AstraZeneca

Drug Product	Faslodex	**SYNOPSIS**	
Drug Substance	ZD9238 (Fulvestrant)		
Study Code	D6995C00006		
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A Randomised, Open-Label, Parallel-Group, Multi-centre, Phase II Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Anastrozole (ARIMIDEX™) 1 mg as First Line Hormonal Treatment for Postmenopausal Women with Hormone Receptor Positive Advanced Breast Cancer

Study centre(s)

This study was conducted at 62 centres in 9 countries (Brazil, Bulgaria, Czech Republic, France, Italy, Poland, Spain, UK and the USA).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	06 February 2006	Phase II (therapeutic exploratory)
Last patient enrolled	11 July 2007	
Analysis data cut-off	10 January 2008	

Objectives

The primary objective of this study was to compare the clinical benefit rate in patients treated with fulvestrant 500 mg with the clinical benefit rate in patients treated with anastrozole 1 mg.

Secondary objectives for this study were:

- To compare the objective response rate of patients treated with fulvestrant 500 mg with the objective response rate of patients treated with anastrozole 1 mg.
- To compare the time to progression of patients treated with fulvestrant 500 mg with the time to progression of patients treated with anastrozole 1 mg.
- To describe the duration of response of patients treated with fulvestrant 500 mg and the duration of response of patients treated with anastrozole 1 mg.
- To describe the duration of clinical benefit of patients treated with fulvestrant 500 mg and the duration of clinical benefit of patients treated with anastrozole 1 mg.
- To assess the safety and tolerability of fulvestrant 500 mg treatment compared with anastrozole 1 mg treatment.

Exploratory objectives for this study were:

- To explore the best overall response to the first subsequent systemic breast cancer therapy for patients randomised to fulvestrant 500 mg and patients randomised to anastrozole 1 mg.
- To evaluate subsequent clinical outcome in patients demonstrating changes in serum tumour markers for patients randomised to fulvestrant 500 mg and patients randomised to anastrozole 1 mg.

These exploratory objectives are not addressed in detail in this report.

Study design

This was a randomised, open-label, parallel-group, multi-centre, phase II study comparing the efficacy and tolerability of fulvestrant 500 mg with 1 mg anastrozole as first line hormonal treatment for postmenopausal women with hormone receptor positive advanced breast cancer.

Target patient population and sample size

The target population was postmenopausal women presenting with advanced disease who had either never received hormonal treatment for advanced disease or had received previous hormonal treatment for early breast cancer, which was completed at least 12 months prior to randomisation into the study. The study was open to patients with measurable disease (as per RECIST [response evaluations criteria in solid tumours]) or patients with non-measurable disease, provided those patients had at least one lytic bone lesion.

The primary end-point was clinical benefit rate. The clinical benefit rate for anastrozole in hormone receptor positive patients is estimated as 60% from previous studies of anastrozole in the current patient population (Studies 1033IL/0027 and 1033IL/0030).

One-hundred randomised patients per treatment group, were required to give 80% power to rule out an absolute deficiency of 20% in clinical benefit rate for fulvestrant 500 mg; ie, 2-sided 95% confidence interval to exclude a 20% deficiency.

Investigational product and comparator(s): dosage and mode of administration

Fulvestrant (ZD9238, FASLODEX™) 500 mg was administered as two 5 ml intramuscular injections on Days 0, 14 (±3), 28 (±3) and every 28 (±3) days thereafter with time windows extending to ±7 days after 24 weeks.

Anastrozole (ARIMIDEX™) 1 mg was administered orally as a single daily tablet.

Duration of treatment

Treatment continued until disease progression as per RECIST, unless any of the criteria for treatment discontinuation were met first.

Criteria for evaluation (main outcome variables)

Efficacy

- Primary outcome variable: clinical benefit rate (% of patients in the full analysis set with clinical benefit), where clinical benefit is defined as complete response, partial response or stable disease ≥24 weeks, defined by modified RECIST*.

- Secondary outcome variables: objective response rate (% of patients in the Evaluable for Response analysis set with an objective response), where objective response is defined as complete response or partial response, defined by RECIST. Other secondary outcome variables were time to progression, duration of response and duration of clinical benefit.

Safety

- Frequency and severity of adverse events as assessed by Common Terminology Criteria (CTC) grade and laboratory assessments.

* Modified RECIST relates to patients with non-measurable disease only who had metastatic bone disease with a lytic component. For these patients the only allowable responses were stable disease or progression.

Statistical methods

The primary outcome variable of clinical benefit rate was compared in the two treatment arms by absolute difference, and an odds ratio with associated 95% confidence intervals and p-value. The same statistical methods were used for the secondary outcome variable of objective response rate. Time to progression was compared in the two treatment arms using a hazard ratio with associated 95% confidence intervals and p-value.

