Sponsor

Novartis UK Limited

Generic Drug Name

Letrozole/FEM345

Therapeutic Area of Trial

Localized ER and/or PgR receptor positive breast cancer

Study Number

CFEM345EGB07

Protocol Title

This study was open-labeled and was originally planned to be conducted in 300 women with localized estrogen-receptor (ER) and/or progesterone-receptor (PgR) positive breast cancer whose tumors were too large for breast conserving surgery (BCS). Letrozole (2.5 mg/day) was given orally (p.o) for up to 12 months. Patients were assessed clinically and by ultrasound every two months to establish suitability for BCS.

Phase of Development

Phase IV

Study Start/End Dates

Study initiation date: 28-Feb-2006 (first patient treated)
Early termination date: 16-Nov-2010

Study Design/Methodology

This was multicenter phase IV open-labelled study conducted in the UK only. Postmenopausal women diagnosed with ER and/or PgR positive localised primary breast cancer whose tumors were assessed, in the 14 days prior to the study, to be too large (≥T2 i.e. ≥ 20 mm) for BCS, were considered for participation into a trial. Consenting patients, who met the entry criteria, were treated with letrozole, 2.5 mg/day p.o. for a period of up to 12 months. Suitability for BCS was assessed by the investigator every two months taking into consideration, decrease in the tumor volume on ultrasound scan (in relation to the size of breast) and location. Baseline and pre-surgical ultrasound scans and, where available, mammograms were evaluated by the Central Radiology Laboratory and tumor volumes were determined. BCS was defined as being any operation that left breast tissue behind e.g. lumpectomy or quadrantectomy.
This was an open-label non-comparative study of 2.5 mg/day letrozole.

Centres

Study center(s): 21 centres in the UK

Objectives

Primary objective(s)

To determine the optimal duration of treatment with letrozole (2.5 mg/day p.o.), preoperatively, to permit BCS in patients with early breast cancer, who are initially not suitable for BCS at study entry. Response will be assessed by clinical examination and breast ultrasound.

Secondary objective(s)

To determine the reduction in tumor volume every 2 months throughout the study;
To determine the response rate in line with the RECIST 1.0 criteria;
To monitor the long term (5-year) local recurrence rate;
To establish the safety and tolerability of the treatment prior to surgery.
To determine the extent and nature of patient's psychological distress and concerns while undergoing treatment with letrozole.

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

Test product, dose and mode of administration: 2.5 mg tablet – oral administration

Criteria for Evaluation

Primary variables

The primary efficacy variable was the duration of letrozole treatment required to achieve a level of tumor shrinkage sufficient to permit BCS. The patient's tumor response was assessed by the investigator every two months by clinical examination, bi-lateral ultrasound and, sometimes, also mammography.

Patients were considered to have completed the study (1) at the time that the decision was made that the patient met the criteria for BCS or (2) at the time that the decision was made that the patient did not meet the criteria for BCS and they withdrew or were withdrawn from the study for further treatment i.e. mastectomy or (3) when they withdrew or were withdrawn for other reasons and (4) when the patient completed 12 months of letrozole treatment without a decision for BCS or otherwise having been reached

Secondary variables

The second efficacy variables included tumor volume and change from tumor volume from baseline:

• The investigator assessments of tumor volume were determined clinically, from the bilateral ultrasound scans and mammograms (if performed) taken at baseline, at each 2 monthly visit and immediately pre-surgery.

• The central laboratory assessment of tumor volume was made on the same baseline and pre-surgery ultrasound scans (or in the absence of a pre-surgery scan, the last scheduled visit scan from which the decision for BSC was taken) which were sent into the Central Radiology Laboratory for analysis, along with mammograms (if performed) at the same time points.

On the ultrasound scans, two dimensions were recorded for sagittal and two for the transverse orientation. To calculate the average diameter 'D' for the volume calculation, the diameters were simply averaged.

On mammography, similarly 'D' is the simple average of the two oblique diameters and the two craniocaudal diameters.

An estimate of the tumor volume was calculated, as follows:

$$\frac{D^3 \pi}{6}$$

D = mean diameter

Note: if one or more tumor diameters were not recorded, 'D' was calculated from the available diameters.

