between the two arms in the rate of change.With regard to T4 statistically higher baseline values were noted in the high dose group which declined over the next three months. No difference in the low dose group was detected at any time point. With regard to TSH baseline levels and levels obtained during treatment were much higher in the L-2.5 mg group as indicated by a significant treatment effect in the statistical analysis for this group. When the data by center was analyzed, the treatment effect was due to one patient with a very high TSH level in France. This patient was determined to have subclinical hypothyroidism. One patient had subclinical hyperthyroidism with low TSH and mildly elevated T3 and T4 levels. Another patient had decreased TSH levels at baseline with no change in T3 and T4. Four other patients had mildly elevated TSH levels without abnormalities of T3 or T4. One patient in the L-0.5 arm developed TSH levels below the lower limit of normal with slight elevation of T4 at three months, normal T3, and no signs of clinical hyperthyroidism.

Safety Profile

Adverse Events

No deaths have occurred in the study population at the time of this report. The following table (AR/ES - 4) provides a summary and a description of the adverse events reported in this trial.

Table AR/ES - 4: Summary of Adverse Events

	Letrozole 0.5	Letrozole 2.5
No. of Adverse Events	21	17
No. of Patients Reporting Adverse Events	10 / 22 (45%)	7/24 (29%)
No. with Serious Adverse Events	1	3
No. of "Drug Related" Adverse Events : Possibly, Probably, or Highly Probably	9	5
No. of Withdrawals due to Adverse Event	-	1

Review of the six serious adverse events for which short histories were provided did not reveal a relationship to study drug. In one case in a patient treated with L-0.5 the elevated LFTs were probably due to tolbutamide introduced fifteen days after study drug. The patient's liver function returned to normal. One adverse event led to removal of the patient from trial. This patient developed elevated liver function studies due to biliary stenosis which required stint placement for relief. Since the biliary stenosis was thought to be due to a second tumor the patient was removed from trial. One grade 3/4 hematological abnormality was reported in a patient undergoing palliative RT while on study. Table AR/ES - 5 describes the types of adverse events reported in this study which were related to the study drug.

Table AR/ES - 5: Number of Patients and the Nature of Adverse Experiences

Type of Adverse Event	Letrozole 0.5	Letrozole 2.5
Diarrhea	1	1
Hot Flushes	2	2
Alopecia	1	
Sleep Disorder	1	
Somnolence	1	
Nausea	1	
Vomiting	1	
Abnormal LFTs	1	
Increased Appetite		1
Increased Weight		1

All of the above adverse events were of grade 2 or less except for the abnormal liver functions which, as noted above, were probably NOT related to letrozole therapy.

Other Physical Exam and Laboratory Measurements

Three patients had change in weight, two with weight loss and one with weight gain. No blood pressure abnormalities due to study drug were reported. One patient who has elevated diastolic blood pressure at baseline required treatment after seven months on study. No reports of new abnormalities in EKG tracing were reported for any patients on trial. No laboratory abnormalities which could be related to the study drug were observed during this trial.

Pharmacokinetic Assessments

In the 0.5 mg letrozole group the plasma concentration of letrozole increased until a steady state value of 50 nmol/L (range: nmol/L) was reached at visit 3. In the letrozole 2.5 mg group the plasma steady state was reached on the fourth visit with a concentration of 400 nmol/ approximately eightfold greater the letrozole 0.5 mg group concentration.

SUMMARY:

In this phase II randomized double blind trial letrozole 0.5 mg and letrozole 2.5 mg were studied in patients with advanced breast cancer to determine (1) the effect on estrogen suppression, namely estrone and estradiol during three months of therapy; (2) the effects of multiple doses on cortisol and aldosterone levels using the Synacthen™-test; (3) the effect of two doses of letrozole on other endocrine parameters; (4) the trough plasma drug concentration levels during treatment with daily doses of 0.5 and 2.5 mg letrozole; (5) the tolerability of study drug, and (7) if any antitumor activity was observed. Forty-six women with breast cancer were enrolled in this trial, twenty-two on the letrozole 0.5 mg arm and twenty-four on the letrozole 2.5 mg. arm.

Letrozole at either dose level suppressed the level of estrone below the limits of detection in 73% of the 0.5 mg group and in 86% of the patients at one month on study. Estradiol levels were suppressed from 14.2 - 18% of baseline values. After suppression of estrogen levels occurred in the first weeks of study no increase in estrogen levels was noted at any time (no rebound). No statistical difference in the degree of estrogen suppression was noted between the two study arms. Since the majority of patients had depression to values below the limits of detection as defined by the assay no differentiation in the degree of suppression due to different dose level could be detected.

With regard to tumor response more complete and partial responders (four) were observed in the letrozole 0.5 mg arm as compare to the letrozole 2.5 mg arm (two responders). The time to progression and the time to treatment failure were reported to be 101 days in the L-0.5 arm and 92 days in the L-2.5 arm. No survival information is available. No deaths had occurred at the time of study completion. Duration of response in both arms was greater than 170 days.

Cortisol levels measured during the study showed no suppression as compared to baseline. In both treatment groups after stimulation a statistically significant 15% decrease in the peak

plasma cortisol level was noted. An increase from baseline in aldosterone levels was noted over the first three months. After Synacthen™ testing (stimulation) a statistically significant decrease in the peak aldosterone level in the high dose group as compared to the low dose group was noted. Testosterone and 17 *a*-hydroxyprogesterone were stable while androstenedione levels increased over time. Increase in FSH and LH levels was attributed to antiestrogen withdrawal. Most patients were started on study within three weeks of stopping antiestrogen therapy.

With regard to adverse events the one adverse event which resulted in study removal was not related to study drug. No serious laboratory events related to study drug were reported. All adverse events were of grade 2 or less and include: diarrhea, hot flushes, alopecia, sleep disorders, somnolence, nausea, vomiting, increased appetite, and weight gain. Many of the side effects are related to the hormonal nature of the drug.

CONCLUSION:

This randomized double blinded phase II study in patients with breast cancer previously treated with antiestrogens demonstrates that letrozole 0.5 mg and letrozole 2.5 mg adequately suppress estrogen production through aromatase inhibition. Both dose levels produce objective responses in patients with advanced breast cancer with durations of response of > 170 days. The sample size is inadequate to determine if a differential antitumor effect exists for letrozole 0.5 mg as compare to 2.5 mg. The confounding factor of possible response due to antiestrogen withdrawal also complicated interpretation of response data. Time to progression and time to treatment failure are problematic since several patients were continued on study after progression was noted. No drug related adverse events were reported all adverse events were grade 2 or less. Most were related to hormonal changes. Nausea, vomiting, diarrhea, and alopecia attributable to letrozole were reported. This phase II study demonstrates that letrozole has efficacy with regard to estrogen suppression, has antitumor efficacy in advanced breast cancer as a second line therapy, and has an acceptable adverse effect profile.

STUDY REPORT: AR/BC 2

DESCRIPTION OF STUDY

Introduction

Protocol AR/BC2 is a double-blind, randomized, multicenter, comparative Phase II trial comparing daily doses of 0.5 mg CSG 20267 (letrozole), 2.5 mg CGS 20267 (letrozole), and 160 mg megestrol acetate as second line endocrine therapy in postmenopausal women with advanced breast cancer which is known to be hormone receptor positive or in which the receptor status is unknown.

