Clinical Study Report Synopsis

Drug Substance	Fulvestrant (ICI 182,720)
Study Code	D6997C00004 (9238IL0066)
Edition Number	1
Date	12 November 2008

A Randomised, Double-blind, Parallel-group, Multicentre, Phase II Study to Evaluate the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 250 mg, Fulvestrant (FASLODEX™) 250 mg (plus 250 mg Loading regimen) and Fulvestrant (FASLODEX™) 500 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

Study dates: First patient randomised: 7 March 2006
Last patient randomised: 4 September 2007
Data cut-off for primary analysis: 19 March 2008

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

This study was conducted at 43 centres in Japan and patients were recruited from 40 of the 43 centres.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to evaluate the objective response rate (ORR) of patients treated with fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg.

The secondary objectives of this study were as follows:

- To estimate the pharmacokinetic characteristics of fulvestrant in patients treated with fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg by measuring C_{max}, Clearance and Volume of distribution at steady state.
- To evaluate the efficacy of fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg treatment in terms of time to progression (TTP).
- To evaluate the clinical benefit rate (CBR) of patients treated with fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg.
- To evaluate the duration of response (DoR) in patients treated with fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg.
- To assess the tolerability of fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg by adverse events (AEs), safety clinical laboratory tests and vital signs, electrocardiogram and physical examination.

Study design

This was a randomised, double-blind, parallel-group, multicentre study. Eligible patients were randomised 1:1:1 to receive either fulvestrant 250 mg; fulvestrant 250mg (plus 250 mg loading regimen), referred to hereafter as fulvestrant 250 mg + LD; or fulvestrant 500 mg.

Target population and sample size

The target population was postmenopausal women with oestrogen receptor (ER) positive advanced breast cancer who had either: relapsed whilst on adjuvant endocrine therapy; or progressed whilst on first endocrine therapy for advanced disease; or who had recurrent disease within 12 months after completion of adjuvant therapy.

Forty-five patients per treatment arm (a total of 135 patients) were needed to provide ≥90% probability that the best dose regimen would be correctly selected, assuming a lowest objective response rate of 19.2% in the fulvestrant 250 mg arm.

A total of 143 patients were randomised into the study.

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

Fulvestrant 250 mg dose

Fulvestrant 250 mg was given as two 5 ml intramuscular injections (1 fulvestrant injection + 1 placebo injection), one in each upper lateral quadrant of the buttock, on days 0, 28 (± 3) and every 28 (± 3) days. Additional 2 placebo injections were given on Day 14 (± 3). Time windows extended to ± 7 days after 24 weeks.

Fulvestrant 250 mg + LD dose

An initial dose of 500 mg (2 fulvestrant injections) was given on Day 0, followed by 250 mg (1 fulvestrant injection and 1 placebo injection) on Days 14 (±3), 28 (±3) and every 28 (±3) days. Time windows extended to ± 7 days after 24 weeks.

Fulvestrant 500 mg dose

Fulvestrant 500 mg was given as two 5 ml intramuscular injections (2 fulvestrant injections), one in each upper lateral quadrant of the buttock, on days 0, 14 (± 3), 28 (± 3) and every 28 (± 3) days. Time windows extended to ± 7 days after 24 weeks.

Duration of treatment continued until disease progression or until any other criterion for treatment discontinuation were met.

Criteria for evaluation - efficacy and pharmacokinetics

- Primary outcome variable for efficacy: ORR
- Secondary outcome variables for efficacy: TTP, CBR, DoR
- Secondary outcome variables for pharmacokinetics: C_{max}, Clearance (CL/F), Volume of distribution at steady state (Vd_{ss}/F)

Criteria for evaluation – safety

- Outcome variables for safety: AEs (and their severity), clinical laboratory tests (haematology, clinical chemistry), vital signs, electrocardiogram (ECG) and physical examination

Statistical methods

Point estimates and the corresponding two-sided 95% confidence intervals (CIs) for ORR and CBR were calculated for each treatment group. TTP and DoR were summarised using the Kaplan-Meier method.

The primary analysis was performed when all patients, except withdrawals, had been followed up for at least 24 weeks.

Patient population

In total 143 patients were randomised in the study from 40 centres in Japan. The data cut-off for primary analysis presented in this document was 19 March 2008.