Assessment of the tumor in accordance with the RECIST 1.0 criteria (Protocol Appendix 2) was another secondary efficacy variable. Patients with evidence of progressive disease (PD) were taken off study to undergo further treatment, usually mastectomy. Patients with an

overall partial response (PR), insufficient for BCS or stable disease (SD), either underwent mastectomy right away or remained on treatment until the next scheduled 2 monthly visit for up to 12 months. The decision to withdraw or continue was made by the investigator following discussion with the patient.
The third efficacy variable was survival and the local recurrence rate post-operatively for up to 5 years. Local recurrence was defined as:
- any recurrence within the surgical scar or ipsilateral breast, within the same quadrant as the primary tumor
- or ipsilateral chest wall and skin recurrence if mastectomy undertaken
Progression of the disease was also recorded.

Safety and tolerability

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. There were also regular assessments of vital signs and physical condition.
Full information about the definition of AEs and SAEs, the procedures for reporting them and the assessment of other safety variables is given in the Section 7 of the protocol.
Appropriateness of safety assessments
Letrozole is licensed for treatment of patients with breast cancer in the neoadjuvant setting. The safety assessments performed were consistent with the terms of the license for letrozole in the UK.

Statistical Methods

The primary objective of this study was to determine the optimal duration for treatment with letrozole, as indicated by the proportion of patients achieving the primary endpoint (tumour response sufficient for BCS) after different periods of treatment. The Kaplan-Meier product limit method was used to calculate the survival function. The proportion of patients achieving the primary endpoint together with 95% confidence intervals for the population value was produced for the proportion achieving endpoint at 2 month intervals from 2 months to 12 months. Other descriptive statistics for the survival curve (e.g. median response time) are also provided.

A supportive analysis was carried out using Cox's proportional hazards model. The model fitted included the following factors: baseline breast tumor and axillary lymph node assessments together with demographic and other background variables observed at baseline.
Summary statistics are provided for changes from baseline in the diameter and volume of tumors

based in the investigator analysis of the ultrasounds scans at all available time points and the central radiology laboratory analysis of the baseline and pre-surgery ultrasound scans (or last scan on which the end point decision was made).
An interim analysis of the primary outcome was conducted after nearly 3 years of recruitment to the study at a time when approximately one third of patients (100) had completed at least one post-baseline assessment of tumor response.
Following the interim analysis, it was determined that the majority of patients who achieved a response sufficient for BCS, did so by 8 months. The Kaplan-Meier estimates from the interim analysis showed that adequate precision was achieved for time points up to 8 months. If patients did not respond sufficiently by 8 months they tended to be withdrawn and receive mastectomy. The investigators considered that clinical practice, as followed at that time, would not tend to treat patients much more than 8 months if they had not responded by then. There were ethical concerns about continuing recruitment in order to get sufficient precision at 10 and 12 months when current clinical practice would not favour this length of neoadjuvant endocrine therapy

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Postmenopausal women who were to able to comply with the protocol requirements* with a diagnosis of primary invasive breast cancer, histologically confirmed by core needle biopsy, whose tumors were ER and/or PgR positive, defined by core biopsy immunohistochemistry with > 30% positive malignant epithelial cells. Where tumors were bilateral, the reference side was the larger or largest of the tumors at baseline.

2. Clinical Stage T2 or >T2 tumors (T2 = tumor 2-5 cm in diameter) which in the investigators opinion were not eligible for BCS. The nodal status was evaluated by palpation and/or ultrasound.

3. Post menopausal status was defined as being one of the following:

   Women with an intact uterus and
   ≥ 55 years of age OR
   < 55 years of age without menses for the last 5 years OR
   < 55 years of age and no menses for at least the last 12 months (but had menses in the last 5 years) and had postmenopausal levels of FSH (according to the postmenopausal range of the individual laboratory, and performed at least four weeks after stopping HRT/oral contraceptives).
   OR

   Women without an intact uterus and
   ≥ 55 years of age OR
   >55 years of age and postmenopausal levels of FSH (according to the postmenopausal range of the individual laboratory, and performed at least four weeks after stopping HRT/oral contraceptives)

Bilateral oophorectomy (prior to the diagnosis of breast cancer).