Trial Objectives:

The primary objective of AR/BC2 was to assess the anti-tumor efficacy, as evaluated by objective tumor response, duration of tumor response, time to treatment failure, and time to progression in the three treatment arms: letrozole 0.5 mg/day, letrozole 2.5 mg/ day, and megestrol acetate 160 mg/day and to compare the treatment arms to each other. Secondary objectives include: (1) assessment of the tolerability and toxicity of letrozole 0.5 mg/day, letrozole 2.5 mg/ day, and megestrol acetate 160 mg/day and compare them; (2) evaluation of the effect of daily doses of letrozole 0.5 or 2.5 mg on the serum estrogen levels (estrone, E1; estradiol, E2) throughout the trial; and, (3) assessment of trough plasma drug concentration levels during daily therapy with either letrozole 0.5 or 2.5 mg.[4]

Trial Design/Conduct:

This double-blind, randomized parallel group, multicenter trial was conducted at ninty-one sites in ten countries. Computer generated randomization was carried out for each country using a permuted block size of six for all but one country where the block size was three. Table SR-1 provided information about the number of countries , number of sites, number of patients enrolled by country, and information about response rate (as determined by the applicant) by arm for each country.

Since patient enrollment in Italy and Great Britain accounted for ~ 40% of the patient population in this trial, sites in these two countries have been selected for audit which will be completed by the time of the ODAC presentation (December 16, 1996).

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[4] See Appendix 1 for protocol summary

Table SR-1: Enrollment by Country with Response Rates (Ciba)

			Response Rate (CR & PR) (No. Res./No. Arm) (%)		
Country	No. of Sites	No. Enrolled	Letrozole 0.5 mg	Letrozole 2.5 mg	Megestrol
Germany	14	62	0/20 (0.0%)	1/ 17 (5.9%)	4/25 (16.0%)
Italy	20	145	9/48 (18.8%)	17/48 (35.4%)	6 /49 (12.2%)
Belgium	7	21	1/7 (14.3%)	1/6 (16.7%)	1/8 (12.5%)
South Africa	5	52	2/19 (10.5%)	5/16 (31.3%)	3/17 (17.6%)
Great Britain	14	104	7/34 (20.6%)	9/34 (26.5%)	5/36 (13.9%)
Denmark	4	38	1/13 (7.7%)	4/12 (33.3%)	4/13 (30.8%)
Spain	2	25	2/9 (22.2%)	1/8 (12.5%)	2/8 (25.0%)
Sweden	6	25	0/10 (0.0%)	1/9 (11.1%)	1/6 (16.7%)
Canada	13	50	0/18 (0.0%)	1/15 (6.7%)	3/17 (17.6%)
Netherlands	6	29	0/10 (0.0%)	1/9 (11.1%)	2/10 (20.0%)

After randomization patients were treated until disease progression or until for another reason study drug was discontinued. After discontinuation patients were followed for survival. The original trial enrollment period was expected to be eighteen months with a minimum duration of follow-up of twenty-seven months. Information in the first study report (AR/BC2 Core) spans the period from the initiation of the trial on March 25, 1993 until June 26, 1995 (Vol. 1.71 - 1.095) when the required nine month followup for the last enrollee was completed. Information collected from June 27, 1995 until December 28, 1995, a further six month follow-up, is presented separately (AR/BC2 Update, Vol. 1.096 - 1.110). A Combined Data Set which includes information from the Core and Update on the five hundred fifty-two patients enrolled in AR/BC2 was compiled by the FDA. The database included the patient number, the treatment randomization, date on study, date of response if CR or PR, date of progression or treatment failure if applicable, date of death with cause of death if known, censor date for patients who remained alive at time of study report submission, and comments on site(s) of progression and/or type of treatment failure. Information from the . provided by Ciba was linked with this database to provide information about certain variables (ie. receptor status, previous AntiE_2 therapy, sites of disease, etc.).

The sample size estimate of five hundred forty was based on both the endpoint of objective tumor response (CR + PR) and the time to progression. The hypotheses of a 15% difference in response between treatments would be tested at the 5% level of significance ($a = 0.05$, two-sided) with the expected lower level of response [for the comparator] of 10% with 90% power. Likewise, a 50% difference in objective progression between treatment arms would be detected at $a = 0.05$ with 90% power with this sample size.

Four amendments were made to the original protocol. Amendment No. 1 (5/5/93) allowed for bone scan to replace systemic skeletal survey as the screen for bone disease with a requirement for follow-up x-rays of any "hot" areas on bone scan. Amendment No. 2 (1/29/94) allowed revision of the inclusion criteria so that patients who had progressed on chemotherapy for advanced disease either after failure of first line antiestrogen therapy or disease progression within twelve months of discontinuation of adjuvant anti-estrogen therapy. Amendment No. 2 also excluded patients with a history of adrenal insufficiency. Amendment No. 3 (7/16/94) defined the organization and working procedure for the Peer Review Committee. Amendment No. 4 (8/9/94) provided a revised patient information sheet and patient consent form updating the safety profile of letrozole. A local Peer Review Committee was organized by each country which consisted of two oncologists and one radiologist, none of whom had participated in the trial in any way. All relevant patient tumor assessment information was provided to this group including photographs, x-rays, bone scans, CT scans, liver ultrasound images, computerized line listing from the CRF, tumor assessment data, and written information on concomitant therapy and visit remarks. The final statistical analysis plan for analysis of AR/BC2 was completed on April 20, 1995.

Unblinding:

The blind was broken at the in September, 1994 for use in the measurement of plasma letrozole levels. Codes could be broken at the study site for an actual emergency or at the central office after written request by the individual investigator in cases of progression where further hormonal therapy would be deemed beneficial. Investigators broke the code in twelve instances, six were due to serious adverse reactions (five in the megestrol arm and one in the letrozole 0.5 mg arm) and in the other six for a therapy change. Ciba personnel unblinded the treatment in one hundred sixteen other instances before the data set was frozen. The following table gives the breakdown of unblinding by arm and the reason for the break.

Table SR-2: Unblinding by Treatment Arm by Ciba

Arm	Letrozole 0.5 mg	Letrozole 2.5 mg	Megestrol 160 mg
Number Unblinded (%)	39/188 (20.7%)	28/174 (16.1%)	49/190 (25.8%)
Reason: Adverse Event	1/39	0/28	2/49
Reasons: Therapy Change	38/39	28/28	47/49

The treatments were unblinded at Ciba by a member of the Biometrics division not involved with the trial conduct or analysis and transmitted to the investigator directly or through a Ciba representative not directly involved with the trial.

No information had been provided by Ciba-Geigy about the type of therapy which followed

study drug treatement in patients removed from study for progression who received further therapy. Specifically no information is provided about patients treated on AR/BC2 who at progression were crossed over to opposite hormone therapy.

STUDY RESULTS:

Patient Population Demographics:

The following table (Table SR-3) presents selected demographic characteristics for each arm of the trial. Some of these demographic characteristics were used in the covariate analysis performed by the sponsor.

As indicated by statistical testing the demographic characteristics are balanced between the three arms. With regard to the number of sites of disease no significant difference is detected between arms with regard to single sites (Chi square, $p = 0.48$) versus multiple sites (Chi square, $p = 0.81$). Nor is any significant difference in the dominant site of disease detected between arms.

