Drug Product	Faslodex	**SYNOPSIS**	
Drug Substance	Fulvestrant		
Study Code	D6997L00004		
Edition Number	1.0		
Date	26th Nov. 2007		

A double blind, double dummy, randomised, multicentre study to compare the efficacy and safety of Fulvestrant 250mg with Arimidex 1mg in the postmenopausal women with oestrogen receptor positive advanced breast cancer progressing or relapsing after previous antioestrogen therapy

Study dates		**Phase of development**
First subject enrolled	7th Nov. 2005	Local registration trial
Last subject completed	10th Sept. 2007	

Objectives

The primary objective of this study was:

- To compare the efficacy of fulvestrant 250mg with Arimidex 1mg in terms of time to progression.

The secondary objectives of the study were:

- To compare the objective response rate of patients treated with fulvestrant 250mg with the objective response rate of patients treated with Arimidex 1mg

- To compare clinical benefit rate of patients treated with fulvestrant 250mg with the clinical benefit rate of patients treated with Arimidex 1mg

- To compare time to treatment failure of patients treated with fulvestrant 250mg and Arimidex 1mg

- To assess the safety and tolerability of fulvestrant 250mg compared with Arimidex 1mg

Study design

This was a double blind, double dummy, randomised, parallel group, multi-centre study comparing the efficacy and safety of fulvestrant 250mg with Arimidex 1mg in the postmenopausal women with oestrogen receptor positive advanced breast cancer progressing or relapsing after previous antioestrogen therapy. Treatment continued until disease progression, unless any of the criteria for treatment discontinuation were met first. Approximately 222 postmenopausal women with oestrogen receptor positive advanced breast cancer progressing or relapsing after previous antioestrogen therapy, were to be recruited across 19 hospitals in China.

Target subject population and sample size

Eligible patients were postmenopausal women with oestrogen receptor positive advanced breast cancer who had either relapsed whilst on adjuvant anti-oestrogen therapy, or progressed whilst on first anti-oestrogen treatment for advanced disease.

A sample size of 100 evaluable subjects per treatment arm was requested by China State Food and Drug Administration (SFDA) for imported drug registration purpose. Initially, the rate of non-evaluable subjects was estimated to be of 20%, the total sample size was planed to be 250 subjects with 125 patients in each treating arm. On March 2007, while the first batch of data including 52 subjects was checked and entered into database without unblinding. 4 out of the 52 subjects had been considered presenting protocol violation, giving a rate of 7.69%. Considering the non-evaluable rate at 10% instead of previously estimated 20% and the minimum regulatory requirement from Chinese SFDA, the total sample size was estimated around 222 subjects with 111 in each arm.

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

Study drug: Fulvestrant was supplied as a castor oil based solution in clear neutral glass pre-filled syringes. Each syringe contained 250mg of fulvestrant in 5 ml.

Matching placebo was supplied as a castor oil based solution in clear neutral glass pre-filled syringes. Each syringe contained 5 ml.

Control drug: Arimdiex 1mg was supplied as round white, film coated tablets.

Matching placebo was supplied as round white, film coated tablets.

All patients received the corresponding placebo medication (fulvestrant and Arimidex) following the appropriate schedule, (see below).

Duration of treatment

Eligible patients were randomised 1:1 to the following treatment groups:

- Fulvestratnt 250mg given as intramuscular injection, on week 0, 4, 8, 12, 16, 20, 24 and every 4 weeks afterwards, Matching placebo to Arimidex 1mg, p.o. once daily
- Matching placebo to Fulvestrant 250mg, given as intramuscular injection, on week 0, 4, 8, 12, 16, 20, 24 and every 4 weeks afterwards, Arimdex 1mg, p.o. once daily

All active and placebo medication were to be administered until objective progression of disease or any of the discontinuation criteria was met first.

Criteria for evaluation (main variables)

Efficacy

Primary variable:

- Time to Progression (TTP)

Secondary variables:

- Objective Response Rate (ORR)
- Duration of response (DoR)
- Clinical Benefit Rate (CBR)
- Time to treatment failure (TTF)

Safety

Tolerability and safety was assessed for serious and non-serious adverse events (AEs), laboratory measurements and vital signs for all treated patients. All AEs were collected up to 8 weeks after the last study injection or 4 weeks after the last study tablet intake before data cut-off (whichever was longer) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Serious adverse events (SAEs) were followed until resolution or until the patient was lost to follow up, unless, in the investigator's opinion, the condition was unlikely to resolve due to the patient's underlying disease.

Statistical methods

The primary statistical analyses of the efficacy endpoints were performed by randomised study treatment for 'intention to treat' (ITT) population. In addition, secondary supportive analyses for the efficacy endpoints were carried out for 'per protocol' (PP) population defined as all ITT patients without major protocol violations and deviations. Analyses on safety endpoints were performed by study treatment actually received.

