AstraZeneca

Drug product:	FASLODEX®	**SYNOPSIS**	
Drug substance:	Fulvestrant		
Document No.:			
Edition No.:	Final		
Study code:	D6997C00003 (9238IL/0065)		
Date:	08 September 2008		

A Randomized, Open-label, Multicenter, Phase II Study Comparing the Effects on Proliferation and the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg When Given as Neoadjuvant Treatment in Postmenopausal Women with Estrogen-Receptor-Positive Breast Cancer ($T_{2, 3, 4b}$, N_{0-3}, M_0)

International coordinating investigator

[redacted]

Study center

This study was conducted at 36 centers worldwide.

Publications

[redacted]

Study dates

First subject enrolled 7 February 2005

Last subject completed 9 July 2007

Phase of development

II (Therapeutic exploratory)

Objectives

Primary: To compare the effects of fulvestrant 500 mg and fulvestrant 250 mg on the proliferation marker Ki67 after 4 weeks of treatment.

Secondary: To compare the tolerability of fulvestrant 500 mg with that of fulvestrant 250 mg; to compare the effects of fulvestrant 500 mg and fulvestrant 250 mg on serum bone markers,[1] endometrial thickness, and uterine dimensions; to assess the correlation between changes in Ki67 labeling index (LI) and changes in estrogen-receptor (ER) expression and progesterone-receptor (PgR) expression; to compare the effects of fulvestrant 500 and 250 mg on tumor response assessed by ultrasound; to compare actual surgery performed at 16 weeks with the baseline-predicted feasible surgery for each treatment group; and to correlate response after 16 weeks of treatment with biological endpoints detected after 4 and 16 weeks of treatment.[2]

Study design

This study was a randomized, open-label, Phase II multicenter study in postmenopausal women with newly diagnosed ER-positive (ER+) breast cancer. The study incorporated a screening phase, a treatment phase, a study completion visit at Week 16 (unless treatment discontinuation criteria were met earlier), surgery (mastectomy or breast conserving) for tumor removal, and a follow-up safety visit 8 weeks after surgery or Visit 6 (as applicable). Patients who met study entry criteria were assigned to 1 of 2 randomized treatments: either fulvestrant 500 mg intramuscularly (im) every 28 days, with a supplemental loading dose given on Day 14 (total of 5 doses) or fulvestrant 250 mg im every 28 days (total of 4 doses).

Target patient population and sample size

The targeted population included women with histologically or cytologically confirmed invasive ER+ breast cancer who were postmenopausal as defined by one of the following criterion: (1) ≥60 years old, (2) ≥45 years old with amenorrhea for at least 12 months and an intact uterus, (3) history of bilateral oophorectomy, or (4) estradiol and follicle-stimulating-hormone (FSH) levels in the postmenopausal range (as determined by the testing laboratory). Tumors had to be newly diagnosed and either operable or potentially operable depending on the degree of advancement; the largest tumor diameter had to measure at least 2 cm. (Acceptable TNM classifications were $T_{2, 3, 4b}$, N_{0-3}, M_0.[3]) Patients also had to have a World Health Organization (WHO) performance status of 0, 1, or 2 and be willing to undergo biopsies and surgery as outlined in the protocol. Patients with more than 2 major tumor nodules or metastatic disease and patients previously treated for breast cancer were not eligible for study participation. Additional criteria excluded patients with conditions that could potentially interfere with efficacy evaluations or pose unacceptable health risks.

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[1]Alkaline phosphatase, c-telopeptide of type 1 collagen crosslinks (CTX-1), and procollagen type 1 amino terminal peptide (P1NP)

[2] Secondary objectives to assess the pharmacokinetics of fulvestrant and the relationship between pharmacokinetics markers (ie, area under the curve [AUC] and maximum drug plasma concentration [C_{max}]) and pharmacodynamic markers of downregulation and proliferation, along with exploratory objectives, are addressed in the full clinical study report.

[3]TNM classification characterizes tumor (T) size, nodal (N) involvement, and degree of metastases (M).