Since letrozole, an aromatase inhibitor, is considered hormonal in nature, information about the number and type(s) of previous hormone therapy and the response to that therapy is presented for receptor positive (ER and/or PR) and receptor unknown patients in Table SR- 4. The total number of patients in each exposure category is listed. The patient's response to that hormone exposure is indicated. Five patients received more than one therapeutic hormonal manipulation as indicated by the number in parentheses following the total for a specific category.

Table SR-5 is presented to provide information about the number of different systemic therapies that a patient may have experienced. About 20-25% of the study participants had adjuvant antiestrogen therapy only (with tamoxifen). Between 28-40% of each treatment arm had therapeutic antiestrogens only. About 39% of the patients treated on the letrozole 0.5 mg arm had prior therapeutic or adjuvant chemotherapy with 4 (2.1%) patients having both adjuvant and therapeutic chemotherapy. About 33% patients on the letrozole 2.5 mg arm had prior chemotherapy (adjuvant or therapeutic) and 3 (2.9%) had both adjuvant and therapeutic chemotherapy. On the megestrol arm about 36% of the patients had prior chemotherapy with 9 (5.3%) having both adjuvant and therapeutic chemotherapy.

Table SR-3: Demographic Characteristics (FDA Analysis)

Demographic Characteristic	Letrozole 0.5 N = 188 (%)	Letrozole 2.5 N = 174	Megestrol N = 190	Chi Square for Homogeneity
Age				P = 0.22
≤ 55 yrs	38 (20.2)	33 (19.0)	31 (16.4)	
56 - 70 yrs	84 (44.7	95 (54.6)	104 (55.0)	
≥ 70 yrs	66 (35.1)	46 (26.4)	54 (28.6)	
Receptor Status				P = 0.65
ER+, PR+	69 (36.7)	57 (32.8)	71 (37.4)	
ER or PR +	35 (18.6)	43 (24.7)	41 (21.6)	
ER -, PR -	84 (44.7)	74 (42.5)	78 (41.0)	
Performance Status				P = 0.22
WHO Grade 0	94 (50.0)	89 (51.0)	87 (45.8)	
WHO Grade 1	72 (38.3)	60 (34.5)	86 (45.3)	
WHO Grade 2	22 (11.7)	25 (14.5)	17 (8.9)	
Body Mass Index				P = 0.37
< 30	152 (80.8)	130 (74.7)	147 (77.3)	
≥ 30	36 (19.2)	44 (25.3)	43 (22.6)	
Sites of Disease				P = 0.66
Soft Tissue Only	57 (30.3)	44 (25.3)	49 (25.8)	
Bone Only	39 (20.7)	32 (18.4)	34 (17.9)	
Visceral Only	22 (11.7)	26 (14.9)	15 (7.9)	
More than One Site	66 (35.6)	68 (39.1)	88 (46.3)	
Soft Tissue, Bone	19	20	26	
Soft Tissue, Visceral	15	19	18	
Bone, Visceral	21	14	26	
Soft Tissue, Bone, Visceral	12	15	18	
None	3 (1.6)	4 (2.3)	4 (2.1)	
Previous Hormonal Therapy				P = 0.48
Adjuvant Only	65 (34.6)	57 (32.8)	61 (32.1)	
Therapeutic Only	108 (57.4)	93 (53.4)	105 (55.3)	
Adjuvant & Therapeutic	15 (8.0)	24 (13.8)	24 (12.6)	
Disease Free Interval				P = 0.49
Stage IV at presentation	21 (11.2)	13 (7.5)	22 (11.6)	
Less than 24 months	48 (25.5)	55 (13.6)	57 (30.0)	
Greater than 24 months	119 (63.3)	106 (60.9)	111 (58.4)	
History of Bisphosphonate Therapy	8 (4.3)	4 (2.3)	7 (3.7)	---

Table SR-4: Receptor Status and Response to Previous Hormonal Therapy

Treatment	Letrozole 0.5 mg (N = 188)		Letrozole 2.5 mg (N = 174)		Megestrol 160 mg (N = 190)	
Receptor Status	Positive (N = 104)	Unknown (N = 84)	Positive (N = 100)	Unknown (N = 74)	Positive (N = 112)	Unknown (N = 78)
Prior Hormone Therapy	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Adjuvant Therapy Only	39 (37.5)	26 (31.0)	36 (36.0)	21 (28.4)	37 (33.0)	24 (30.8)
Therapeutic	55 (52.9)	53 (63.1)	49 (49.0)	44 (59.5)	62 (55.4)	43 (55.1)
CR/PR	14	23 (1)*	17	13	17	18
NC > 6 Mo..	34	20	24 (1)*	25	26	16 (1)*
PD < 6 Mo..	4	7 (1)*	7	4	15	7 (1)*
Not Known	3	3	1	2	4	2
Adjuvant and Therapeutic	10 (9.6)	5 (5.9)	15 (15.0)	9 (12.1)	13 (11.6)	11 (14.1)
CR/PR	2	1	2	0	4	1
NC > 6 mo..	5	1	7	7	6	8
PD < 6 mo..	1	3	8	1	3	2
Not Known	2	0	0	1	0	0

* No. of patients with two prior therapeutic hormonal treatments with response to most recent previous therapy.

SR-5: Distribution of Patients by the Number of Prior Hormonal and Chemotherapies

Treatment: Letrozole 05 mg (N = 188)								
	Receptor Unknown (N = 84)				Receptor Positive (N = 104)			
Hormonal Therapy	Adjuvant Only	Therapeutic Only	Adjuvant & Therapeutic	(Total)	Adjuvant Only	Therapeutic Only	Adjuvant & Therapeutic	(Total)
No Chemotherapy	20	29	2	(51)	30	28	5	(63)
Adjuvant Chemo Only	6	6	2	(14)	8	15	4	(27)
Therapeutic Chemo Only	0	15	1	(16)	1	11	1	(13)
Adjuv & Therap. Chemo	0	3	0	(3)	0	1	0	(1)
Letrozole 2.5 mg								
	Receptor Unknown (N = 74)				Receptor Positive (N = 100)			
Hormonal Therapy	Adjuvant Only	Therapeutic Only	Adjuvant & Therapeutic	(Total)	Adjuvant Only	Therapeutic Only	Adjuvant & Therapeutic	(Total)
No Chemotherapy	13	31	7	(51)	26	33	10	(69)
Adjuvant Chemo Only	7	7	0	(14)	9	9	4	(22)
Therapeutic Chemo Only	1	5	1	(7)	1	4	1	(6)
Adjuv & Therap. Chemo	0	1	1	(2)	0	3	0	(3)
Megestrol 160 mg.								
	Receptor Unknown (N= 78)				Receptor Positive (N = 112)			
Hormonal Therapy	Adjuvant Only	Therapeutic Only	Adjuvant & Therapeutic	(Total)	Adjuvant Only	Therapeutic Only	Adjuvant & Therapeutic	(Total)
No Chemotherapy	15	25	9	(49)	24	30	10	(64)
Adjuvant Chemo Only	5	5	1	(11)	12	16	2	(30)
Therapeutic Chemo Only	3	10	1	(14)	1	11	1	(13)
Adjuv & Therap. Chemo	1	3	0	(4)	0	5	0	(5)

Patient Disposition

In Table SR-6 the disposition of patients on each arm of the study at the end of update period is shown. The majority of the patients had progressed by the end of update period (December 28, 1995). About 20% of the patients enrolled on the letrozole 2.5 mg arm, about 12% of the patients on the letrozole 0.5 mg arm, and about 8% of the patients on the megestrol arm remained on study at the cutoff date of December 28, 1996. With regard to those patients who were withdrawn from study for reasons other than progression, more deaths (one definitely related to study drug) and more adverse reactions occurred in the megestrol arm. The "Unknown" category includes those patients for whom the reason that the patient was removed from study is not clearly discernable after review of the information in the NDA. The administrative category

includes patients in whom the proper disease assessments or other protocol requirements were not met prior to the time of study removal. Patients who were removed from study by the investigator for progression who were found not to have progressed are included in the "Misinterpretation of Disease Status" Group.

