Sponsor

Novartis

Generic Drug Name

Letrozole

Therapeutic Area of Trial

Breast cancer

Approved Indication

Letrozole is 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

CFEM345DDE10

Title

An open phase III trial with Letrozole as Early Adjuvant treatment of postmenopausal patients with primary breast cancer "LEAD"

Phase of Development

Phase III

Study Start/End Dates

21 Mar 2006/15 Jul 2010

Study Design/Methodology

This study was a prospective one arm phase III trial designed to evaluate the use of Letrozole 2.5 mg administered p.o. daily for 24 months as adjuvant therapy for postmenopausal patients with primary breast cancer. After two years of treatment within study physicians were strongly encouraged to continue treatment of the patients with Letrozole for further 36 months.

If osteoporosis was present at baseline, 4mg/5mL Zoledronic acid (4mg or adjusted dose based on renal function) was to be administered additionally as concomittant medication every 6 months as an infusion. Zoledronic acid was to be administered at the same dosage, if BMD (bone

mineral density) loss exceeded 5 % during the study period. Zoledronic acid was provided to the patients after the 24 months of study duration, if the patient showed a benefit during the term of the study.

Amendment 2 of the study stopped the Follow-Up assessments with LPLV of the treatment phase. The rationale for stopping the Follow-Up was based on the fact that an increased relapse rate may be expected for the first two years after diagnosis (Mansell et al. 2009) and the assumption that it is very unlikely that new scientific knowledge may be generated by analyzing the Follow-Up data in respect to what is already described by the recommendations of the Working Party of Gynecologic Oncology (AGO).

Reference:

Mansell J et al. Patterns and predictors of early recurrence in postmenopsausal women with estrogen receptor-positive early breast cancer. Breast Cancer Res Treat 2009;117:91-98

Centres

63 centres in Germany

Publication

None

Objectives

Primary objective(s)

- To assess the recurrence in postmenopausal patients with breast cancer treated with Letrozole for 24 months

Secondary objective(s)

To compare the combined treatment of Letrozole and Zoledronic acid with Letrozole monotherapy with respect to:

- Disease free survival (DFS)
- Quality of life
- Safety and tolerability

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

Letrozole tablets orally at the dose of 2.5 mg/day.

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

None

Criteria for Evaluation

Efficacy:

Recurrence was measured by protocol defined tumor assessments: Abdominal Ultrasound, CT or liver scan, bone scan, chest X-ray and mammography. If the bone scan showed areas suspicious for tumor then these areas had to b be confirmed by X-ray or MRI; or by a second bone scan at least three months later that shows progressive changes.

Safety:

The assessment of safety was based mainly on the frequency of adverse events and on laboratory values. Toxicities and adverse events were classified and presented in frequency tables.

Statistical Methods

To estimate the DFS after 24 months of treatment with Letrozole the Kaplan-Meier method was applied. The estimation was presented together with the corresponding two-sided 95% confidence interval. The Kaplan-Meier estimate was used rather than the crude rate of patients without recurrence in order to handle adequately patients who discontinue the study years prior to suffering from recurrence.

Two approaches were considered for calculating DFS, a more conservative approach whereby the last tumor assessment was considered for censoring purposes. Another approach, less conservative, was considered by using the last visit date for censoring purposes.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Age > 18 years
- Performance status 0-2 (ECOG)
- Nodal status negative or positive
- Compliant postmenopausal, i.e. at time of tumor diagnosis, women with primary operable breast cancer after complete surgery and suitable for endocrine treatment
    - Age ≥ 55 years with cessation of menses.
    - Age < 55 but no spontaneous menses for at least 1 year.
    - Age < 55 and spontaneous menses within the past 1 year, but currently amenorrheic (e.g., spontaneous, or secondary to hysterectomy), and with postmenopausal gonadotrophin levels (luteinizing hormone and follicle stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.

Note: It was not possible to assign menopausal status to women who were receiving an LH-RH agonist or antagonist or those who become amenorrheic due to chemotherapy or surgical ovarian ablation (i.e. recently postmenopausal).

- Hormone receptor positive (defined as ER and/or PgR ≥10 fmol/mg cytosol protein; or ≥

10% of the tumor cells positive by immunohistochemical evaluation)

- Adequate marrow function (WBC > 3.0 x 10^9/L, platelets > 100.0 x 10^9/L, and hemoglobin > 10 g/dL)
- Adequate hepatic function (bilirubin < 30 µmol/L, ALT (SGPT) or AST (SGOT) ≤ 1.5x ULN of the institution).

