Sponsor

Novartis

Generic Drug Name

Letrozole

Therapeutic Area of Trial

Breast Cancer

Approved Indication

Indicated for the treatment of

- Adjuvant treatment of post menopausal women with hormone receptor positive (HR+) early stage breast cancer.
- Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy
- First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer.

Study Number

CFEM345DUS59

Title

Open-label, single-arm, multicenter study to evaluate the rheumatological tolerability of letrozole as an adjuvant breast cancer treatment in postmenopausal women who are intolerant and discontinue anastrozole due to grade 2-3 arthralgia-myalgia.

Phase of Development

Phase IV

Study Start/End Dates

06 Mar 2008 to 01-Jun-2009

Study Design/Methodology

This was a multicenter, prospective, non-randomized, single-arm, open-label trial in postmenopausal hormone receptor-positive (HR+) early breast cancer patients who experienced grade 2-3 arthralgia-myalgia while on anastrozole, resulting in discontinuation of anastrozole. The patients had a 2-3 week period without any aromatase inhibitor treatment, following which the patients were given 2.5 mg of letrozole once a day orally for 24 weeks. Patients had the following 4 visits

during the study: Visit 1 (baseline), Visit 2 (Week 6), Visit 3 (Week 12) and Visit 4 (Week 24). Any patient who took a single dose of letrozole was considered for the safety analyses. After the study treatment, patients had the option to continue receiving letrozole at the discretion of the treating physician, provided that patients did not have symptoms of recurrent breast cancer either locally or systemically. Letrozole was to be provided for the remainder of their initial adjuvant treatment recommendation for up to a total of five years.

Centres

58 centers were initiated and 45 centers enrolled patients,, all in the United States.

Publication

None

Objectives

To evaluate whether patients who were intolerant and discontinued anastrozole secondary to grade 2-3 arthralgia-myalgia obtained clinical benefit from letrozole.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral tablets of letrozole 2.5 mg, once daily for a period of 24 weeks.

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable

Criteria for Evaluation

Efficacy: None.

Safety:

Primary variable

The proportion of patients discontinuing due to grade 2 or higher arthralgia-myalgia.

Secondary variables

Time to discontinuation due to grade 2 or higher arthralgia-myalgia.

The proportion of patients discontinuing, irrespective of the cause.

Quality of life (QoL) variables

Change in Brief Pain Inventory (BPI) composite score

Change in Disability Index as assessed by Health Assessment Questionnaire (HAQ)

Change in pain as assessed by Visual Analog Scale (VAS) of HAQ

Additional safety variables included adverse events, pregnancies, laboratory evaluations, blood chemistry (estrogen, calcium, creatinine phosphokinase (CPK), C-reactive protein (CRP), phosphorus, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and vitamin D), and physical examination.

Pharmacology: Pharmacokinetic evaluations were not done.

Statistical Methods

Unless otherwise specified, all statistical tests were performed against a two-sided alternative hypothesis, employing a significance level of 0.05. The assessments at V1 were considered baseline for all safety analysis. A window of ±7 calendar days was applied to Week 6 (V2), Week 12 (V3), and Week 24/EOS (V4). All time to variables were calculated using Baseline (V1) as time zero.Missing data were not imputed, and the last observation was not carried forward. All analyses of safety and QoL variables were considered exploratory in nature for generation of hypothesis only.

The sample size for this study was based on the assumption that the primary safety variable - proportion of patients discontinuing due to arthralgia-myalgias will be 50%. It was estimated it would be necessary to enroll 228 patients so that the proportion would be within 6.5% of the true proportion with 95% confidence. All the patients who took one or more doses of letrozole were included in the safety analysis of the study. The primary variable, the proportion of patients discontinuing the study due to grade 2 or higher arthralgia-myalgia, was analyzed by estimating the proportion and the associated 95% confidence interval (CI) using the normal approximation to the binomial distribution. The proportion of patients who discontinued study irrespective of cause was analyzed in a similar manner.

The time to discontinuation due to grade 2 or higher arthralgia-myalgia was estimated and

graphed using the Kaplan Meier method. A Cox proportional methods analysis was performed to identify predictors for time to discontinuation due to grade 2 or higher arthralgia-myalgia.