Table SR - 6: Patient Disposition

Parameter	Letrozole 0.5 mg	Letrozole 2.5 mg	Megestrol
Patient Enrollment	N=188 (%)	N=174 (%)	N=190 (%)
Discontinuation for Disease Progression	127 (67.6)	120 (67.0)	144 (75.8)
Continuation on Study on 1/28/95	22 (11.7)	36 (20.7)	15 (7.9)
Discontinuations for Other Reasons	39 (20.7)	18 (10.3)	31 (16.3)
Death on Study	3 (1.6)	3 (1.7)	7 (3.7)
For Adverse Events	7 (3.7)	5 (2.9)	9 (4.7)
Did not meet entry criteria	5 (2.7)	4 (2.3)	3 (1.6)
Withdrawal of Consent	5 (2.1)	0	2 (1.1)
Administrative Problems	4 (2.7)	0	1 (0.5)
Non-compliance	5 (2.7)	0	0
Misinterpretation of Disease Status	7 (3.7)	4 (2.3)	8 (4.2)
Unknown	3 (1.6)	2 (1.1)	1 (0.5)
Deaths after Study Discontinuation	96 (51.1)	99 (56.9)	99 (52.1)

Efficacy Endpoints

Response By Treatment Arm:

All tumor response information contained in the initial trial report and in the update was reviewed and a response category was assigned in the reviewer's database. Patients who were enrolled on study without evidence of disease or who did not have the appropriate studies done to assess disease status were considered non-evaluable. With regard to complete and partial responses two cases in the letrozole 0.5 mg arm and in one case in the letrozole arm 2.5 arm the final response assessment by the reviewer is different from that of Ciba-Geigy due to information found in the NDA. The majority of differences in assessment were between the stable disease (seventy-three) and progressive disease category (fifty-seven). Patients were considered stable disease by the FDA unless or until objective proof of progression was found **even if** the interval to progression was $\leq$ six months. The assessment of stable disease (progression) is based on the tumor measurement listing and peer review comments, unless a measurement for a specific disease site was missing in which case the patient is considered nonevaluable.

SR-7: Objective Response by Treatment Arm

	Letrozole 0.5 mg (N = 188)		Letrozole 2.5 mg (N = 174)		Megestrol (N = 190)	
Response Category	FDA	Ciba	FDA	Ciba	FDA	Ciba
CR + PR (CR) (PR)	22 (11.7%) 4 18	24 (12.8%) 6 18	41 (23.6%) 11 30	41 (23.6%) 12 29	31 (16.3%) 8 23	31 (16.4%) 8 23
Stable Disease (No Change)	59 (31.4%)	27 (14.4%)	36 (20.7%)	19 (10.9%)	53 (27.9%)	29 (15.3%)
Progressive Disease	81 (43.1%)	105 (55.9%)	79 (45.4%)	93 (53.4%)	87 (45.8%)	106 (56.1%)
Non-Evaluable	26 (13.8%)	32 (17.0%)	18 (10.3%)	21 (12.1%)	19 (10.2%)	23 (12.2%)

Table SR- 8 presents the unadjusted statistical comparison of the response rates in the three treatment arms using the FDA statistical analysis. The agency has used the results from the unadjusted analyses in this report rather than attempt to adjust for the many covariates with varying degrees of significance. No adjustment in the p-value is made for the multiple comparisons between study arms.

SR-8: Statistical Comparison of the Objective Response Rates, Unadjusted (FDA Analysis)

Treatment Comparison	Odds Ratio	95% Confidence Interval	P-Value, two sided
Letrozole 0.5 mg vs 2.5 mg	0.43	(0.24, 0.76)	p = 0.004
Letrozole 0.5 mg vs Megestrol	0.68	(0.38, 1.22)	p = 0.191 ~ 0.20
Letrozole 2.5 mg vs Megestrol	1.57 1.58	(0.93, 2.64)	p= 0.089 ~ 0.08

Comparison of the response rates indicates that, in this study, the 2.5 mg dosage of letrozole has a significantly better response rate than the 0.5 mg dose. No significant difference in the response rates in detected between the letrozole 0.5 arm and the megestrol arm or between letrozole 2.5 mg and megestrol acetate arm. The confidence intervals around the odds ratio suggests that the two treatments have a similar effect in terms of response with a trend in favor of letrozole over megestrol. When the response rate is adjusted using eleven baseline covariants[5] by Ciba-Geigy, the odds ratio, 0.42, for the adjusted response rate for the comparison of letrozole 2.5 mg to megestrol achieves significance (p = 0.004, two sided). Concerned that these covariants some of which were prospectively defined are not of equal importance in affecting the outcome, those

[2] Covariates included: age class, dominant site of disease, number of involved anatomical sites, disease-free interval, overall hormone receptor status, WHO performance status, prior chemotherapy, prior antiestrogen therapy, response to prior anti-estrogen therapy, previous or concomitant use of bisphosphonates, body mass index. Eight of these covariants were defined in the original protocol. Body mass index, number of anatomical sites, prior antiestrogen therapy were added to the final statistical plan..

SR-7: Objective Response by Treatment Arm

	Letrozole 0.5 mg (N = 188)		Letrozole 2.5 mg (N = 174)		Megestrol (N = 190)	
Response Category	FDA	Ciba	FDA	Ciba	FDA	Ciba
CR + PR (CR) (PR)	22 (11.7%) 4 18	24 (12.8%) 6 18	41 (23.6%) 11 30	41 (23.6%) 12 29	31 (16.3%) 8 23	31 (16.4%) 8 23
Stable Disease (No Change)	59 (31.4%)	27 (14.4%)	36 (20.7%)	19 (10.9%)	53 (27.9%)	29 (15.3%)
Progressive Disease	81 (43.1%)	105 (55.9%)	79 (45.4%)	93 (53.4%)	87 (45.8%)	106 (56.1%)
Non-Evaluable	26 (13.8%)	32 (17.0%)	18 (10.3%)	21 (12.1%)	19 (10.2%)	23 (12.2%)

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[2] Covariates included: age class, dominant site of disease, number of involved anatomical sites, disease-free interval, overall hormone receptor status, WHO performance status, prior chemotherapy, prior antiestrogen therapy, response to prior anti-estrogen therapy, previous or concomitant use of bisphosphonates, body mass index. Eight of these covariants were defined in the original protocol. Body mass index, number of anatomical sites, prior antiestrogen therapy were added to the final statistical plan..

criteria which considered most likely to influence outcome were examined in exploratory subset analyses by the FDA.

Since receptor positivity is the most important predictor of response to hormone therapy, the response rates (CR + PR) in the receptor positive population and the receptor unknown population were determined (Table SR-9).