Exclusion Criteria:

- Patients with clinical or radiological evidence of metastatic breast cancer
- Breast Cancer which is ER and PgR negative or unknown
- Inflammatory breast cancer
- Abnormal renal function as evidenced by a calculated creatinine clearance < 30 mL/min. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula:
  - CrCl = $\frac{[140\text{-age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]}$ {x 0.85 for female patients}
- Active dental problems including infection of the teeth or jawbone (maxilla or mandibular); dental or fixture trauma, or a current or prior diagnosis of osteonecrosis of the jaw (ONJ), of exposed bone in the mouth, or of slow healing after dental procedures.
- Recent (within 6 weeks) or planned dental or jaw surgery (e.g.. extraction, implants).
- Known hypersensitivity to Zoledronic acid or other bisphosphonates.
- Patients with previous or concomitant malignancy (not breast cancer) within the past 5 years except adequately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix. Patients who have had a previous other malignancy must have been disease-free for five years.
- Patients with other non-malignant systemic diseases including uncontrolled infections, uncontrolled type 2 diabetes mellitus, uncontrolled thyroid dysfunction, cardiovascular, renal, hepatic, and lung diseases which would prevent prolonged follow-up. Patients with previous history of thrombosis or thromboembolism could be included only if medically suitable. Patients with a known history of HIV were excluded.
- Patients with primary hyperparathyreoidism
- Severe physical or psychological concomitant diseases that might impair compliance with the provisions of the study protocol or that might impair the assessment of drug or patient safety, e.g. clinically significant ascites, cardiac failure, NYHA III or IV, clinically relevant pathologic findings in ECG.
- Patients treated with systemic investigational drug(s) and/or device(s) within the past 30 days or topical investigational drugs within the past 7 days.
- History of non-compliance to medical regimens and patients who are considered potentially unreliable.
- Mental illness that precludes the patient from giving informed consent.

Number of Subjects

Patient disposition

		Total (N=655) n (%)
Study completion	treated	655 (100.0)
	discontinued	129 (19.7)
	completed	526 (80.3)
Reason for discontinuation	adverse event(s)	81 (12.4)
	Patients condition no longer requires study drug	1 (0.2)
	protocol violation	6 (0.9)
	patient withdrew consent	25 (3.8)
	lost to follow-up	7 (1.1)
	administrative problems	3 (0.5)
	death	6 (0.9)

Demographic and Background Characteristics

Demographic characteristics by treatment group for the ITT population

			Total
Variable		**Statistic**	**(N=655)**
Age [yrs]		NMiss	0
		Mean	63
		Std	7.5
		Min	43.0
		Median	64
		Max	82.0
	< 65 years	n (%)	358 (54.7)
	>= 65 years	n (%)	297 (45.3)
Sex	female	n (%)	655 (100.0)
Race	Caucasian	n (%)	647 (98.8)
	Oriental	n (%)	2 (0.3)
	Other	n (%)	6 (0.9)

Primary Objective Result(s)

Rate of patients without recurrence after 24 months, using last tumor assessment for censoring, in the ITT population

Percent of patients without recurrence	lower 95% confidence limit	upper 95% confidence limit
92.15	84.83	99.47

Rate of patients without recurrence after 24 months, using last visit date for censoring, in the ITT population

Percent of patients without recurrence	lower 95% confidence limit	upper 95% confidence limit
91.52	82.18	100

The percent of patients without recurrence was not appreciatively different using the two approaches. In both cases over 90% of the patients did not have a recurrence.

Median time to recurrence or median survival time was not observed, as only 20 recurrences occurred in the 655 enrolled patients.

Secondary Objective Result(s)

Change in Bone Densitometry from baseline in the ITT population

Visit Report Number	Variable	N	N miss.	Mean	SD	Min	Median	Max
Visit - Month 6	t-score change from baseline	19	636	0.1	1.02	-0.9	0.0	3.2
	z-score change from baseline	16	639	-0.2	1.26	-3.2	-0.2	3.2
Visit - Month 12	t-score change from baseline	80	575	-0.2	0.91	-2.9	-0.1	4.0
	z-score change from baseline	66	589	-0.2	0.98	-6.3	0.0	1.3
Visit - Month 18	t-score change from baseline	39	616	-0.3	1.65	-6.4	-0.4	3.4
	z-score change from baseline	28	627	-0.4	1.21	-3.8	-0.3	2.0
Visit - Month 24	t-score change from baseline	330	325	-0.2	0.99	-5.7	-0.2	3.7
	z-score change from baseline	281	374	-0.1	0.72	-2.9	-0.1	2.7

Changes from Baseline to Month 24/Final Visit in EORTC C-30 and BR-23 functional scales and items (ITT)

a) EORTC C-30 Functional Scales	N	N miss.	Mean	SD	Min	Median	Max
Physical functioning	439	216	-1.43	15.27	-80.00	0.0	46.7
Role functioning	433	222	3.66	30.95	-100.00	0.0	100.0
Emotional functioning	435	220	1.07	22.70	-100.00	0.0	100.0
Cognitive functioning	436	219	-5.54	22.39	-100.00	0.0	83.3
Social functioning	436	219	5.01	26.60	-100.00	0.0	100.0
Global Health status/QOL	430	225	1.38	22.94	-66.67	0.0	83.3
Fatigue	437	218	0.03	24.56	-66.67	0.0	88.9
Nausea/Vomiting	437	218	-1.45	16.06	-83.33	0.0	100.0
Pain	438	217	6.58	30.55	-100.00	0.0	100.0
Dyspnoea	433	222	5.70	27.75	-66.67	0.0	100.0
Insomnia	435	220	8.43	34.47	-100.00	0.0	100.0
Appetite loss	435	220	-4.29	25.34	-100.00	0.0	100.0
Constipation	431	224	2.78	27.04	-100.00	0.0	100.0
Diarhoea	432	223	-1.00	22.05	-100.00	0.0	66.7
Financial Problems	428	227	-3.58	24.63	-100.00	0.0	100.0
b) BR-23 Functional Scales							
Body Image	422	233	3.62	21.01	-75.00	0.0	83.3
Sexual functioning	342	313	1.80	23.79	-100.00	0.0	100.0
Sexual enjoyment	69	586	-6.76	24.64	-66.67	0.0	33.3
Future perspective	421	234	15.91	35.23	-100.00	0.0	100.0
Systematic therapy	427	228	1.09	19.77	-61.90	0.8	85.7