The changes from baseline of BPI composite scores, Disability Index, and VAS scores were summarized for each visit descriptively by mean, median, standard deviation, 25^{th} and 75^{th} percentiles, minimum and the maximum. For exploratory purposes, a paired t-test (or non-parametric version if needed) was used to test the null hypothesis that the mean change was not different from zero against the alternative hypothesis that the change was different from zero.

Adverse events were recorded throughout the study, from study entry to study completion or premature discontinuation. Treatment-emergent adverse events were identified, analyzed and coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population included 261 postmenopausal women with HR+ early stage breast cancer who had prior adjuvant hormonal treatment with anastrozole. Prior to enrollment, none of the eligible patients demonstrated any clinical or radiological evidence of recurrent or metastatic breast cancer.

Inclusion criteria:

- Postmenopausal women with HR+ early stage breast cancer at the time of initial diagnosis. For study purposes, postmenopausal was defined as:
  - Age = 50 years and amenorrheic for 12 or more months.
  - Age = 50 years and amenorrheic for 3 or more months after receiving adjuvant chemotherapy.
  - Age < 50 years and amenorrheic for 12 or more months.
  - Prior bilateral oophorectomy.
  - Prior hysterectomy and had postmenopausal levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol as per local institutional standards.
  - Age > 55 years and prior hysterectomy.
- Patients who were intolerant and discontinued anastrozole as adjuvant treatment 2-3 weeks prior to study entry due to grade 2-3 arthralgia-myalgia (based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 3).
- HR+ tumors as defined by institutional standards.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Exclusion criteria:

- Postmenopausal women with HR+ metastatic or locally relapsed breast cancer, excluding chest wall recurrence with no evidence of systemic disease.
- Recent history of pain associated with non-traumatic bone fracture.
- Pain requiring chronic use of analgesics (due to any reason).
- History of rheumatological disease except osteoarthritis.
- Prior hormonal therapy with AIs other than anastrozole.

- Systemic hormone replacement therapy (HRT) less than 4 weeks before study entry other than estradiol vaginal ring, vagifem®, or low dose estrogen vaginal cream.
- Concomitant disease, which significantly affected quality of life.

Number of Subjects

Patient disposition

	Letrozole 2.5 mg N = 261
Number (%) of patients	
Enrolled	261 (100.0)
Safety population	261 (100.0)
Completed	228 (87.4)
Discontinued	33 (12.6)
Main reason for discontinuation	n (%)
Adverse event(s)	28 (10.7)
Abnormal laboratory value(s)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)
Patient withdrew consent	2 (0.8)
Lost to follow-up	0 (0.0)
Administrative problems	1 (0.4)
Death	0 (0.0)
Disease progression	0 (0.0)
Protocol violation(s)	2 (0.8)

Demographic and Background Characteristics

Baseline demographic summary by treatment group (All enrolled patients)	**Letrozole 2.5 mg N = 261**
Age (years)[a]	
N	261
Mean (SD)	61.6 (10.2)
Median	61.0
Percentiles (25^{th} – 75^{th})	54.0 - 68.0
Range (minimum - maximum)	32 - 88
Age groups – n (%)	
= 65 years	168 (64.4)
> 65 years	93 (35.6)
Race - n (%)	
Caucasian	235 (90.0)
Black	14 (5.4)
Asian	3 (1.1)
Other	9 (3.4)
ECOG performance status[b]	
1.	166 (63.6)
2.	90 (34.5)

3.	5 (1.9)
4.	0 (0.0)
5.	0 (0.0)
Relevant medical and surgical history – n (%)	
Yes	261 (100.0)
No	0 (0.0)
Rheumatology history – n (%)	
Yes	261 (100.0)
No	0 (0.0)

a Age = integer (date of informed consent sign – date of birth)/365.25

b Eastern Cooperative Oncology Group (ECOG) performance status categories are as follows: 1. Fully active, able to carry on all pre-disease performance without restriction; 2. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 3. Ambulatory and capable of all selfcare but unable to carry out any work activities; Up and about more than 50% of waking hours; 4. Capable of only limited selfcare, confined to bed or chair more than 50% of working hours; 5. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Results

Number of patients discontinuing due to grade 2 or higher arthralgia-myalgia (Safety population)

	Letrozole 2.5 mg N = 261	**95% CI**
Number (%) of patients who discontinued due to grade 2 or higher arthralgia-myalgia	25 (9.58)	6.01, 13.15
Number (%) of patients censored	236 (90.42)	

CI = confidence interval

The 95% CI of the proportion was calculated using the normal approximation to the binomial distribution.