Table SR-9: Response by Receptor Status as Analyzed by the FDA

Receptor Status	Letrozole 0.5 mg	Letrozole 2.5 mg	Megestrol
Receptor Positive (ER +, PR+) (ER or PR+)	6/104 (5.8%) 5/69 (7.2%) 1/35 (2.9%)	23/100 (23 %) 16/57 (28.1%) 7/43 (16.3%)	19/112 (17 %) 10/70 (14.3%) 9/41 (22.0%)
Receptor Unknown	16/84 (19 %)	18/74 (24.3%)	12/78 (15.4%)

Exploratory subset analysis of the receptor positive (ER and/or PR +) group reveals the odds ratio for the comparison of letrozole 0.5 mg : letrozole 2.5 mg is 0.21 with 95% CI (0.07, 0.56; p=0.0007, two-sided) and the odds ratio for the comparison of letrozole 0.5 : megestrol is 0.30 with the 95% CI (0.09, 0.82; p=0.01, two-sided). In these two comparisons (L0.5: L2.5 and L0.5:M) both receptor subgroups (ER and PR +; ER or PR +) the odds ratios are significant for the same treatment arm and can be combined .

In the letrozole 2.5 mg: megestrol comparison the odds ratio for the ER and PR positive subgroup is 2.34 in favor or letrozole 2.5 mg with 95% CI of 0.89, 6.35 (p = 0.09, two sided) while in one receptor (ER or PR) positive subgroup the odds ratio is 0.69 tending to favor megestrol with 95% CI (0.19, 2.39; p = 0.51, two sided). The lack of consistency in the results in the one receptor positive (ER or PR) subgroup results in the a loss of significance for the letrozole 2.5 mg: megestrol comparison in receptor positive patient subgroup.

If the ER and PR positive subgroup of the letrozole 2.5 mg:megestrol comparison is adjusted in terms of dominant site of disease, the odds ratio for the difference in response rates is significant favoring letrozole 2.5 in all sites (soft tissue, bone, and visceral). If the odds ratio for the comparison of letrozole 2.5 mg : megestrol ER or PR positive receptor subgroup is adjusted for dominant site of disease, the adjusted odds ratio is 1.71 with 95% CI: 0.99, 2.97 (p = 0.036) in favor of letrozole 2.5 mg. This exploratory subset analysis suggests that letrozole 2.5 mg may be as beneficial if not more beneficial then megestrol in the receptor positive women.

The failure to attain significance with the unadjusted odds ratio for the comparison of the response rates of letrozole 2.5 mg: megestrol may well be related to the large percentage of patients (40 - 45% of the study enrollment) with unknown receptor status. An undectable imbalance between arms in the number of positive vs negative receptor patients may have existed. Receptor status imbalance may explain the failure to show a significant difference between the letrozole 2.5 mg and the megestrol treatment arms. While letrozole 2.5 mg has not

been shown to be significantly better than megestrol in this study, the confidence intervals around the odds ratios for the comparison of response rate between the letrozole 2.5 mg; megestrol comparison overlap suggesting that the response rates for the drugs are at least similar.

Response rates were analyzed in terms of the type of prior treatment. In particular responses rate must be explored in those patients who had adjuvant antiestrogen therapy (tamoxifen) only and in those patients who have had only therapeutic antiestrogen therapy without exposure to any chemotherapy. Table SR-10 presents the response rates for patients who have been treated with only hormonal therapy, either adjuvant or therapeutic. In six cases patients had two prior therapeutic hormonal therapies. Seven patients on the letrozole 0.5 mg arm, seventeen patients on the letrozole 2.5 mg arm, and nineteen patients on the megestrol arm had both therapeutic and adjuvant hormonal therapies (*).

SR-10: FDA Analysis of Response Rates by Type of Previous Hormone Therapy

Treatment Arm	Letrozole 0.5 mg (N = 114)		Letrozole 2.5 mg (N =120)		Megestrol (N = 113)	
Type of Hormone Therapy	Adjuvant (N = 50)	Therapeutic* (+/- Adj.Rx) (N = 64)	Adjuvant (N = 39)	Therapeutic* (+/- Adj Rx) (N = 81)	Adjuvant (N = 39)	Therapeutic* (+/- Adj.Rx) (N = 74)
CR and PR	8 (16%)	12 (18.8%)	6 (15.4%)	21 (25.9%)	7 (17.9%)	12 (16.2%)
Stable Disease	20 (40%)	17 (26.6%)	10 (25.6%)	19 (23.5%)	14 (35.9%)	18 (24.3%)
Progressive Dis.	24 (48%)	21 (32.8%)	21 (53.8%)	31 (38.3%)	16 (41.0%)	34 (45.9%)
Non- Evaluable	2 (4%)	14 (21.9%)	2 (5.1%)	10 (12.3%)	2 (5.1%)	10 (13.5%)

*More than one hormonal therapy

Unadjusted odds ratios for comparisons between the treatment arms in terms of prior exposure to adjuvant or therapeutic (alone or with adjuvant) hormonal therapies do not show any significant difference between the treatment arms in terms of response rates.

Objective Responses and Antiestrogen Withdrawal Response

In the literature objective withdrawal responses on discontinuation of antiestrogen therapy for progression are reported for patients who have previously had a complete or partial response or disease stabilization for periods of $\geq$ 6 months on antiestrogen therapy. The objective response rate is reported to be 3 - 8% with prolonged disease stabilization seen in up 17% of patients.

Table SR-11: Response by Treatment Arm with Respect to Antiestrogen Therapy Discontinuation

Treatment Arm (N)	AntiE2 > 60 Days (CR + PR)	AntiE2 < 60 Days (CR + PR)	Total No. of CR + PR by Arm
Letrozole 0.5 Arm (N = 188)	3/16 (18.8%)	19/172 (11.0%)	22
Letrozole 2.5 Arm (N = 174)	4/12 (33.3%)	37/ 162 (22.8%)	41
Megestrol (N = 190)	4/21 (19.0%))	27/179 (14.2%)	31

Forty nine patients completed antiestrogen therapy (twenty-seven as adjuvant therapy and twenty-two as therapeutic treatment for metastatic disease) greater than sixty days before initiation of study therapy. Three objective (complete or partial responses) were observed in the letrozole 0.5 mg arm, four in the letrozole 2.5 mg arm, and four in the megestrol arm for patients who completed antiestrogen therapy > 60 days before initiation of study treatment. For the five hundred three patients who started study drug treatment within sixty days of completing antiestrogen therapy nineteen responses were observed in the letrozole 0.5 mg arm, thirty-seven were observed in the letrozole 2.5 mg arm, and twenty-seven were observed in the megestrol arm.

The possibility of an antiestrogen withdrawal response was also evaluated by dividing the population into two groups: the **"at risk group"** which included patients who discontinued antiestrogens within sixty days of study entry and had a CR, PR, or SD response of 6 months or greater on antiestrogen therapy, and the **"not at risk"** group which included patients who failed antiestrogen therapy, and patients who had progression on adjuvant antiestrogens, and patients whose response to therapeutic antiestrogens was unknown. Table SR-12 shows the objective response rates (CR or PR) in each groups.

Table SR-12: Objective Response and Antiestrogen Withdrawal Therapy

Treatment Arm	**Not at Risk** for Withdrawal	**At Risk** for Withdrawal
Letrozole 0.5 mg	7/99 (7.1%)	15/89 (16.9%)
Letrozole 2.5 mg	17/88 (19.5%)	24/86 (27.9%)
Megestrol	19/99 (19.2%)	12/91 (13.2%)

The response rates on the two letrozole arms in the groups "at risk for withdrawal" are higher than those in "the not at risk" group suggesting that estrogen withdrawal response may have inflated the response rate especially in the letrozole 0.5 mg arm. The response rates for the letrozole 2.5 mg arm and for megestrol are similar in the patients "not at risk for estrogen withdrawal" suggesting that response rates are similar.