Overall 69.2% (99/143) of study patients discontinued study treatment (68.9% [31/45] in the 250 mg arm, 66.7% [34/51] in the 250 mg + LD arm and 72.3% [34/47] in the 500 mg arm). One of the patients who discontinued from the fulvestrant 500 mg treatment arm did so due to incorrect enrolment and so didn't actually receive the investigational product. The main reason for discontinuation of study treatment prior to the data cut-off was disease progression.

Demographic and baseline characteristics are summarised in Table S1. All randomised patients were Japanese female and ER positive. Demographic and baseline characteristics were similar among the three treatment arms with no major discrepancies between the three treatment arms.

Table S1 Demographic and baseline characteristics: Full Analysis Set

Demographic and baseline characteristics	250 mg (n=45)	250 mg + LD (n=51)	500 mg (n=47)	Total (n=143)
Sex (n [%])				
Female	45 (100.0)	51 (100.0)	47 (100.0)	143 (100.0)
Age (year)				
Median	61	62	61	61
Range	50 to 77	43 to 86	45 to 83	43 to 86
Weight (kg)			N=46	N=142
Median	55	54	52	54
Range	41 to 78	39 to 76	39 to 73	39 to 78
WHO performance status (n [%])				
0	39 (86.7)	44 (86.3)	40 (85.1)	123 (86.0)
1	6 (13.3)	6 (11.8)	7 (14.9)	19 (13.3)
2	0	1 (2.0)	0	1 (0.7)
Oestrogen receptor status (n [%])				
Positive	45 (100.0)	51 (100.0)	47 (100.0)	143 (100.0)
Progesteron receptor status				
Positive	32 (72.1)	36 (70.6)	30 (63.8)	98 (68.5)
Negative	13 (28.9)	15 (29.4)	17 (36.2)	45 (31.5)
Her-2 receptor status [a]				

Table S1 Demographic and baseline characteristics: Full Analysis Set

Demographic and baseline characteristics	250 mg (n=45)	250 mg + LD (n=51)	500 mg (n=47)	Total (n=143)
Positive	6 (13.3)	1 (2.0)	7 (14.9)	14 (9.8)
Negative	36 (80.0)	50 (98.0)	40 (85.1)	126 (88.1)
Unknown	3 (6.7)	0	0	3 (2.1)
Tumour grade				
Grade 1	6 (13.3)	5 (9.8)	3 (6.4)	14 (9.8)
Grade 2	20 (44.4)	19 (37.3)	18 (38.3)	57 (39.9)
Grade 3	7 (15.6)	12 (23.5)	13 (27.7)	32 (22.4)
Not assessable	1 (2.2)	0	3 (6.4)	4 (2.8)
Unknown	11 (24.4)	15 (29.4)	10 (21.3)	36 (25.2)
Metastatic status				
Locally advanced breast cancer only	1 (2.2)	2 (3.9)	0	3 (2.1)
Metastatic disease	44 (97.8)	49 (96.1)	47 (100.0)	140 (97.9)
Visceral involvement [b]				
No	19 (42.2)	23 (45.1)	20 (42.6)	62 (43.4)
Yes	26 (57.8)	28 (54.9)	27 (57.4)	81 (56.6)

a HER-2 status is positive if "FISH result was positive" or "FISH test was not performed and IHC result is 3+". Otherwise, HER-2 status is negative.
b Visceral includes patients with disease site at baseline of adrenal, bladder, CNS, colorectal, oesophagus, liver, lung, peritoneum, pleura, renal, small bowel, stomach, pancreas or thyroid.

Previous radiotherapy (received by 48/143 patients [33.6%]), chemotherapy (received by 95/143 patients [66.4%]) and hormonal therapy (received by all patients) were similar with no major discrepancies among the three treatment regimens.

The proportion of patients in each of the relapse categories was similar across the 3 treatment arms with 63/143 patients (44.1%) having relapsed during adjuvant endocrine therapy.

Summary of efficacy results

Summary of efficacy results are presented in the Table S2

The ORR as primary efficacy variable was similar across the three treatment regimens. The ORR was numerically higher in the 250 mg + LD regimen (17.6%, 95% confidence interval[CI]: 8.4 - 30.9%) than other treatment regimens (11.1%, 95% CI: 3.7 - 24.1% in 250 mg regimen, 10.6%, 95% CI: 3.5 - 23.1% in 500 mg regimen) although the CIs of all 3 treatment groups overlapped. In the secondary analysis by per-protocol set, similar results to the full analysis set were obtained.