Sample size was calculated relative to change in Ki67 LI from baseline to Week 4. Using a standard deviation of 0.616% (taken from earlier Study 0018[4], which looked at pre- and postdose Ki67 LI after a single 250-mg dose of fulvestrant), 80 patients per treatment group were required to provide 80% power to detect a 24% decrease in Ki67 LI at Week 4 for fulvestrant 500 mg relative to fulvestrant 250 mg at a 2-sided 0.05 significance level.

Investigational product: dosage, mode of administration, and batch numbers

Fulvestrant was supplied in a 5% castor-oil-based solution in a clear, neutral-glass, prefilled syringe. Each syringe contained 250 mg of fulvestrant in 5 mL of solution (Formulation No. F006521; Batch Nos. US311015 [UK20115D04], US207005 [UK90308D02], US351043 [UK22588J04]). The 250-mg dosage was administered im as one 5-mL injection into a single buttock. The 500-mg dosage was administered im as two 5-mL injections, one into each buttock.

Duration of treatment

Treatment at each dosage extended across a 16-week period. Patients assigned to the 250-mg dosage received single injections on Days 0, 28, 56, and 84. Patients assigned to the 500-mg dosage received 2 injections on Days 0, 14, 28, 56, and 84. In consultation with AstraZeneca, the international coordinating investigator had the authority to approve up to a maximum of 8 additional weeks of fulvestrant therapy (as randomized) if the investigator believed that additional benefit could be achieved prior to surgery. The full 8 weeks of additional treatment comprised an additional injection at Week 16 (Day 112) and another at Week 20 (Day 140).

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Ki67 LI at Week 4 (change from baseline)
- Secondary variables: changes from baseline in ER index, PgR index, and Ki67 LI (at Weeks 4 and 16); tumor response rate as assessed by changes in tumor volume (per ultrasound); extent of breast surgery; change from baseline in Ki67 LI, ER index, PgR index, and HER-2, by responder status at Week 16; responder status at Week 16 by HER-1 and HER-2 expression at baseline

Safety

Safety was assessed relative to incidences of adverse events (AEs) and AE severity (per National Cancer Institute Common Terminology Criteria [NCI-CTC], Version 3, as applicable); incidences of serious AEs (SAEs), SAEs leading to death, and AEs leading to discontinuation from the study (DAEs); laboratory test results; change from baseline in bone alkaline phosphatase, CTX-1, and P1NP levels over time; changes in vital signs, physical examination results, and WHO performance status; change from baseline in endometrial thickness and uterine dimensions at Week 16 (per transvaginal ultrasound) and change in ovarian abnormalities.

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[4] From an analysis of variance (ANOVA) model with a residual variance of 0.379%.

Statistical methods

All statistical tests were 2-sided, with a significance level of α=0.05; tests were performed using SAS™ (Version 8.2). The intent-to-treat (ITT) data set—the primary population for efficacy analyses—comprised all patients who were randomized. No examination of primary or secondary efficacy variables was done by subgroup (other than that for the per-protocol [PP] analysis set for the primary efficacy variable [Ki67 LI at 4 weeks] and select safety variables). For the primary efficacy variable, the difference between treatment groups was determined using an ANOVA (modeling natural log transformed change from baseline in Ki67 LI at 4 weeks), with treatment included as a factor. Results were back-transformed for presentation purposes. For secondary efficacy variables, statistical methods included use of Pearson's correlation coefficient to assess correlations between Ki67 LI, ER, and PgR in change from baseline, and use of logistic regression for analysis of tumor response rates and improvement rates for extent of surgery at Week 16. An ANOVA model was also used to compare changes from baseline in endometrial thickness for patients with baseline endometrial thickness of ≤5 mm. Change from baseline in uterine volume was analyzed using a paired t-test. A repeated-measure analysis of covariance (ANCOVA) was used to compare changes from baseline in serum bone-turnover markers, with treatment and patients included as class variables and average baseline level included as a continuous covariate. Exploratory analyses to examine change from baseline in ER and PgR indices mirrored those used for the primary efficacy variable.