Response by Country with Respect to Disease Sites

In looking at the response data Italy, South Africa, Great Britian were noted to have better

response rates for letrozole than the other countries which participated in the study (Germany, Belgium, Denmark, Spain, Sweden, Canada, and the Netherlands). In order to explain the difference in response the number of disease sites / patient were evaluated by country. The number of patients with soft tissue only, bone involvement only, and with visceral involvement with or without other involvement along with the response rates by treatment arm are presented in the following table.

Table SR- 13: Response Rates by Country (Sponsor) and Site(s) of Disease

Country	No. Enrolled	No. with Visceral (+/- other)	No. with Bone Only	No. with Soft Tissue Only	Response Rate (CR & PR) by Arm (No. Res./No. Arm) (%)		
					Letrozole 0.5 mg	Letrozole 2.5 mg	Megestrol
Germany	62	26 (41.9)	13 (21.0)	8 (12.9)	0/20 (0.0%)	1/17 (5.9%)	4/25 (16.0%)
Italy	145	58 (40.0)	23 (15.9)	37 (25.5)	9/48 (18.8%)	17/48 (35.4%)	6 /49 (12.2%)
Belgium	21	8 (38.1)	6 (28.6)	4 (19.0)	1/7 (14.3%)	1/6 (16.7%)	1/8 (12.5%)
South Africa	52	15 (28.8)	6 (11.5)	25 (48.1)	2/19 (10.5%)	5/16 (31.3%)	3/17 (17.6%)
Great Britain	104	31 (29.8)	14 (13.5)	48 (46.2)	7/34 (20.6%)	9/34 (26.5%)	5/36 (13.9%)
Denmark	38	12 (31.6)	7 (18.4)	19 (50.0)	1/13 (7.7%)	4/12 (33.3%)	4/13 (30.8%)
Spain	25	13 (52.0)	2 (8.0)	11 (44.0)	2/9 (22.2%)	1/8 (12.5%)	2/8 (25.0%)
Sweden	25	12 (48.0)	5 (20.0)	4 (16.0)	0/10 (0.0%)	1/9 (11.1%)	1/6 (16.7%)
Canada	50	19 (38.0)	14 (28.0)	12 (24.0)	0/18 (0.0%)	1/15 (6.7%)	3/17 (17.6%)
Nether lands	29	9 (31.0)	15 (51.7)	1 (3.4)	0/10 (0.0%)	1/9 (11.1%)	2/10 (20.0%)

Best response rates for any arm are associated with a predominance of soft tissue only involvement. Countries where bone and visceral (+/- other involvement) involvement were predominant did not have as many responders.

Duration of Response

The median duration of response on the letrozole 2.5 arm for the forty-one responders has not been reached with fourteen (34.1%) patients having progressed after a complete or partial response. On the letrozole 0.5 mg arm, median duration of response is 552 days (95% CI: 439, -) with seven (31.8%) of the twenty-two responders having progressed after a complete or partial response. On the megestrol arm the median duration of response is 551 days (95% CI: 476, 635) for the thirty-one responders of whom fourteen (45.2%) have progressed.

Time to Progression

In Table SR-11 the time to progression as determined by Ciba-Geigy and by the FDA are shown. The median time to progression in days is similar as calculated by the applicant and the FDA . The number of censored patients is slightly different in the applicant's and the FDA's analysis. No significant difference in the unadjusted risk ratio is found in the time to progression in a comparison between the low dose letrozole arm and the high dose letrozole arm. A statistically significant difference in the unadjusted relative risk of progression is observed in a comparison of the time to progression between letrozole 2.5 mg and megestrol in favor of letrozole. No significant difference in risk of progression is observed in a comparison of letrozole 0.5 mg to megestrol.

SR-13: Analysis of Time to Progression

Treatment Arm	Letrozole 0.5 mg		Letrozole 2.5 mg		Megestrol	
Parameter	Ciba	FDA	Ciba	FDA	Ciba	FDA`
Number Enrolled Number Censored	188 60	188 61	174 54	174 54	189* 44	190 46
Median Time to Progression (days) [95% Confidence Interval, days]	154 [93, 176]	154 [93, 175]	169 [95, 231]	170 [94, 200]	168 [101, 183]	168 [112, 183]
Risk Ratio, Unadjusted (FDA Analysis)	L0.5: L 2.5 = 1.24 (95% CI: 0.97, 1.59) Log rank p = 0.085					
	L2.5: MA = 0.77 (95% CI: 0.60, 0.98) Log Rank p = 0.03					
	L0.5: MA = 0.97 (95% CI: 0.76, 1.23) Log Rank p = 0.77					

* One patient enrolled on the megestrol arm was never treated and is not included in the applicant's analysis. Since FDA uses intent -to-treat all enrolled patients are included in the analysis.

Duration of Response

The median duration of response on the letrozole 2.5 arm for the forty-one responders has not been reached with fourteen (34.1%) patients having progressed after a complete or partial response. On the letrozole 0.5 mg arm, median duration of response is 552 days (95% CI: 439, -) with seven (31.8%) of the twenty-two responders having progressed after a complete or partial response. On the megestrol arm the median duration of response is 551 days (95% CI: 476, 635)for the thirty-one responders of whom fourteen (45.2%) have progressed.

Time to Progression

In Table SR-11 the time to progression as determined by Ciba-Geigy and by the FDA are shown. The ...edian time to progression in days is similar as calculated by the applicant and the FDA . The number of censored patients is slightly different in the applicant's and the FDA's analysis. No significant difference in the unadjusted risk ratio is found in the time to progression in a comparison between the low dose letrozole arm and the high dose letrozole arm. A statistically significant difference in the unadjusted relative risk of progression is observed in a comparison of the time to progression between letrozole 2.5 mg and megestrol in favor of letrozole. No significant difference in risk of progression is observed in a comparison of letrozole 0.5 mg to megestrol.

SR-13: Analysis of Time to Progression

Treatment Arm	Letrozole 0.5 mg		Letrozole 2.5 mg		Megestrol	
Parameter	Ciba	FDA	Ciba	FDA	Ciba	FDA
Number Enrolled Number Censored	188 60	188 61	174 54	174 54	189* 44	190 46
Median Time to Progression (days) [95% Confidence Interval, days]	154 [93, 176]	154 [93, 175]	169 [95, 231]	170 [94, 200]	168 [101, 183]	168 [112, 183]
Risk Ratio, Unadjusted (FDA Analysis)	L0.5: L 2.5 = 1.24 (95% CI: 0.97, 1.59) Log rank p = 0.085					
	L2.5: MA = 0.77 (95% CI: 0.60, 0.98) Log Rank p = 0.03					
	L0.5: MA = 0.97 (95% CI: 0.76, 1.23) Log Rank p = 0.77					

* One patient enrolled on the megestrol arm was never treated and is not included in the applicant's analysis. Since FDA uses intent -to-treat all enrolled patients are included in the analysis.