4. Tumor measurable by clinical examination, mammography and ultrasound.
5. Adequate bone marrow function as shown by: WBC ≥3.5 x 109/L, ANC ≥ 1.5 x 109/L, Platelets ≥ LLN, hemoglobin >10g/dL.
6. Adequate liver function as shown by: serum bilirubin ≤ 1.5 x ULN, albumin ≥ 3 g/dl, serum transaminases activity ≤ 2.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN.
7. Normal renal function (serum creatinine ≤ 1.5 x ULN, blood urea nitrogen ≤ 1.5 x ULN).
8. A life expectancy of at least 6 months.
9. Written informed consent to the core study.

Exclusion criteria

1. Multifocal disease
2. Prior treatment with aromatase inhibitors or antiestrogens, or known hypersensitivity to these compounds.
3. Uncontrolled endocrine disorders such as diabetes mellitus, confirmed hyper- or hypothyroidism, Cushing´s Syndrome, Addison´s disease (treated or untreated).
4. Patients with unstable angina, uncontrolled cardiac disease (e.g. Class III or IV New York Heart Association's Functional Classification).
5. Patients with bilateral breast tumors
6. Patients who were eligible for BCS.
7. Evidence of inflammatory breast cancer or distant metastases.
8. Other concurrent malignant disease with the exception of cone-biopsied in situ carcinoma of the cervix uteri, or adequately treated basal or squamous cell carcinoma of the skin, or other curable cancers e.g. Hodgkin´s disease or Non Hodgkin’s Lymphoma, provided 5 years had elapsed from completion of therapy, and there had been no recurrence.

9. Concomitant anti-cancer treatments such as chemotherapy, immunotherapy/biological response modifiers, endocrine therapy (including steroids), bisphosphonate therapy and radiotherapy. Bisphosphonate therapy for osteoporosis was NOT excluded, and could be continued as concomitant therapy. Patients who had received hormone replacement therapy were NOT excluded, provided that therapy had been discontinued at least 2 weeks prior to entry into the study.

10. Concomitant treatment with steroids, e.g. glucocorticoids for indications other than cancer, except aerosol for obstructive airways diseases and steroid injection to the joints for treatment of inflammation.

11. Use of other investigational drugs within the 30 days prior to entry into the trial or during the trial.

12. History of non-compliance to medical regimens and patients who were considered to be potentially unreliable.

13. Current frank or uncontrolled osteoporosis (previously "any history of frank or un-controlled osteoporosis" to permit enrolment of patients with current controlled osteo-porosis. Amended in protocol amendment 4, dated 7th May 2008)

14. Any other condition which may affect participation in the study.

Number of Subjects

	Novartis product	Comparator
Planned N	300	N/A
Randomised n	146	N/A
Intent-to-treat population (ITT) n (%)	139	N/A
Completed n (%)	70.5%	N/A
Withdrawn n (%)	29.5%	N/A
Withdrawn due to adverse events n (%)	5.5%	N/A
Withdrawn due to lack of efficacy n (%)	16.4%	N/A
Withdrawn for other reasons n (%)	7.5%	N/A

Demographic and Background Characteristics

	Novartis product	Comparator
N (ITT)	139	N/A
Females : males	100:0	N/A
Mean age, years (SD)	73.49	N/A
Mean weight, kg (SD)	70.85	N/A
Race White n (%) Black n (%)	 96.4% 2.2%	N/A

Asian n (%) Other n (%)	1.4%	
Characteristics relevant to study population (eg, mean FEV1 % predicted [SD])	N/A	N/A

Primary Objective Result(s)

Time to be Ready for Breast Conserving Surgery

Time to ready for breast conserving surgery (Kaplan-Meier estimates)
Intent-to-treat population

	Time (days) to ready for BCS		Time (months) to ready for BCS	
Ready for BCS (%)	Point estimate	95% confidence interval	Point estimate	95% confidence interval
25	149	(126, 181)	4.9	(4.1, 5.9)
50	227	(191, 258)	7.5	(6.3, 8.5)
75	NR	(375, NR)	NR	(12.3, NR)

Failures censored at maximum time on treatment (391 days); NR = not reached

Secondary Objective Result(s)

Most of the ultrasound scans were sent in for central review; 125/135 at baseline and 120/136 end point scans.With the central ultrasound scans, the median volume decreased from 5.77 to 2.00 cm3, representing a percentage decrease of -75.31%.