The TTP was similar across the three treatment regimens (median TTP was 6.0 months in the 250 mg regimen, 7.5 months in the 250 mg + LD regimen, 6.0 months in the 500 mg regimen). The TTP as seen in Kaplan-Meier curves (Figure S1) was similar across the three treatment regimens. Event rate of progression was also similar across the three treatment regimens (66.7% in the 250 mg regimen, 60.8% in the 250 mg + LD regimen, 66.0% in the 500 mg regimen).

The CBR was similar across the three treatment regimens. The CBR was numerically higher in the 250 mg + LD regimen (54.9%, 95% CI: 40.3 - 68.9%) than other treatment regimens (42.2%, 95% CI: 27.7 - 57.8% in 250 mg regimen, 46.8%, 95% CI: 32.1 - 61.9% in 500 mg regimen) although the CIs of all 3 treatment groups overlapped.

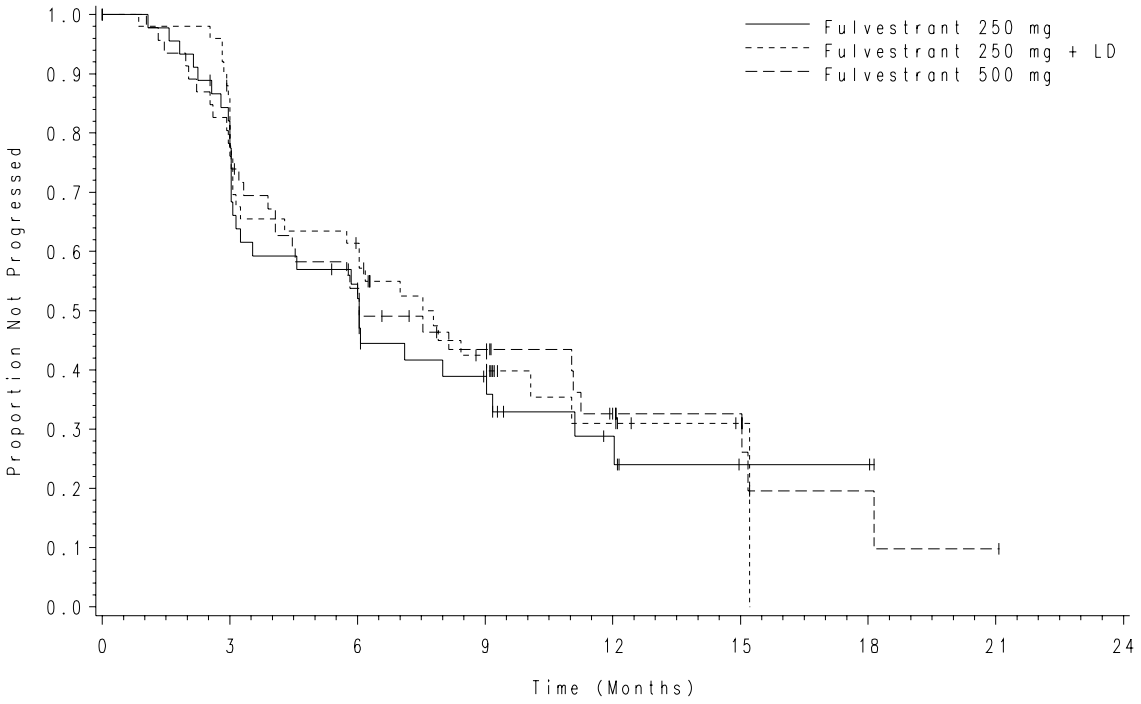
The number of responders was insufficient to assess DoR in each treatment regimen.