The question which is raised is why no significance is detected in the risk of progression in a comparison of the letrozole 0.5 mg: letrozole 2.5 mg treatment arms. In a comparison of the receptor positive subgroups of ltrozole 0.5 mg and letrozole 2.5 mg the risk ratio is 1.29 (stratified log rank p = 0.05, two-sided) in favor of letrozole 2.5 mg. Using the receptor positive subgroup for the comparison of letrozole 2.5 vs megestrol, the relative risk is 0.76 (stratified log rank p = 0.04, two-sided) in favor of letrozole 2.5 mg. This information suggests the possibility that letrozole 2.5 mg did not achieve significance with regard to risk of progression as compared to letrozole 0.5 mg for the overall group due to an undetected differences in the composition of the receptor unknown group in each of the letrozole arms.

Information about time to progression with consideration as to prior hormone therapy is presented in the following table (Table SR -12). The time to progression determinations for patients treated with only adjuvant or therapeutic and possibly adjuvant hormonal regimens are shown. Patients treated with any chemotherapy are excluded from this analysis. Risk ratios were calculated by the FDA for each group. No significant differences were detected in the comparisons of the risk ratios for the adjuvant group only and the therapeutic +/- adjuvant groups

SR-14: FDA Analysis of Time to Progression with Respect to Previous Hormonal Therapies

	Letrozole 0.5 mg (N = 114)		Letrozole 2.5 mg (N = 120)		Megestrol (N = 113)	
Type of Therapy	Adjuvant (N = 50)	Therapeutic +/- Adj. Rx (N = 64)	Adjuvant (N = 39)	Therapeutic +/- Adj. Rx. (N = 81)	Adjuvant (N = 39)	Therapeutic +/- Adj Rx. (N = 74)
Number Progressed	24(48%)	21 (32.8%)	21 (53.8%)	31 (38.3%)	16 (41%)	34 (45.9%)
Time to Progression (95% CI) in Days	98 (84, 171)	88 (100, 469)	102 (88, 181)	193 (91, 365)	182 (100, 433)	167 (91, 220)

In those patients who were considered **not to be at risk** for the estrogen withdrawal response time to progression was analyzed by arm. In the letrozole 0.5 mg arm 94 patients were evaluated for time to progression with sixty-seven patients progressed and twenty-seven patients censored. Median time to progression was 97 days (95% CI: 84, 168 days). In the letrozole 2.5 mg arm eighty-six patients were at risk with sixty-one progressions and twenty-five censored dates. The median time to progression was 176 days (95% CI: 94, 269 days). In the megestrol arm the median time to progression is 168 days (95% CI: 101, 247days) with sixty-seven patients progressed and twenty-two patients censored for progression. Significantly less risk of progression was associated with the letrozole 2.5 mg and the megestrol arm than with the letrozole 0.5 mg arm (p = 0.01).

Time to Treatment Failure

SR - 15: Time to Treatment Failure

Treatment Arm	Letrozole 0.5 mg		Letrozole 2.5 mg		Megestrol	
Parameter	Ciba	FDA	Ciba	FDA	Ciba	FDA
Number Enrolled	188	188	174	174	189	190
Number Censored	41	22	46	36	28	15
Number of Treatment Failures	147	166	128	138	161	175
Median Time to Treatment Failure (days) (95% Confidence Interval)	98 (90, 198)	91 (87, 103)	155 (95, 210)	102 (93, 181)	118 (92, 175)	120 (91, 168)
Risk Ratio, Unadjusted (FDA Analysis)	Letrozole 0.5: Letrozole 2.5 = 1.41 95% CI: 0.83, 1.57 (Log rank p = 0.003)					
	Letrozole 2.5 : Megestrol = 0.72 95% CI: 0.58, 0.91 (Log Rank p = 0.004)					
	Letrozole 0.5: Megestrol = 1.03 95% CI: 0.83, 1.27 (log rank p = 0.78)					

In this study time to treatment failure is defined as the interval from the first day of treatment to diagnosis of progression, withdrawal from the trial for any reason, or death due to any cause, whichever is the earliest event. Table SR-13 includes the time to treatment failure analysis by the applicant and the FDA. Fewer patients are censored by the FDA after review of the data. The median time to treatment failure is slighter longer in both of the letrozole arms in the agency analysis for several reason, most often due to the earlier assignment of progression by the FDA reviewer. (Forty-nine differences in the date for treatment failure were documented between the applicant date listings and the FDA reviewer's database.)

Thirty-nine patients on the letrozole 0.5 mg arm, thirty-one patients on the megestrol arm and eighteen patients on the letrozole 2.5 mg arm discontinued treatment for reasons other than progression. In Table SR-6 the reasons for treatment failure other than progression are outlined. No one reason is assignable for the majority of treatment failure for reasons other than progression or death in any study arm. Three more deaths not related to treatment occurred in the megestrol arm as compared to the other two arms. Nine discontinuations due to adverse reactions were reported in the magistral arm, seven in the low dose letrozole arm, while only five discontinuations occurred in the high dose letrozole arm.

Survival Analysis

Table SR-16: Survival Analysis

Treatment Arm	Letrozole 0.5 mg		Letrozole 2.5 mg		Megestrol	
	FDA	Ciba	FDA	Ciba	FDA	Ciba
	188	188	174	174	190	198
Number Censored	99	97	102	101	96 95	95
Median Time to Death in Days (95% Confidence Interval)	633 645 (544, 734) (34, 734)	633	730 740 (642, +) (634, +)	731	659 (515, 775)	660
Relative Risk, Unadjusted (FDA Analysis)	Letrozole 0.5: Letrozole 2.5 = 1.26 1.28 (95% CI: (0.93, 1.72) 0.94, 1.75) (P value = 0.13) p = 0.11					
	Letrozole 2.5: Megestrol = 0.78 0.79 95% CI: (0.67, 1.06) (0.58, 1.07) (P value = 0.11) p = 0.13					
	Letrozole 0.5: Megestrol = 0.99 1.02 (95% CI: 0.74, 1.33 0.77, 1.37) (P value = 0.96 0.90 - 0.85)					

Concurred 7/11/97 DAB

In the survival analysis conducted by the FDA patients were censored at the last date the patient was known to be alive or at the last date the patients was seen in cases without further follow-up. Ciba censored patients on the last day the patient was seen alive. Thirty-two times a difference in the death or censor date occurred in a comparison of the applicant's time to event listing and the reviewer's listing. The survival analysis for each treatment arm is presented in Table SR-13. The difference in the number censored is due to the handling of patients who were discontinued without further information. In the agency analysis these patients were censored as alive on the last date information was available. Also in review of the printed time to event list provided by Ciba on a few occasions patients were censored as alive for whom a death date was reported in the NDA. No significant difference in the risk of death is seen in any comparison of treatment arms. The overlapping confidence intervals suggest that the risk of death is similar on all arms, with no arm having an increased risk of death.