Patient population

Table S1 summarises the patient disposition and the number of patients in each of the defined analysis sets for the study.

Table S1 Summary of patient disposition and analysis sets

	Number of patients		
	Fulvestrant 500 mg	**Anastrozole 1 mg**	**Total**
Disposition			
Patients enrolled			233
Patients randomised	102	103	205
Patients who received treatment	101	103	204
Patients ongoing any study treatment at data cut-off	64	53	117
Analysis sets			
Full analysis set	102	103	205
Per Protocol analysis set	99	99	198
Safety analysis set	101	103	204
Evaluable for Response analysis set	89	93	182

A total of 205 patients were randomised and included in the full analysis set, with 102 patients randomised to receive fulvestrant and 103 patients randomised to receive anastrozole. Of those patients randomised, 204 went on to actually receive treatment and were included in the safety analysis set for the study.

A total of 198 patients had no major protocol deviations at the time of data cut-off and were included in the per-protocol analysis set.

A total of 182 patients had measurable disease (as defined by RECIST) at baseline and were assessable for objective response. This subset of the full analysis set made up the Evaluable for Response analysis set.

In all, 37.3% (38/102) of treated patients withdrew from treatment in the fulvestrant arm and 48.5% (50/103) withdrew from treatment in the anastrozole arm during the study up to the time of data cut-off for the primary analysis.

At the point of data cut-off 62.7% (64/102) patients randomised to fulvestrant were still receiving treatment. This is compared to 51.5% (53/103) of patients who had been randomised to anastrozole. The main reason for discontinuation of treatment prior to the data cut-off was disease progression. In the fulvestrant arm 27.5% (28/102) of patients discontinued treatment due to disease progression, compared with 36.9% (38/103) of patients in the anastrozole arm.

Table S2 summarises the demography and baseline characteristics at entry for patients in the full analysis set.

Table S2 Demography and baseline characteristics at entry in the full analysis set

Demographic/Baseline characteristic	**Fulvestrant 500 mg (N=102)**		**Anastrozole 1 mg (N=103)**	
Age (years)				
Mean (SD)	66.6	(9.0)	67.6	(9.3)
Median	66		68	
Range	40 to 89		48 to 87	
Race (n [%])				
Caucasian	97	(95.1)	102	(99.0)
Black	3	(2.9)	0	
Other	2	(2.0)	1	(1.0)
Prior hormonal treatment [a] (n [%])				
No prior hormonal treatment	73	(71.6)	80	(77.7)
Completed hormonal treatment ≤12 months prior to randomisation	1	(1.0)	0	
Completed hormonal treatment >12 months prior to randomisation	28	(27.5)	23	(22.3)
Prior chemotherapy[a] (n [%])				
No prior chemotherapy	73	(71.6)	78	(75.7)
Received adjuvant chemotherapy	29	(28.4)	25	(24.3)

Table S2 Demography and baseline characteristics at entry in the full analysis set

Demographic/Baseline characteristic	Fulvestrant 500 mg (N=102)		Anastrozole 1 mg (N=103)	
ER and PgR receptor status (n [%])				
Hormone receptor positive	102	(100.0)	103	(100.0)
ER +ve, PgR +ve	78	(76.5)	78	(75.7)
ER +ve, PgR –ve	19	(18.6)	19	(18.4)
ER +ve, PgR unknown	1	(1.0)	3	(2.9)
ER –ve, PgR +ve	3	(2.9)	3	(2.9)
ER unknown, PgR +ve	1	(1.0)	0	
HER 2 receptor status, by IHC (n [%])				
2+/3+	19	(18.6)	19	(18.4)
Negative	48	(47.1)	49	(47.6)
Unknown	35	(34.3)	35	(34.0)
Disease stage (n [%])				
Locally advanced only	19	(18.6)	18	(17.5)
Metastatic	83	(81.4)	85	(82.5)
Measurable disease				
Yes	89	(87.3)	93	(90.3)
No	13	(12.7)	10	(9.7)
Disease sites at baseline				
Bone only	10	(9.8)	8	(7.8)
Skin/soft tissue only	1	(1.0)	0	
Breast only	1	(1.0)	0	
Any visceral disease	48	(47.1)	58	(56.3)
- any liver	15	(14.7)	14	(13.6)
- any lung	30	(29.4)	42	(40.8)

N: Number of patients; SD: Standard deviation; ER: Oestrogen receptor; PgR: Progesterone receptor.
[a] Previous to study treatment.

Overall, the treatment arms were well balanced with respect to demographic and baseline characteristics.

