Clinical Study Report Synopsis

Drug Substance	Fulvestrant (ZD9238; formerly ICI 182,720)
Study Code	D6997C00006 (9238IL/0068)
Edition Number	Final
Date	13 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: 30 May 2006 Last patient randomised: 30 November 2007 Data cut-off for primary analysis: 13 June 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)

The study was conducted at 34 centres in 8 countries (Belgium [3], Canada [10], France [4], Turkey [1], Czech Republic [3], Romania [3], Poland [5], Hungary [5]).

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, 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 patient 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 144 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. Additionally 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

Treatment with fulvestrant continued until disease progression or until any other criterion for treatment discontinuation was met.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary outcome variable:

- Objective response rate (ORR)

Secondary outcome variables for efficacy:

- Time to progression (TTP)
- Clinical benefit rate (CBR)
- Duration of response (DoR)

Secondary outcome variables for pharmacokinetics (PK):

- C_{max}
- Clearance (CL/F)
- Volume of distribution at steady state (Vd_{ss}/F)

Criteria for evaluation - safety (main variables)

- Adverse events (and their severity)
- Findings of 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 arm. 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 144 patients were randomised in the study from 34 centres in 8 countries. The first patient was randomised into the study on 30 May 2006 and the last patient was randomised on 30 November 2007. The data cut-off for the primary analysis presented in this report was 13 June 2008.

Overall 71.5% (103/144) of randomised patients discontinued study treatment (76.6% [36/47] in the fulvestrant 250 mg arm, 68.6% [35/51] in the fulvestrant 250 mg +LD arm and 69.6% [32/46] in the fulvestrant 500 mg arm). One of the 35 patients who withdrew from the fulvestrant 250 mg +LD treatment arm did so due to incorrect enrolment; they were randomised but never received study treatment. 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 female. In total 142 (98.6%) patients randomised into the study were Caucasian. Demographic characteristics were similar among the 3 treatment arms with no major discrepancies between the 3 treatment arms.

Table S1 Demographic and baseline characteristics: Full analysis set

Demographic/baseline characteristic	250 mg N=47	250 mg +LD N=51	500 mg N=46	Total N=144
Sex (n [%])				
Female	47 (100.0)	51 (100.0)	46 (100.0)	144 (100.0)
Age (year)				
Median	63	69	67	67
Range	42-88	38-85	49-85	38-88
Weight (kg)	N=46	N=50	N=45	N=141
Median	68	70	71	70
Range	42-113	49-106	50-107	42-113
WHO performance status (n[%])				
0	26 (55.3)	31 (60.8)	31 (67.4)	88 (61.1)
1	20 (42.6)	16 (31.4)	14 (30.4)	50 (34.7)
2	0	4 (7.8)	1 (2.2)	5 (3.5)
Oestrogen receptor status (n[%])				
Positive	47 (100.0)	51 (100.0)	46 (100.0)	144 (100.0)
Progesterone receptor status (n[%])				
Positive	30 (63.8)	32 (62.7)	32 (69.6)	94 (65.3)
Negative	16 (34.0)	18 (35.3)	14 (30.4)	48 (33.3)
Not assessed	1 (2.1)	1 (2.0)	0	2 (1.4)
Her-2 receptor status [a] (n[%])				
Positive	2 (4.3)	1 (2.0)	3 (6.5)	6 (4.2)
Negative	37 (78.7)	37 (72.5)	32 (69.6)	106 (73.6)
Unknown	8 (17.0)	13 (25.5)	11 (23.9)	32 (22.2)
Tumour grade (n[%])				
Grade 1	7 (14.9)	8 (15.7)	5 (10.9)	20 (13.9)
Grade 2	15 (31.9)	22 (43.1)	23 (50.0)	60 (41.7)
Grade 3	16 (34.0)	11 (21.6)	10 (21.7)	37 (25.7)
Not assessable	9 (19.1)	9 (17.6)	8 (17.4)	26 (18.1)
Unknown	0	1 (2.0)	0	1 (0.7)
Metastatic status (n[%])				

Table S1 Demographic and baseline characteristics: Full analysis set

Demographic/baseline characteristic	250 mg N=47	250 mg +LD N=51	500 mg N=46	Total N=144
Locally advanced breast cancer only	1 (2.1)	3 (5.9)	2 (4.3)	6 (4.2)
Metastatic disease	46 (97.9)	48 (94.1)	44 (95.7)	138 (95.8)
Visceral involvement [b] (n[%])				
No	13 (27.7)	10 (19.6)	9 (19.6)	32 (22.2)
Yes	34 (72.3)	41 (80.4)	37 (80.4)	112 (77.8)

[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.