Secondary Endpoints:

Performance Status

Performance status was measured using the WHO criteria with 0 being fully functional. Performance status was considered a continuous variable by the FDA and analyzed using repeated measures analysis. In the evaluation of the effect of treatment on performance status patients are grouped into completers or dropouts. Completers are patients who stayed on study ≥

Survival Analysis

Table SR-16: Survival Analysis

Treatment Arm	Letrozole 0.5 mg		Letrozole 2.5 mg		Megestrol	
	FDA	Ciba	FDA	Ciba	FDA	Ciba
	188	188	174	174	190	198
Number Censored	99	97	102	101	96	95
Median Time to Death in Days (95% Confidence Interval)	645 (544, 734)	633	740 (642, +)	731	659 (515, 775)	660
Relative Risk, Unadjusted (FDA Analysis)	Letrozole 0.5: Letrozole 2.5 = 1.26 95% CI: (0.93, 1.72) (P value = 0.13)					
	Letrozole 2.5: Megestrol = 0.78 95% CI: (0.67, 1.06) (P value = 0.11)					
	Letrozole 0.5: Megestrol = 0.99 95% CI: 0.74, 1.33) (P value = 0.96)					

In the survival analysis conducted by the FDA patients were censored at the last date the patient was known to be alive or at the last date the patients was seen in cases without further follow-up. Ciba censored patients on the last day the patient was seen alive. Thirty-two times a difference in the death or censor date occurred in a comparison of the applicant's time to event listing and the reviewer's listing. The survival analysis for each treatment arm is presented in Table SR-13. The difference in the number censored is due to the handling of patients who were discontinued without further information. In the agency analysis these patients were censored as alive on the last date information was available. Also in review of the printed time to event list provided by Ciba on a few occasions patients were censored as alive for whom a death date was reported in the NDA. No significant difference in the risk of death is seen in any comparison of treatment arms. The overlapping confidence intervals suggest that the risk of death is similar on all arms, with no arm having an increased risk of death.

Secondary Endpoints:

Performance Status

Performance status was measured using the WHO criteria with 0 being fully functional. Performance status was considered a continuous variable by the FDA and analyzed using repeated measures analysis. In the evaluation of the effect of treatment on performance status patients are grouped into completers or dropouts. Completers are patients who stayed on study ≥

6 months. Dropouts are patients who had less than six months of treatment with study drug. In each treatment arm the baseline performance status for completers was better than the baseline performance status for the dropouts. In the letrozole treatment arms the performance status was stable over the the nine months of analysis for both responders (patients with complete or partial response) and for nonresponders (patients with stable disease or progression) who continued on study. On the megestrol arm in the completers whether responders (CR or PR) or nonresponders (SD or PD) performance status decreased over the nine month interval, with more decline in performance status in nonresponders. For the dropouts (patients with less than six months of study drug treatment) on any arm a decline in performance status is noted. The rate of decline in performance status on the two letrozole arms is similar, while the rate of decline on the megestrol arm is more pronounced than on either letrozole arms. (See Statistical Review for further details.)

Pain Severity

Information on pain was collected by: (1) completion of severity of pain measurements with none = 0 and intractable = 4; (2) information of the use of analgesics; (3) scores from the EORTC Quality of Life (QLQ- C30) questions relating to pain. Table SR-15 shows the changes in the pain severity scoring by treatment arm over time for the first six months of study.

At baseline between 40 - 50% of the participants on each arm had no pain. During the first six months of follow-up (Table SR-15) at any time about half the study participants had no complains of pain. At study entry more patients in the letrozole arms had severe pain although over time the percentage of patients reporting more serious pain increased in the megestrol arm. If change in pain severity as compared to baseline (Ciba analysis) is compared by arm about equal numbers of patients in each arm had an increase in severity of pain: on the letrozole 0.5 mg arm 49.5%; on the letrozole 2.5 mg arm 40.8%; and, the megestrol arm 48.7%. Transient improvement in pain as compared to baseline was noted in 29.8% of patients on the letrozole 0.5 mg arm, in 36.8% of patients on the letrozole 2.5 mg arm, and in 34.9% of the patients on the megestrol acetate arm. No information about the analgesia consumption of the trial is reported by Ciba in connection with changes in the pain scores.

The FDA used repeated measures analysis to analyze the response to questions dealing with pain on the EORTC questionnaire completed by patients had each visit for the first nine months on study. For all three arms of study the baseline pain scoring for the completers was much lower (0 = no pain, no interference with activities of daily living) than for the dropouts. On the letrozole arms the pain scoring for the entire group was constant for the duration of the study, while in the megestrol arm a slight improvement in pain scoring was noted over time. For completers on both letrozole arms the pain scores remained constant over nine months of follow-up with no difference between responders (CR + PR) and nonresponders. On the megestrol arm improvement in pain scores is noted in the completers who had objective response to therapy and in the nonresponders (SD, PD) with more improvement in pain in the objective responders. On all three arm for the "dropouts" (less than six months on study) the pain scores improve over time. This improvement is probably artifactual and related to the earlier study discontinuation of

patients whose pain is progressively worse so only "dropouts" with less severe pain remain on study.

Table SR - 17: Pain Severity Scores by Treatment Arm for Cycles 1 - 6

	Visit 1 N (%)	Visit 2 N (%)	Visit 3 N (%)	Visit 4 N (%)	Visit 5 N (%)	Visit 6 N (%)
Letrozole 0.5 mg						
Study Enrollment	188 (100)	188 (100)	165 (100)	142 (100)	104 (100)	65 (100)
No. No Pain	86 (45.7)	87 (46.3)	73 (44.2)	72 (50.7)	52 (50.0)	34 (53.8)
No. Slight Pain	54 (28.7)	59 (29.3)	57 (34.5)	36 (25.4)	36 (34.6)	21 (32.3)
No. Moderate Pain	36 (19.1)	27 (14.4)	18 (10.9)	25 (17.6)	6 (5.8)	7 (10.8)
No. Severe Pain	12 (6.4)	14 (7.4)	13 (7.9)	9 (6.3)	4 (3.8)	2 (3.1)
No. Intractable Pain	0	0	0	0	0	0
No. Missing Values	0	5 (2.7)	4 (2.4)	0	6 (5.8)	0
Letrozole 2.5 mg.						
Study Enrollment	174 (100)	174 (100)	168 (100)	153 (100)	105 (100)	74 (100)
No. No Pain	80 (46.0)	75 (43.1)	72 (42.9)	73 (47.7)	55 (52.4)	40 (54.1)
No. Slight Pain	43 (24.7)	55 (31.6)	50 (29.8)	43 (28.1)	31 (29.5)	25 (33.8)
No. Moderate Pain	39 (24.6)	32 (18.4)	38 (22.6)	25 (16.3)	13 (12.4)	7 (9.5)
No. Severe Pain	12 (6.9)	12 (6.9)	6 (3.6)	11 (7.2)	1 (1.0)	2 (2.7)
No. Intractable Pain	0	0	1 (0.6)	1 (0.7)	0	0
No. Missing Values	0	0	1 (0.6)	0	5 (4.0)	0
Megestrol						
Study Enrollment	189 (100)	189 (100)	174 (100)	152 (100)	111 (100)	79 (100)
No. No Pain	82 (43.4)	89 (47.1)	83 (47.7)	66 (43.4)	54 (48.6)	41 (51.9)
No. Slight Pain	57 (30.2)	55 (29.1)	49 (28.3)	47 (30.9)	34 (30.6)	15 (19.0)
No. Moderate Pain	46 (24.3)	37 (19.6)	28 (16.1)	23 (15.1)	12 (10.8)	16 (20.3)
No. Severe Pain	3 (1.6)	4 (2.1)	11 (6.3)	14 (9.2)	9 (8.1)	3 (3.8)
No. Intractable Pain	1 (0.5)	4 (2.1)	0	1 (0.7)	0	0
Missing Values	0	0	3 (1.7)	1 (0.7)	2 (1.8)	4 (5.1)

Quality of Life Data

The EORTC Quality of Life (QLQ-30) was to be completed by all patients at each scheduled