Tumor Volume – Central Radiology Laboratory
Tumor volume (cm^3): changes from baseline (central review)
Intent-to-treat population

Breast tumor assessment	Visit	n	Mean	SD	Min	Max	Median
Ultrasound	Baseline	125	10.34	16.69	0.4	155.1	5.77
	End-point	120	2.99	3.78	0.0	25.5	2.00
	Change from baseline	120	-6.03	9.85	-62.4	9.7	-3.45

Breast tumor assessment	Visit	n	Mean	SD	Min	Max	Median
	% Change from baseline	120	-37.46	160.17	-99.5	1512.4	-75.31

Tumor Volume – Investigator

Tumor volume (cm^3): changes from baseline (Investigator)
Intent-to-treat population

Breast tumor assessment	Visit	n	Mean	SD	Min	Max	Median
Clinical examination	Baseline	136	46.78	51.72	1.2	294.0	33.51
	End-poirt	127	21.04	31.01	0.0	179.6	9.74
	Change from baseline	124	-26.27	41.61	-234.6	61.3	-16.62
	% Change from baseline	124	-23.35	187.01	-100.0	1462.5	-68.03
Ultrasound	Baseline	135	17.61	25.96	0.4	147.1	9.20
	End-poirt	136	5.53	9.36	0.0	80.2	3.05
	Change from baseline	134	-12.09	24.05	-146.9	29.0	-4.92
	% Change from baseline	134	-49.19	69.36	-100.0	298.1	-75.83

Breast tumor assessment	Visit	n	Mean	SD	Min	Max	Median
Mammography	Baseline	122	25.83	30.72	0.5	179.6	14.14
	End-point	55	9.20	12.04	0.0	56.1	4.19
	Change from baseline	53	-14.88	24.00	-138.6	42.0	-8.68
	% Change from baseline	53	-39.52	113.68	-100.0	641.5	-72.26

Safety Results

In total, 61.6% of the study population experienced an AE during the course of the study. Musculoskeletal and connective tissue disorders were the most prevalent (24.7%), followed by nervous system disorders (16.4%), both of which are considered to be common events on the summary of product characteristics (SPC). Vascular disorders, infections and respiratory, thoracic and mediastinal disorders were also reported frequently. The prevalence of AEs in the other primary system organ classes was consistent with the SPC.

Adverse Events: overall and frequently affected system organ classes
n (%) of patients >=5%
Safety population

Primary system organ class	Letrozole N= 146 n (%)
Any primary system organ class	90 (61.6%)
Gastrointestinal disorders	16 (11.0%)
General disorders and administration site conditions	20 (13.7%)
Infections and infestations	20 (13.7%)
Musculoskeletal and connective tissue disorders	36 (24.7%)
Nervous system disorders	24 (16.4%)
Psychiatric disorders	9 (6.2%)
Respiratory, thoracic and mediastinal disorders	8 (5.5%)
Skin and subcutaneous tissue disorders	13 (8.9%)
Vascular disorders	23 (15.8%)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

	Novartis product	Comparator
Nasopharyngitis	7 (1.1)	6 (0.9)
Headache	4 (0.6)	4 (0.6)
Influenza	4 (0.6)	4 (0.6)
Diarrhea	4 (0.6)	4 (0.6)
Depression	3 (0.5)	2 (0.3)
Sinusitis	2 (0.3)	2 (0.3)
Bronchitis	2 (0.3)	2 (0.3)
Hypotension	2 (0.3)	2 (0.3)
Palpitations	2 (0.3)	2 (0.3)
Vertigo	2 (0.3)	2 (0.3)

Serious Adverse Events and Deaths

Percentage of patients with SAEs (including death) by preferred term during the treatment period Safety population

Preferred term	Letrozole N= 146 n(%)
Any serious adverse event	15 (10.3%)
Metastases to liver	3 (2.1%)
Myocardial infarction	2 (1.4%)
Aortic stenosis	1 (0.7%)
Arthroscopic surgery	1 (0.7%)
Carpal tunnel syndrome	1 (0.7%)
Cerebral haemorrhage	1 (0.7%)
Cerebrovascular accident	1 (0.7%)
Colon cancer	1 (0.7%)
Dyspnoea	1 (0.7%)
Endometrial cancer	1 (0.7%)
Escherichia sepsis	1 (0.7%)
Hypotension	1 (0.7%)
Polycythaemia	1 (0.7%)
Vaginal haemorrhage	1 (0.7%)

Date of Clinical Trial Report

28 Sept 2011

Date Inclusion on Novartis Clinical Trial Results Database

15 Nov 2011