Clinical Study Report Synopsis

Drug Substance	Fulvestrant
Study Code	D6997C00002
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A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

Study dates: First patient randomised: 08 February 2005
Last patient randomised: 31 August 2007
Data cut-off for primary analysis: 28 February 2009

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centres

One-hundred and twenty-eight centres in 17 countries (Belgium, Brazil, Chile, Colombia, Czech Republic, Hungary, India, Italy, Malta, Mexico, Poland, Russia, Slovakia, Spain, USA, Ukraine and Venezuela). The US, Mexico, Italy, Brazil, Spain, Chile, Colombia and Venezuela also participated in health-related quality of life (HRQoL) assessments during the study.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression (TTP).

The secondary objectives of the study were:

- To compare the objective response rate (ORR) of patients treated with fulvestrant 500 mg with the objective response rate of patients treated with fulvestrant 250 mg.
- To compare clinical benefit rate (CBR) of patients treated with fulvestrant 500 mg with the clinical benefit rate of patients treated with fulvestrant 250 mg.
- To compare duration of response (DoR) of patients treated with fulvestrant 500 mg with the duration of response of patients treated with fulvestrant 250 mg.
- To compare the duration of clinical benefit (DoCB) of patients treated with fulvestrant 500 mg with the duration of clinical benefit of patients treated with fulvestrant 250 mg.
- To compare the overall survival (OS) of patients treated with fulvestrant 500 mg with the overall survival of patients treated with fulvestrant 250 mg.
- To assess the tolerability of fulvestrant 500 mg treatment compared with fulvestrant 250 mg treatment.
- To assess the health-related quality of life (HRQoL) of patients treated with fulvestrant 500mg as compared to fulvestrant 250 mg in a subgroup of patients.

Study design

This was a randomised, double-blind, parallel-group, multicentre, phase III study to compare 2 dose levels of fulvestrant in postmenopausal women with oestrogen receptor

positive (ER+ve) advanced breast cancer who had either relapsed whilst on adjuvant endocrine therapy, or progressed whilst on first endocrine therapy for advanced disease.

Target patient population and sample size

A total of 720 postmenopausal women with histological/cytological confirmation of ER+ve breast cancer who had relapsed or progressed on previous endocrine therapy were planned to be recruited; a total of 736 were actually randomised.

The sample size calculation was based on the primary variable, TTP, and assumed exponential progression times. The sample size was driven by the number of required events. In order to detect a hazard ratio of ≤0.8 (or ≥1.25) for fulvestrant 500 mg compared to fulvestrant 250 mg, at a 2-sided significance level of 5%, with 80% power, approximately 632 events were required to have occurred in the study (ie, approximately 632 patients to have progressed or died).

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

Fulvestrant 500 mg was given as two 5 ml intramuscular (im) injections, one in each buttock, on days 0, 14, 28 and every 28 (±3) days thereafter. Batch numbers are listed in Appendix 12.1.6 of the CSR.

Fulvestrant 250 mg was given as two 5 ml im injections (1 fulvestrant injection plus 1 placebo injection), one in each buttock, on days 0, 14 (2 placebo injections only), 28 and every 28 (±3) days thereafter. Batch numbers are listed in Appendix 12.1.6 of the CSR.

Duration of treatment

Treatment was to continue until disease progression occurred, unless any of the criteria for treatment discontinuation were met first.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Efficacy

The primary outcome variable TTP; secondary variables were ORR, CBR, DoR, DoCB and OS.

Patient reported outcomes

The primary patient reported outcome for HRQoL was the Trial Outcome Index (TOI) derived from the Functional Assessment of Cancer Therapy - Breast cancer (FACT-B) questionnaire.

Criteria for evaluation - safety (main variables)

Outcome variables for safety were frequency and severity of adverse events (AEs), including pre-specified AEs of interest.

Statistical methods

For the primary endpoint TTP, the primary analysis was an unadjusted log-rank test and the secondary analysis was a Cox proportional hazard model, adjusted for treatment and other predefined covariates.

For OS, the unadjusted log-rank test was performed. For ORR and CBR, a logistic regression model with treatment factor only was fitted. DoR and DoCB were analysed in those patients who had an OR and CB, respectively. For HRQoL endpoints, a longitudinal model with treatment and other covariates was used.

The hypotheses for TTP, ORR, CBR, DoR, DoCB, OS, FACT-B score and TOI score were:

H_0: fulvestrant 500 mg is not different from fulvestrant 250 mg, vs.