Breast symptoms	429	226	-10.70	21.81	-91.67	-8.3	58.3
Arm Symptoms	428	227	2.78	26.03	-66.67	0.0	100.0
Hair loss	86	569	-5.81	46.07	-100.00	0.0	100.0

Safety Results

Number of AE / patients with AE, summarized by system organ class and preferred term: Safety population

System organ class

	Number of patients	% of patients (n=655)	% of all AEs
Blood and lymphatic system disorders	35	(5.3)	(1.6)
Cardiac disorders	47	(7.2)	(2.1)
Congenital, familial and genetic disorders	2	(0.3)	(0.1)
Ear and labyrinth disorders	28	(4.3)	(1.3)
Endocrine disorders	10	(1.5)	(0.5)
Eye disorders	43	(6.6)	(2.0)
Gastrointestinal disorders	169	(25.8)	(7.7)
General disorders and administration site conditions	177	(27.0)	(8.0)
Hepatobiliary disorders	19	(2.9)	(0.9)
Immune system disorders	5	(0.8)	(0.2)
Infections and infestations	112	(17.1)	(5.1)
Injury, poisoning and procedural complications	105	(16.0)	(4.8)
Investigations	99	(15.1)	(4.5)
Metabolism and nutrition disorders	53	(8.1)	(2.4)
Musculoskeletal and connective tissue disorders	412	(62.9)	(18.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38	(5.8)	(1.7)
Nervous system disorders	132	(20.2)	(6.0)
Psychiatric disorders	133	(20.3)	(6.0)
Renal and urinary disorders	16	(2.4)	(0.7)
Reproductive system and breast disorders	73	(11.1)	(3.3)
Respiratory, thoracic and mediastinal disorders	74	(11.3)	(3.4)
Skin and subcutaneous tissue disorders	184	(28.1)	(8.4)
Vascular disorders	237	(36.2)	(10.8)

Number (%) of patients with most frequent AEs (5% or more of the patients)

Preferred term	**n**	**% of patients (n=655)**	**% of all AEs**
No. of Patients with AEs	597	(91.1)	
Total no. of AEs	2955		(100.0)
Nausea	35	(5.3)	(1.2)
Fatigue	91	(13.9)	(3.1)
Edema peripheral	34	(5.2)	(1.2)
Radiation skin injury	58	(8.9)	(2.0)

	Arthralgia	183	(27.9)	(6.2)
	Back pain	44	(6.7)	(1.5)
	Bone pain	135	(20.6)	(4.6)
	Myalgia	38	(5.8)	(1.3)
	Pain in extremity	45	(6.9)	(1.5)
	Headache	35	(5.3)	(1.2)
	Depression	39	(6.0)	(1.3)
	Sleep disorder	53	(8.1)	(1.8)
	Dyspnoea	36	(5.5)	(1.2)
	Alopecia	63	(9.6)	(2.1)
	Erythema	41	(6.3)	(1.4)
	Hot flush	153	(23.4)	(5.2)
	Hypertension	38	(5.8)	(1.3)
	Lymphoedema	54	(8.2)	(1.8)

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	TOTAL	
	No. (%) of AEs	**No. (%) of patients**
		(n=655)
All AEs	2955 (100.0)	597 (91.1)
with suspected letrozole relation	931 (31.5)	372 (56.8)
with suspected Zolerdronic acid relation	67 (2.3)	33 (5.0)
with suspected Combination relation	21 (0.7)	14 (2.1)
leading to dose adjustment or temp. interruption	39 (1.3)	33 (5.0)
leading to permanent discontinuation	132 (4.5)	80 (12.2)
requiring concomitant medication/non-drug therapy	913 (30.9)	394 (60.2)
Serious AEs	206 (7.0)	104 (15.9)
Deaths		6 (0.9)
SAEs with suspected Letrozole relation	9 (0.3)	7 (1.1)
SAEs with suspected Zoledronic relation	1 (0.0)	1 (0.2)
SAEs with suspected Combination relation	1 (0.0)	1 (0.2)
SAEs leading to permanent discontinuation	15 (0.5)	12 (1.8)

Other Relevant Findings

None

Date of Clinical Trial Report

21 Jun 2011

Date Inclusion on Novartis Clinical Trial Results Database

12 Jul 2011

Date of Latest Update