Patient population

In total, 211 women were enrolled and assigned to treatment with either fulvestrant 500 mg (n=109) or fulvestrant 250 mg (n=102). On overview, patients enrolled with good adherence to the entry criteria and represented the types of patients who present with newly diagnosed disease, having little or no relevant history of skeletal or gynecologic disease. This was reflected in limited prior use of bisphosphonates, corticosteroids, or hormone replacement therapy. Three patients withdrew before starting treatment, and all but 1 of the remaining patients received treatment as assigned. Baseline patient demographics, disease characteristics, and study completion rates were similar between treatment groups (Table S1).

Table S1 Patient population and disposition

Parameter		Treatment group		Total
		Fulvestrant 500 mg (n=109)	Fulvestrant 250 mg (n=102)	Any fulvestrant (N=211)
Demographic characteristics[a]				
Age (years)	Mean (SD)	66.9 (9.78)	66.8 (9.23)	66.8 (9.50)
	Range	47 to 94	47 to 87	47 to 94
Age distribution, No. (%)	<65 years	46 (42.2)	44 (43.1)	90 (42.7)
	≥65 years	63 (57.8)	58 (56.9)	121 (57.3)
Race, No. (%)	White	92 (84.4)	88 (86.3)	180 (85.3)
	Black	5 (4.6)	3 (2.9)	8 (3.8)
	Oriental	1 (0.9)	3 (2.9)	4 (1.9)
	Other[b]	11 (10.1)	8 (7.8)	19 (9.0)
Weight (kg)	Mean (SD)[c]	69.1 (14.67)	65.4 (15.06)	67.3 (14.95)

Table S1 Patient population and disposition

Parameter		Treatment group				Total	
		Fulvestrant 500 mg (n=109)		Fulvestrant 250 mg (n=102)		Any fulvestrant (N=211)	
Baseline characteristics, No. (%) of patients							
Performance status[d]	0	88	(80.7)	84	(82.4)	172	(81.5)
	1 or 2	19	(17.4)	16	(15.7)	35	(16.6)
	3 or 4	0		0		0	
	Missing	2	(1.8)	2	(2.0)	4	(1.9)
ER status	Positive	108	(99.1)	101	(99.0)	209	(99.1)
	Unknown	1	(0.9)	1	(1.0)	2	(0.9)
ER/PgR status	ER+/PgR+	76	(69.7)	72	(70.6)	148	(70.1)
	ER+/PgR–	23	(21.1)	20	(19.6)	43	(20.4)
	ER or PgR unknown	10	(9.2)	10	(9.8)	20	(9.5)
Intact uterus	Yes	87	(79.8)	82	(80.4)	169	(80.1)
	No	16	(14.7)	14	(13.7)	30	(14.2)
	Unknown	6	(5.5)	6	(5.9)	12	(5.7)
Disposition, No. (%) of patients							
Completed study	Yes	91	(83.5)	82	(80.4)	173	(82.0)
	No	18	(16.5)	20	(19.6)	38	(18.0)
Included in analysis set	ITT[e]	109	(100)	102	(100)	211	(100)
	PP[f]	60	(55.0)	61	(59.8)	121	(57.3)
	Safety[g], PK[h]	107	(98.2)	101	(99.0)	208	(98.6)

[a] All patients were women.
[b] Includes unspecified mixed race and parda (Brazilian term for brown people encompassing a mix of ethnic groups).
[c] n=106 patients in the 500-mg treatment group and n=100 patients in the 250-mg treatment group.
[d] World Health Organization criteria.
[e] All patients who were randomized.
[f] Patients who received at least 1 dose of fulvestrant and did not have major violations or deviations relative to protocol requirements.
[g] All patients who received at least 1 dose of fulvestrant.
[h] All patients who received study drug and had at least 1 blood sample, drawn after baseline, with measurable drug levels.
ER Estrogen receptor. ITT Intention to treat. PgR Progesterone receptor. PK Pharmacokinetics. PP Per-protocol.

Efficacy results

Primary: The fulvestrant 500-mg regimen reduced Ki67 LI to a significantly greater extent, compared with fulvestrant 250 mg (mean % change: –78.8% vs –47.4%, respectively, $p<0.0001$) after 4 weeks of treatment. These results were consistent with those seen for the PP analysis set.