Table S2 Summary of efficacy results

Efficacy variables	250 mg N=45	250 mg + LD N=51	500 mg N=47	Total N=143
Objective response rate (FAS)				
Total (%) [95% CI]	5 (11.1) [3.7 - 24.1]	9 (17.6) [8.4 - 30.9]	5 (10.6) [3.5 - 23.1]	19 (13.3) [8.2 - 20.0]
Time to progression (FAS)				
Total number of events (%)	30 (66.7)	31 (60.8)	31 (66.0)	92 (64.3)
Median (months)	6.0	7.5	6.0	6.2
Clinical benefit rate (FAS)				
Total (%) [95% CI]	19 (42.2) [27.7 - 57.8]	28 (54.9) [40.3 - 68.9]	22 (46.8) [32.1 - 61.9]	69 (48.3) [39.8 - 56.8]

Objective response is defined as Complete Response + Partial Response
Clinical benefit is defined as Complete Response + Partial Response + SD ≥ 24 weeks
FAS: Full Analysis Set, CI: Confidence interval

Figure S1 Kaplan-Meier plot of TTP: Full analysis set



Number Of Patients At Risk:

Months	0	3	6	9	12	15	18	21	24
Fulvestrant 250 mg	45	36	22	13	6	2	2	0	0
Fulvestrant 250 mg + LD	51	42	29	16	7	3	0	0	0
Fulvestrant 500 mg	47	36	24	15	8	5	2	1	0

Tick marks indicate censored observations

Summary of pharmacokinetic results

A 2-compartment model, with first-order absorption and first-order elimination, was fitted to the fulvestrant concentration-time data. CL/F was estimated at a mean of 35.4 L/h and varied between individuals by approximately 31%. The mean estimate of Vd/F at steady state (Vd_{ss}/F) was 35300 L ($Vd_1/F + Vd_2/F$). Vd_1/F varied among individuals by approximately 42%.

Mean $t_{½}$ and median accumulation ratio were similar among the treatment regimens at approximately 29 days and 2-fold, respectively. In the 250 mg + LD and 500 mg dose regimens, C_{min} in the 1st month (Visit 4) was higher than C_{min} in the 3rd month (Visit 7), which shows that steady-state exposures were reached (and exceeded) in the 1st month of dosing. This was the result of an additional dose of fulvestrant given around day 14. In the 250 mg regimen, steady-state was approached in the 3rd month of dosing.

The pharmacokinetics of fulvestrant appeared to be linear across the 3 treatment regimens studied and to be similar in this patient population to that determined in previous Japanese and western studies

Summary of safety results

A summary of AEs in each category is presented in the Table S3.

A total of 765 AEs were reported by 137 (96.5%) of the 142 patients in the safety analysis set. A total of 8 patients (5.6%) reported a SAE. Three patients (2.1%) were discontinued treatment due to an AE. No patient died due to an AE. The incidence of AEs was generally well balanced among the three treatment regimens.

Table S3 Summary of number (%) of patients who had at least 1 AE in any category: Safety analysis set

AE category	Number (%) of patients [a]			
	250 mg N=45	250 mg + LD N=51	500 mg N=46	Total N=142
Any AE	44 (97.8)	49 (96.1)	44 (95.7)	137 (96.5)
Any AE with outcome = death	0	0	0	0
Any SAE with outcome other than death [b]	2 (4.4)	5 (9.8)	1 (2.2)	8 (5.6) [c]
Any AE of CTCAE grade 3 or higher	5 (11.1)	10 (19.6)	8 (17.4)	23 (16.2)
Any AE leading to discontinuation of treatment	1 (2.2)	1 (2.0)	1 (2.2)	3 (2.1)
Number of AEs	253	256	256	765

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b All patients experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE).
c The investigators reported that two other patients had SAEs. Since one patient had a SAE after the data cut-off date and another patient had a SAE after the follow-up period defined in the study protocol, these SAEs were not included in the study database for the primary analysis.

A variety of AEs were reported in this study. The most commonly reported AE in each treatment arm was nasopharyngitis (37.8% [17/45] in the 250 mg arm, 29.4% [15/51]) in the 250 mg + LD arm and 34.8% [16/46] in the 500 mg arm). AEs with an incidence of ≥10% in total were nasopharyngitis, injection site pain, hot flush, nausea, injection site induration, fatigue, constipation and headache.

Overall, the incidence of AEs with a CTCAE grade ≥ 3 was low and well balanced across the three treatment regimens.

There were no clinically important findings or abnormalities in haematology, clinical chemistry, vital signs, or physical findings.

Fulvestrant 250 mg, 250 mg + LD and 500 mg regimens were well tolerated in the study.

Date of the report

12 November 2008