Patients who did not discontinue study by Visit 4/end-of-study visit were considered censored at 24 weeks (end of study).

Time to discontinuation due to grade 2 or higher arthralgia-myalgia using Kaplan-Meier method (Safety population)

	Letrozole 2.5 mg N = 261
Time to discontinuation due to arthralgia-myalgia (days)	
Mean (SE)	156.98 (1.94)
SE = standard error of the mean.	

Discontinuation of patients from study, irrespective of cause:

Of the 261 patients in the safety population, 33 patients (12.64%), 95% CI 8.61 – 16.68 discontinued the study prematurely

Change in BPI composite score (Safety population)

Visit	**Statistic**	**Letrozole N = 261**		
		Score	**Change**	**P-value**
Visit 1 (Baseline visit)	n	257		
	Mean (SD)	2.78 (2.00)		
	25th percentile	1.00		
	Median	2.50		
	75th percentile	4.25		
	Range	0.00, 9.25		
Visit 2 (Week 6)	n	238	234	
	Mean (SD)	2.31 (1.99)	-0.45 (1.68)	<0.001
	25th percentile	0.75	-1.25	
	Median	1.75	-0.25	
	75th percentile	3.50	0.50	
	Range	0.0, 8.75	-5.00, 4.50	
Visit 3 (Week 12)	n	226	222	
	Mean (SD)	2.14 (1.95)	-0.62 (1.90)	<0.001
	25th percentile	0.75	-1.50	
	Median	1.75	-0.50	
	75th percentile	3.00	0.00	
	Range	0.0, 8.50	-5.75, 7.75	
Visit 4 (Week 24)/Early Discontinuation	n	243	240	
	Mean (SD)	2.29 (2.26)	-0.46 (2.09)	0.001
	25th percentile	0.25	-1.63	
	Median	1.50	-0.38	
	75th percentile	3.50	0.50	
	Range	0.00, 9.50	-5.75, 6.75	

BPI = Brief Pain Inventory; SD = standard deviation.

Change in Disability Index as assessed by HAQ (Safety population)

Visit	Statistic	Letrozole N = 261		
		Score	Change	P-value
Visit 1 (Baseline visit)	N	260		
	Mean (SD)	0.54 (0.55)		
	25th percentile	0.00		
	Median	0.38		
	75th percentile	0.88		
	Range	0.00, 2.25		
Visit 2 (Week 6)	N	241	240	
	Mean (SD)	0.46 (0.52)	-0.09 (0.39)	0.001
	25th percentile	0.00	-0.25	
	Median	0.25	0.00	
	75th percentile	0.75	0.13	
	Range	0.00, 2.13	-1.38, 1.13	
Visit 3 (Week 12)	N	235	234	
	Mean (SD)	0.46 (0.56)	-0.09 (0.40)	0.001
	25th percentile	0.00	-0.38	
	Median	0.25	0.00	
	75th percentile	0.75	0.13	
	Range	0.00, 2.13	-1.50, 1.63	
Visit 4 (Week 24)/Early Dis-continuation	N	253	252	
	Mean (SD)	0.47 (0.56)	-0.07 (0.47)	0.019
	25th percentile	0.00	-0.38	
	Median	0.25	0.00	
	75th percentile	0.75	0.13	
	Range	0.00, 2.13	-1.50, 1.88	

HAQ = Health Assessment Questionnaire; SD = standard deviation.