Secondary: At Week 16, reduction in Ki67 LI was still greater at the higher dosage (–77.4% and –62.8% for the 500- and 250-mg dosages, respectively) but, in an exploratory analysis, the difference was not statistically significant. Both dosages of fulvestrant reduced ER and PgR expression at Weeks 4 and 16, with greater effects generally seen at the 500-mg dosage. In an exploratory analysis, mean % reduction in ER expression (downregulation) at Week 4 was significantly greater for the 500-mg treatment group, compared with that for the 250-mg treatment group (–25.0% vs –13.5%, $p=0.0002$). Correlations between change from baseline in Ki67 LI and ER index and in Ki67 LI and PgR index were not apparent.

At We ek 4, tumor response rates were numerically greater for patients in the 500-mg treatment group, compared with those in 250-mg treatment group (19.6% and 12.6%, respectively). Although fewer patients were evaluable for response at Week 16, a similar pattern was seen, with response rates of 36.2% and 30.4% for the 500- and 250-mg treatment groups, respectively.

At Week 4, greater percent reductions from baseline in Ki67 LI, ER index, and PgR index were seen for patients classified as responders (per Week 16 ultrasound assessment) in the fulvestrant 500 mg treatment group than in the 250-mg treatment group. At Week 16, a similar pattern was seen, with exception for Ki67 LI, and then median % change was similar in the 2 treatment groups.

Among patients with tumors negative for HER-1 or HER-2 at baseline, greater proportions of patients treated at the 500-mg dose had objective response, compared with patients treated at the 250 mg dose, at both Weeks 4 and 16. Among the small numbers of patients with tumors positive for HER-1 or HER-2 at baseline, few were evaluable for response; thus, between-treatment comparisons were not meaningful.

A numerically greater proportion of patients in the 500-mg treatment group (21.0%) had improved surgical outcomes compared with patients in the 250-mg treatment group (16.9%).

Safety results

Neoadjuvant treatment with fulvestrant 500 mg every 28 days (+supplemental dose on Day 14) or 250 mg every 28 days was generally safe and well tolerated. These aspects were reflected in the limited number of patients (n=2) who withdrew because of AEs (Table S2). These AEs, which included transient ischemic attack and pulmonary embolism in the 500- and 250-mg treatment groups, respectively, were serious (SAEs) but not considered drug related by the investigator. Of 26 patients with SAEs (Table S2), 11 in the 500-mg treatment group and 7 in the 250-mg treatment group had SAEs that occurred beyond the 28-day interval following last fulvestrant injection, with events commonly associated with surgical intervention or complication. One patient died late in the follow-up period of unknown cause.

Table S2 Number (%) of patients with adverse events in any category: safety population

Category	Treatment group		Total
	Fulvestrant 500 mg (n=107)	Fulvestrant 250 mg (n=101)	Any fulvestrant (N=208)
Patients, number (%)[a]			
With any AE	78 (72.9)	70 (69.3)	148 (71.2)
With AEs that led to death	0	1 (1.0)	1 (0.5)
With SAEs other than death	14 (13.1)	12 (11.9)	26 (12.5)
With AEs that led to study withdrawal	1 (0.9)	1 (1.0)	2 (1.0)
With SAEs that led to study withdrawal	1 (0.9)	1 (1.0)	2 (1.0)
With NCI-CTC Grade 3 or 4 AEs	15 (14.0)	12 (11.9)	27 (13.0)

T able S2 Number (%) of patients with adverse events in any category: safety population

Category	Treatment group		Total
	Fulvestrant 500 mg (n=107)	Fulvestrant 250 mg (n=101)	Any fulvestrant (N=208)
With any causally related AE	40 (37.4)	31 (30.7)	71 (34.1)
With causally related AEs that led to death	0	0	0
With causally related SAEs other than death	1 (0.9)	3 (3.0)	4 (1.9)
With causally related AEs that led to withdrawal	0	0	0
With causally related SAEs that led to withdrawal	0	0	0
With causally related NCI-CTC Grade 3 or 4 AEs	1 (0.9)	3 (3.0)	4 (1.9)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
AE Adverse event. NCI-CTC National Cancer Institute's Common Terminology Criteria.
SAEs Serious adverse events.