Prior radiotherapy (received by 79/144 patients [54.9%]), chemotherapy (received by 79/144 patients [54.9%]) and hormonal therapy (received by all patients) were similar with no major discrepancies among the 3 treatment regimens.

Regarding when patients relapsed on previous endocrine therapy, the proportion of patients in each of the relapse categories was similar across the 3 treatment arms, with the majority of patients either having relapsed during adjuvant endocrine therapy (39.6%) or on an endocrine therapy given as first treatment for de novo advanced breast cancer (37.5%).

Summary of efficacy results

Summary of efficacy results are presented in Table S2.

For the primary outcome variable, ORR was similar across the 3 treatment regimens. ORR was 8.5% (4/47 patients; 95% confidence interval [CI]: 2.4%, 20.4%) in the 250 mg treatment arm, 5.9% (3/51 patients; 95% CIs: 1.2%, 16.2%) in the 250 mg +LD treatment arm, and 15.2% (7/46 patients; 95% CIs: 6.3%, 28.9%) in the 500 mg treatment arm. The point estimate for ORR in the fulvestrant 500 mg regimen was numerically higher than in the other 2 dose regimens, but the CIs of all 3 treatment arms overlapped.

The medians for TTP in the fulvestrant 500 mg and fulvestrant 250 mg +LD treatment arms (6.0 months and 6.1 months, respectively) were numerically longer than the median TTP of the fulvestrant 250 mg treatment arm (3.1 months); however the percentage of progression events was similar between the 3 treatment arms (67.4%, 66.7% and 74.5%, respectively). A Kaplan Meier plot of TTP in the full analysis set is shown in Figure S1.

The CBRs were similar across the 3 treatment arms. CBR was 31.9% (15/47 patients, 95% confidence interval [CI]: 19.1%, 47.1%) in the 250 mg treatment arm, 47.1% (24/51 patients,

95% CIs: 32.9%, 61.5%) in the 250 mg +LD treatment arm and 47.8% (22/46 patients, 95% CIs: 32.9%, 63.1%) in the 500 mg treatment arm. The point estimates for CBR in the fulvestrant 500 mg and 250 mg +LD regimen were numerically higher than the 250 mg regimen, but the CIs of all 3 treatment arms overlapped.

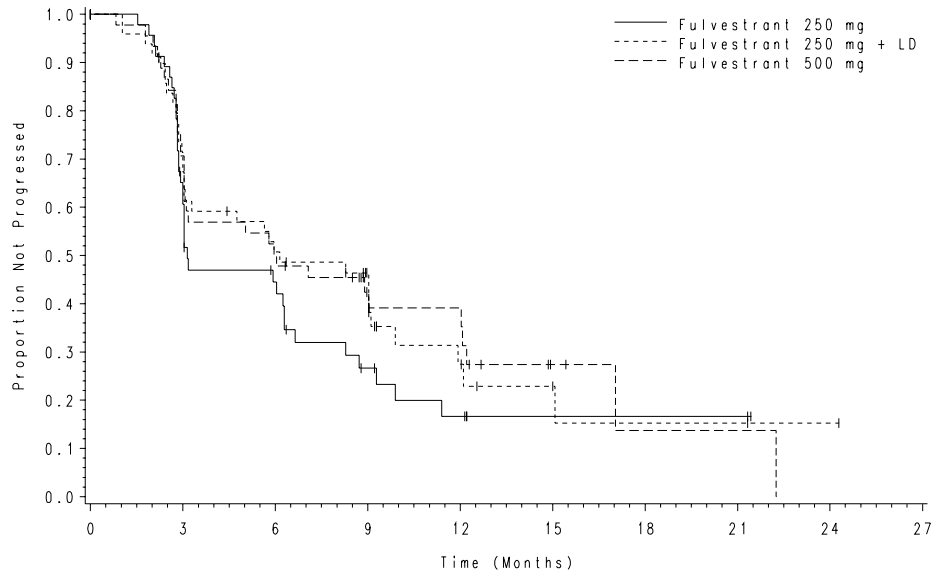
The number of responders was insufficient to assess DoR in each treatment regimen.