Change in pain as assessed by VAS scale of the HAQ (Safety population)

Visit	Statistic	Letrozole N = 261		P-value
		Score	Change	
Visit 1 (Baseline visit)	N	255		
	Mean (SD)	28.9 (24.22)		
	25th percentile	9.00		
	Median	25.00		
	75th percentile	45.00		
	Range	0.0, 100		
Visit 2 (Week 6)	N	237	234	
	Mean (SD)	22.3 (21.96)	-7.3 (23.31)	<0.001
	25th percentile	4.00	-21.00	
	Median	16.00	-4.00	
	75th percentile	34.00	5.00	
	Range	0.00, 93.00	-91.00, 57.00	
Visit 3 (Week 12)	N	233	228	
	Mean (SD)	20.9 (23.22)	-7.8 (25.41)	<0.001
	25th percentile	2.00	-20.00	
	Median	14.00	-4.00	
	75th percentile	31.00	5.00	
	Range	0.00, 94.00	-100.00, 61.00	
Visit 4 (Week 24)/Early Dis-continuation	N	250	245	
	Mean (SD)	22.4 (24.79)	-6.4 (29.30)	0.001
	25th percentile	0.0	-22.0	
	Median	13.0	-5.0	
	75th percentile	38.0	10.0	
	Range	0.0, 100.0	-100.0, 81.0	

HAQ = Health Assessment Questionnaire; SD = standard deviation; VAS = Visual Analog Scale

Safety Results

Number of patients with the most frequent AEs (occurring in at least 2% of patients) by preferred term (Safety population)

	Common Toxicity Criteria Grades				Letrozole 2.5 mg N = 261
	1	2	3	4	
No. (%) of patients with any adverse event	83 (31.8)	84 (32.2)	33 (12.6)	3 (1.1)	203 (77.8)
Arthralgia	31 (11.9)	36 (13.8)	21 (8.0)	0 (0.0)	88 (33.7)
Myalgia	35 (13.4)	28 (10.7)	14 (5.4)	1 (0.4)	78 (29.9)
Hot flush	23 (8.8)	13 (5.0)	1 (0.4)	0 (0.0)	37 (14.2)
Fatigue	23 (8.8)	9 (3.4)	0 (0.0)	0 (0.0)	32 (12.3)
Nausea	11 (4.2)	2 (0.8)	0 (0.0)	0 (0.0)	13 (5.0)
Depression	8 (3.1)	4 (1.5)	0 (0.0)	1 (0.4)	13 (5.0)
Diarrhea	7 (2.7)	1 (0.4)	0 (0.0)	0 (0.0)	8 (3.1)
Constipation	7 (2.7)	1 (0.4)	0 (0.0)	0 (0.0)	8 (3.1)
Headache	4 (1.5)	4 (1.5)	0 (0.0)	0 (0.0)	8 (3.1)
Sinusitis	3 (1.1)	4 (1.5)	0 (0.0)	0 (0.0)	7 (2.7)
Pain in extremity	3 (1.1)	2 (0.8)	1 (0.4)	0 (0.0)	6 (2.3)
Insomnia	3 (1.1)	3 (1.1)	0 (0.0)	0 (0.0)	6 (2.3)
Alopecia	5 (1.9)	1 (0.4)	0 (0.0)	0 (0.0)	6 (2.3)
Hypertension	1 (0.4)	5 (1.9)	0 (0.0)	0 (0.0)	6 (2.3)
Peripheral Edema	9 (3.4)	1 (0.4)	0 (0.0)	0 (0.0)	10 (3.8)

AE = adverse event; CTC = Common Toxicity Criteria.

AEs are coded using MedDRA version 12.0.

A particular AE is counted under its maximum grade rating only.

Summary of serious or significant adverse events by treatment (safety population)

	Letrozole N = 261 n (%)
Number (%) of patients with any serious or significant AE	42 (16.1)
Death	0 (0.0)
Non-fatal SAE	5 (1.9)
SAE leading to discontinuation	0 (0.0)
Non-serious AE leading to discontinuation	28 (10.7)
AE leading to a dose adjustment or temporary interruption	11 (4.2)

AE = adverse event; SAE = serious adverse event.

Other Relevant Findings

Laboratory tests and vital signs remained similar through the study, and there were no meaningful differences in the mean parameters from baseline.

Date of Clinical Trial Report

30 Oct 2009

Date Inclusion on Novartis Clinical Trial Results Database

18-Oct-2010

Date of Latest Update