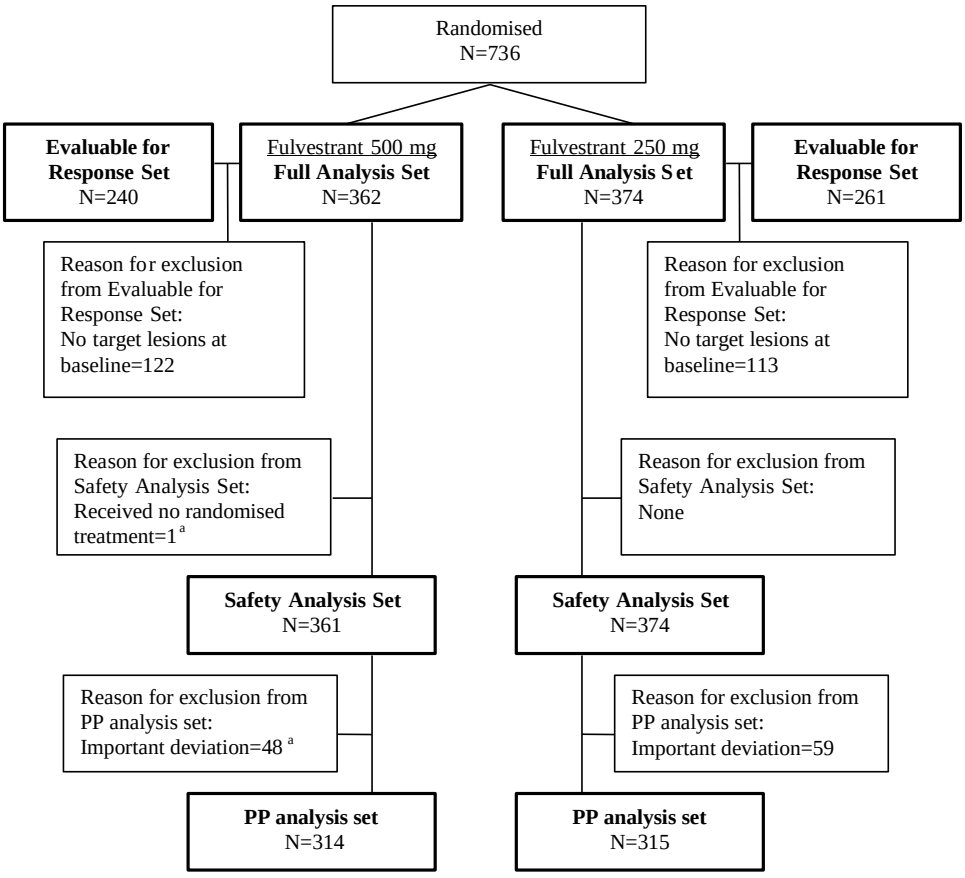
H_1: fulvestrant 500 mg is different from fulvestrant 250 mg

For efficacy and HRQoL endpoints, summaries and analyses were carried out according to the randomised treatment ie, using the Full Analysis Set. For safety endpoints, summaries and analyses were carried out according to the treatment actually received, ie, using the safety analysis set. The primary endpoint was also analysed in the per protocol set (PPS).

Patient population

A total of 720 patients were planned to be recruited; 736 were actually randomised. Figure S1 shows the number of patients randomised to each of the 2 treatment groups and the number in each of the populations analysed. In addition, HRQoL was analysed in 145 of the patients in the Full Analysis Set (72 patients in the fulvestrant 500 mg group and 73 patients in the fulvestrant 250 mg group). The patient population was consistent with the one intended to be recruited. In the fulvestrant 500 mg group, 41 patients were ongoing study treatment at data cut off (DCO) compared with 31 patients in the fulvestrant 250 mg group.

Figure S1 Analysis sets



[a] The patient who was excluded from the safety analysis set was also classified as a deviator, therefore these n values are not mutually exclusive.

Summary of demographics and baseline characteristics

A total of 96.1% of patients randomised into the study were Caucasian. The mean age of patients was 60.9 years and the mean weight of patients was approximately 70 kg.

Tumour characteristics were well balanced across the 2 treatment groups. Most patients (507 [68.9%]) were ER+ve and PgR+ve at primary diagnosis and almost all patients (721 [98%]) had metastatic disease at baseline. In this study, 42.5% of patients had relapsed or progressed on AI therapy and 57.5% had relapsed or progressed on AOs. Most patients had relapsed or progressed either during previous adjuvant endocrine cancer therapy (344 patients [46.7%]) or during endocrine therapy given as a first treatment for *de novo* advanced disease (255 patients [34.6%]). Approximately two thirds of patients had shown a response[1] to their last endocrine therapy.

[1] Defined as patients who experienced recurrence after ≥2 years on adjuvant endocrine therapy and/or patients who received clinical benefit (CR, PR or SD ≥24 weeks) from first-line therapy for advanced disease.