Patients who participated in this study were considered to be representative of a first line population of postmenopausal women with hormone receptor positive advanced breast cancer.

Efficacy results

A summary of the efficacy data is given in Table S3.

Table S3 Summary of efficacy results for the main outcome variables

Variable	Result	Analysis
Primary outcome variable		
CBR	CBR for fulvestrant 500 mg =72.5% CBR for anastrozole 1 mg =67.0%	Odds ratio = 1.302 (95%: CI: 0.717, 2.380)[a] p-value = 0.386 Absolute difference = 5.6%[b] (95% CI: –7.8%, 15.8%)
Secondary outcome variables		
ORR	ORR for fulvestrant 500 mg =36.0% ORR for anastrozole 1 mg =35.5%	Odds ratio = 1.021 (95% CI: 0.556, 1.874)[a] p-value = 0.947 Absolute difference = 0.5%[b] (95% CI: –12%, 15.2%)
TTP[c]	Median TTP for fulvestrant 500 mg =Not reached Median TTP for anastrozole 1 mg =381 days.	Hazard ratio = 0.6266 (95% CI: 0.3929, 0.9991)[d] p-value = 0.0496
DoR	Median DoR for fulvestrant 500 mg =Not reached (from first response) =Not reached (from randomisation) Median DoR for anastrozole 1 mg =337 days (from first response) =433 days (from randomisation)	N/A
DoCB	Median DoCB for fulvestrant 500 mg = Not reached Median DoCB for anastrozole 1 mg = Not reached	N/A

CBR: Clinical benefit rate; ORR: Objective response rate; TTP: Time to progression; DoR: Duration of response; DoCB: Duration of clinical benefit; CI: Confidence interval; N/A: Not applicable.

[a] An odds ratio >1 favours fulvestrant

[b] Conditioned on the anastrozole arm.

[c] TTP ≡ progression free survival.

[d] A hazard ratio <1 favours fulvestrant.

Analysis of the efficacy data indicate that:

- The clinical benefit rates for the fulvestrant and anastrozole arms were 72.5% (74/102) and 67.0% (69/103), respectively. Comparison of the clinical benefit rates of the two treatment arms gives an odds ratio of 1.302 (95% CI: 0.717, 2.380), with a p-value of 0.386.

- The absolute difference in the clinical benefit rates (fulvestrant minus anastrozole) was 5.6% (95% CI: -7.8% to 15.8%).

- For the primary endpoint of clinical benefit rate, the concordance between the local investigator read and the blinded independent review was high (88.4% in the fulvestrant arm compared to 86.3% in the anastrozole arm). The clinical benefit rates from the blinded independent review (69.5%for fulvestrant, 66.3% for anastrozole) were similar to the clinical benefit rates obtained by the local investigator read (72.5% and 67%, respectively). The blinded independent review corroborates the primary analysis.

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objective response rate obtained with anastrozole 1 mg (35.5%).

- Treatment with fulvestrant 500 mg results in a significantly longer time to progression compared to treatment with anastrozole 1 mg (hazard ratio = 0.6266 [95% CI: 0.3929, 0.9991], p-value = 0.0496). Fewer progression events were detected by blinded independent review on each treatment arm, compared to the local investigator read, but there was still a numerical difference in favour of fulvestrant 500 mg (24/95 [25%] on fulvestrant 500 mg versus 27/95 [28%] on anastrozole 1 mg).

Safety results

Analysis of the safety data indicate that

- There were no significant differences between the two treatment arms for any of the individual pre-specified AE categories. A higher number of events describing joint disorders were observed in the fulvestrant 500 mg arm. Although this difference was not statistically significant, these events are known to be associated with anastrozole and therefore the clinical relevance of this will be evaluated in future ongoing studies.

- In total there were 11 patient deaths during the study, with fewer deaths in the fulvestrant treatment arm compared to the anastrozole treatment arm (4 deaths

[4.0%] vs 7 deaths [6.8%], respectively). The majority of the patient deaths were due to disease progression.

- One patient, in the anastrozole treatment arm, died following an adverse event (death, the cause unknown to the investigator). The adverse event leading to death was not considered to be treatment-related by the investigator.

- The incidence of serious adverse events with an outcome other than death was low in both treatment arms and similar between treatment arms (11.9% [12/101] in the fulvestrant arm compared to 8.7% [9/103] in the anastrozole arm).

- The incidence of discontinuations due to an adverse event was low and well balanced between the two treatment arms (3 patients [3.0%] in the fulvestrant arm and 3 patients [2.9%] in the anastrozole arm).

- There were no clinically relevant laboratory findings. The clinical laboratory data were consistent with the patient population and disease under investigation.

Date of the report

19 June 2008