Table S2 Summary of efficacy results

Efficacy endpoint (analysis set)	250 mg N=47	250 mg +LD N=51	500 mg N=46	Total N=144
Objective response rate (FAS)				
Total (%) [95% CI]	4 (8.5) [2.4-20.4]	3 (5.9) [1.2-16.2]	7 (15.2) [6.3-28.9]	14 (9.7) [5.4-15.8]
Time to progression (FAS)				
Total number of events (%)	35 (74.5)	34 (66.7)	31 (67.4)	100 (69.4)
Median (months)	3.1	6.1	6.0	5.9
Clinical benefit rate (FAS)				
Total (%) [95% CI]	15 (31.9) [19.1-47.1]	24 (47.1) [32.9-61.5]	22 (47.8) [32.9-63.1]	61 (42.4) [34.2-50.9]

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	27
Fulvestrant 250 mg	47	29	18	9	5	2	2	2	0	0
Fulvestrant 250 mg + LD	51	35	24	17	7	4	2	2	1	0
Fulvestrant 500 mg	46	31	22	13	10	3	1	1	0	0

Tick marks indicate censored observations

Summary of PK results

A 2-compartment model with a 1st order absorption and 1st order elimination process was fitted to the fulvestrant concentration-time data. Clearance (CL/F) was estimated at a mean of 31.0 L/hr and varied between individuals by approximately 39%. The mean estimate of volume of distribution at steady state (Vd_{ss}/F [Vd1/F + Vd2/F]) was 56300 L (Vd1/F, coefficient of variation [CV]: 40%); individual estimates of Vd1/F were significantly positively correlated to body weight. Residual variability was proportional in nature (CV 22%) and parameters were well estimated. The mean population clearance seen in this study was similar to those determined for Western patients in Studies 9238IL/0020 and 9238IL/0021.

In the 250 mg + LD and 500 mg regimens, C_{min} in the 1st month was higher than C_{min} in the 3rd month , which shows that steady-state exposures were reached (and exceeded) in the 1st month of dosing. In the 250 mg regimen, C_{max}, C_{min} and $AUC_{0-\tau}$ at Months 1 and 3 were similar to those previously reported and patients were approaching steady state exposure to fulvestrant by the 3rd month of dosing. These data provide evidence of linear PK over the dose range studied.

As noted above, a relationship between weight and Vd1/F was determined. The consequence of an increase in Vd1/F tends to be an increase in effective $t_{½}$ and therefore an increase in the time to achieve steady-state concentrations. However, effective $t_{½}$ did not appear to alter with weight in this patient population with a mean effective $t_{½}$ of approximately 55 days across the

3 treatment groups. There was also no apparent relationship with weight for any of the secondary parameters, $AUC_{0-\tau}$, C_{max} and C_{min}. The reason for this finding is not clear, however, these data suggest that if time to steady-state is increased in patients at the upper limit of the weight range, it is likely to fall within the range of values encountered across the clinical program to date. In addition, this effect is not relevant for the 250 mg +LD and 500 mg regimens because steady-state concentrations were demonstrated within the first month of dosing.

Summary of safety results

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

A total of 663 AEs were reported by 104 (72.7%) of the 143 patients in the safety analysis set. Seventeen patients (11.9%) reported an SAE with outcome other than death; 3 patients (2.1%) died due to an AE. Only 6 patients (4.2%) discontinued study treatment due to an AE.

The incidence of AEs was well balanced among the 3 treatment arms and there was no evidence of a dose response for any of the AE categories.

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=47	250 mg +LD N=50	500 mg N=46	Total N=143
Any AE	36 (76.6)	36 (72.0)	32 (69.6)	104 (72.7)
Any AE with outcome = death	1 (2.1)	1 (2.0)	1 (2.2)	3 (2.1)
Any SAE with outcome other than death [b]	4 (8.5)	9 (18.0)	4 (8.7)	17 (11.9)
Any AE of CTCAE grade 3 or higher	7 (14.9)	13 (26.0)	10 (21.7)	30 (21.0)
Any AE leading to discontinuation of treatment	2 (4.3)	3 (6.0)	1 (2.2)	6 (4.2)

[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).

The most frequently reported AEs for each treatment arm were: nausea in the fulvestrant 250 mg arm (25.5% [12/47]); fatigue in the fulvestrant 250 mg +LD arm (22.0% [11/50]); and back pain, fatigue and nausea in the fulvestrant 500 mg arm (each with an individual incidence of 15.2% [7/46]). AEs with a total incidence in the study population of ≥10% were back pain, arthralgia, fatigue, injection site pain, nausea, dyspnoea, cough and hot flush.

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

13 November 2008