The most commonly reported AEs among patients in the 500-mg treatment group, namely, injection site pain (15.0%), fatigue (14.0%), hot flush (14.0%), nausea (10.3%), and headache (9.3%), were also reported among patients in the 250-mg treatment group but with less frequency (Table S3). Events more common at the 250-mg dosage included vomiting (7.9%), hypertension (7.9%), and extremity pain (6.9%) (Table S3).

Table S3 Commonly reported adverse events (incidence ≥5% in either treatment group): safety population

MedDRA SOC[ab] MedDRA preferred term[ac]	Number (%) of patients, by treatment	
	Fulvestrant 500 mg (n=107)	Fulvestrant 250 mg (n=101)
Gastrointestinal	**25 (23.4)**	**26 (25.7)**
Diarrhea	6 (5.6)	6 (5.9)
Nausea	11 (10.3)	7 (6.9)
Vomiting	3 (2.8)	8 (7.9)
General & administration site conditions	**41 (38.3)**	**22 (21.8)**
Fatigue	15 (14.0)	5 (5.0)
Injection site pain	16 (15.0)	4 (4.0)
Injection site pruritus	5 (4.7)	1 (1.0)
Peripheral edema	6 (5.6)	5 (5.0)
Pyrexia	7 (6.5)	2 (2.0)
Investigations	**7 (6.5)**	**8 (7.9)**
Increased blood pressure	3 (2.8)	5 (5.0)

Table S3 Commonly reported adverse events (incidence ≥5% in either treatment group): safety population

MedDRA SOC[ab] MedDRA preferred term[ac]	Number (%) of patients, by treatment Fulvestrant 500 mg (n=107)		Fulvestrant 250 mg (n=101)	
Injury, poisoning, & procedural complications	**21**	**(19.6)**	**18**	**(17.8)**
Postoperative wound infection	5	(4.7)	6	(5.9)
Procedural pain	8	(7.5)	5	(5.0)
Musculoskeletal & connective tissue	**20**	**(18.7)**	**20**	**(19.8)**
Back pain	4	(3.7)	6	(5.9)
Pain in extremity	5	(4.7)	7	(6.9)
Neoplasms benign, malignant, & unspecified	**8**	**(7.5)**	**3**	**(3.0)**
Tumor pain	5	(4.7)	3	(3.0)
Nervous system	**23**	**(21.5)**	**17**	**(16.8)**
Headache	10	(9.3)	8	(7.9)
Respiratory, thoracic & mediastinal	**10**	**(9.3)**	**7**	**(6.9)**
Cough	8	(7.5)	4	(4.0)
Vascular	**22**	**(20.6)**	**25**	**(24.8)**
Hot flush	15	(14.0)	10	(9.9)
Hypertension	7	(6.5)	8	(7.9)

[a] MedDRA SOC sorted alphabetically; MedDRA preferred term sorted alphabetically within SOC.
[b] Patients with multiple events in the same SOC are counted only once in that SOC. Patients with events in more than 1 SOC are counted once in each of those categories.
[c] Patients with multiple occurrences of the same event were counted only once per event. Patients with more than 1 type of AE were counted once in each of the relevant AE categories.
MedDRA Medical Dictionary for Regulatory Activities (Version 10). SOC System organ class.

Neoadjuvant treatment with fulvestrant (over an average of 108 to 109 days) produced marginal to small mean changes from baseline in bone-specific alkaline phosphatase, CTX-1, and P1NP, none of which were suggestive of clinically important changes in bone structure or function. Mean changes from baseline in blood pressure and heart rate in both treatment groups were unremarkable. No changes in hematology or clinical chemistry variables, bone-turnover markers, or vital signs resulted in patient withdrawal from the study. Shifts from baseline in WHO performance status were uncommon, with the majority of patients unchanged from baseline status at each assessment point. Neoadjuvant treatment with fulvestrant resulted in small mean changes (decreases) from baseline in endometrial thickness at Week 16 that were not clinically relevant when considered across the population studied. These results and those for changes in bone-turnover markers were consistent with results reported to the EMEA on 7 June 2007.

Conclusions

- [redacted]

Date of the report

08 September 2008