Summary of efficacy results

A summary of efficacy data is presented in Table S1.

Table S1 Summary of efficacy results for the main outcome variables

Variable	Result
Primary outcome variable	
TTP[a]	Hazard ratio=0.80 (95% CI 0.68–0.94); p=0.006
	Median TTP: fulvestrant 500 mg =6.5 months; fulvestrant 250 mg =5.5 months
	% patients progression free at 12 months: fulvestrant 500 mg=34%; fulvestrant 250 mg = 25%
Secondary outcome variables	
ORR	Odds ratio=0.94 (95% CI 0.57–1.55); p=0.795
	ORR: fulvestrant 500 mg=13.8%; fulvestrant 250 mg=14.6%
CBR	Odds ratio=1.28 (95% CI 0.95–1.71); p=0.100
	CBR: fulvestrant 500 mg=45.6%; fulvestrant 250 mg=39.6%
DoR[b]	Ratio of EDoR=0.894 (95% CI 0.479–1.667); p=0.724
	Median DoR[c]: fulvestrant 500 mg=19.4 months; fulvestrant 250 mg=16.4 months
DoCB	Ratio of EDoCB=1.357 (95% CI 1.067–1.726); p=0.013
	Median DoCB: fulvestrant 500 mg=16.6 months; fulvestrant 250 mg=13.9 months
OS	Hazard ratio=0.84 (95% CI 0.69–1.03); p=0.091
	Median OS: fulvestrant 500 mg=25.1 months; fulvestrant 250 mg=22.8 months
	% patients alive at 24 months: fulvestrant 500 mg=53%; fulvestrant 250 mg=49%

[a] TTP ≡ progression-free survival. At data cut-off, 84% of patients had progressed or died in the absence of progression.
[b] measured from randomisation to progression
[c] from randomisation.

TTP:time to progression; ORR:objective response rate; CBR:clinical benefit rate; DoR:duration of response; DoCB:duration of clinical benefit; OS:overall survival; EDoR:expected duration of response; EDoCB:expected duration of clinical benefit.

Fulvestrant 500 mg was associated with a significantly longer TTP compared with fulvestrant 250 mg (hazard ratio=0.80 [95% CI 0.68–0.94]; p=0.006) corresponding to a reduction in risk of progression of 20%. Subgroup analyses showed a consistent treatment effect across all 6 predefined baseline covariates, including patients treated previously with either an aromatase inhibitor (AI) or antioestrogen (AO).

The ORR for fulvestrant 500 mg and fulvestrant 250 mg were similar (13.8% and 14.6% respectively, odds ratio=0.94 [95% CI 0.57 to 1.55]; p=0.795) but there was a trend for an increased CBR in patients receiving fulvestrant 500 mg compared to those receiving fulvestrant 250 mg (45.6% vs. 39.6%, odds ratio=1.28 [95% CI 0.95 to 1.71]; p=0.100).

There was no statistically significant difference between the 2 treatment groups in expected DoR (EDoR); however, there was a statistically significant improvement in expected DoCB (EDoCB) in patients randomised to receive fulvestrant 500 mg compared with patients randomised to receive fulvestrant 250 mg (9.83 months vs. 7.24 months, ratio of EDoCB=1.357 [95% CI 1.067 to 1.726]; p=0.013).

There was a trend for improved survival for patients treated with fulvestrant 500 mg compared with fulvestrant 250 mg (hazard ratio=0.84 [95% CI 0.69 to 1.03]; p=0.091); this corresponds to a 16% reduction in risk of death.

In the subgroup of patients where it was measured, on-treatment HRQoL for both fulvestrant 500 mg and fulvestrant 250 mg was good (mean TOI score of approximately 60 out of 92). Patients treated with fulvestrant 500 mg had a similar on-treatment HRQoL to patients treated with fulvestrant 250 mg and there were no statistically significant differences between the 2 treatment groups in terms of change in on treatment HRQoL as measured by both the TOI and FACT-B score, although there was a numerical advantage in TOI in favour of fulvestrant 500 mg.

Summary of safety results

Fulvestrant 500 mg was well tolerated and its safety profile was consistent with the known safety profile of fulvestrant 250 mg. The most commonly reported pre-specified AEs of interest were gastrointestinal disturbances and joint disorders (approximately 20% and 19% of patients, respectively, in each of the treatment groups). There were no differences between treatment groups in the incidence or type of AEs, serious AEs and AEs leading to discontinuation. There was no evidence for dose dependence for any AE. There were no clinically important changes in haematology, clinical chemistry, vital signs or physical findings.