The analysis was performed when at least 50% of patients had progressed or died. . All treatment comparisons were done at 2-sided and the nominal level of significance was 5%.

Time to disease progression (TTP) was summarized by treatment using the Kaplan-Meier method. Kaplan-Meier plots and Kaplan-Meier estimates of median TTP time were presented. Patients who had not progressed or died at the time of the data cut-off date or who had been lost to follow-up were right-censored at the date of their last disease assessment. Treatment comparisons were performed using Log-Rank Test. Results were expressed as the hazard ratio together with the corresponding 95% confidence interval and p-value. Similar method was used for the analysis of time to treatment failure (TTF).

Objective response rate (ORR) was calculated for all patients with measurable disease at baseline and was presented for each treatment group. Patients who had measurable disease at baseline but did not have sufficient information (including missing values) for response assessment after baseline were considered as non-responders. Treatment comparisons were performed using the logistic regression model with treatment factor only. Results were expressed as the odds ratio together with the corresponding 95% confidence interval and p-value. The estimate of the difference in response rates (Faslodex - Arimidex) and the corresponding 2-sided 95% CI were also presented.

Clinical benefit rate (CBR) was also calculated for all patients with measurable disease at baseline. Patients who had measurable disease at baseline but did not have sufficient information (including missing values) for response assessment after baseline were considered as non-responders. The logistic regression analysis method described above was also used for CBR analysis.

Duration of Response (DoR) was summarized and presented as a Kaplan-Meier plot and as Kaplan-Meier estimates of the median duration. No formal statistical analysis was performed.

Adverse events were summarized by treatment actually received. The incidence of adverse events was summarized by body system and preferred term for each of the two randomized treatment group.

Physical examination, Laboratory data were summarized using descriptive statistics for continuous variables or frequency counts and percentages for categorical variables.
Laboratory values outside the normal reference ranges were highlighted. No formal treatment comparisons were performed.

Subject population

Table S 1 summarizes the details of patient disposition, the analysis sets and demography. Key patient characteristics at baseline are summarized in Table S2.

Table S 1 Summary of patient disposition, analysis sets, demographic characteristics

		Fulvestrant		Arimidex		Total	
Disposition							
N randomised (N planned)		121	(111)	113	(111)	234	(222)
N who received study treatment		121	(100%)	113	(100%)	234	(100%)
N who discontinued study treatment		93	(77%)	73	(65%)	166	(69%)
N who completed the study [a]		82	(68%)	65	(58%)	147	(61%)
N who were on study treatment at data cut-off		28	(23%)	40	(35%)	68	(28%)
Demographic characteristics							
Age (years)	Mean (SD)	53.4	(8.3)	54.8	(9.8)	54.1	(9.1)
	Range	33 to 78		31 to 77		31 to 78	
	Age group (n, %)						
	<65 years	106	(88%)	93	(82%)	199	(85%)
	≥65 years	15	(12%)	20	(18%)	35	(15%)
Race (n and % of subjects)	Oriental	121	(100%)	113	(100%)	234	(100%)
Analysis sets							
N analysed for safety		121 (100%)		113 (100%)		234 (100%)	
N analysed for efficacy (ITT)		121 (100%)		113 (100%)		234 (100%)	
N analysed for efficacy (PP)		113 (93%)		104 (92%)		217 (93%)	

[a] Patients who completed the study were those patients who experienced disease progression or death for any causes.

ITT=Intention to treat; N=Number; PP=Per-protocol.

In total, 234 patients were enrolled and randomized with 121 patients in the fulvestrant treatment group and 113 in the Arimidex group. 147 discontinued study treatment primarily due to reaching a study endpoint, and 68 patients were ongoing at data cut off (10 July 2007).

The 2 treatment groups were comparable with respect to demographic characteristics. The studied population was exclusively oriental, with a mean (SD) age of 54.1 (9.1) years (age distribution: 85% of patients were <65 years and 15% of patients were ≥65 years of age).

Table S2 Baseline characteristics of the ITT analysis set

Demographic or baseline characteristic	Treatment group					
	Fulvestrant (n=121)		Arimidex (n=113)		Total (n=234)	
Post-menopausal status (n, %):						
Yes	119	98%	112	99%	231	99%
No	2	2%	1	1%	3	1%
Oestrogen receptor status (n, %):						
Positive	120	99%	113	100%	233	100%
Negative	1	1%	0	0%	1	0%
Measurable disease(s) at baseline (n, %):						
Yes	83	69%	83	73%	166	71%
No	38	31%	30	27%	68	29%
Histology type (n, %):	121		113		234	
Infiltrating ductal carcinoma	97	80%	90	80%	187	80%
Infiltrating lobular carcinoma	9	7%	10	9%	19	8%
Medullary	1	1%	1	1%	2	1%
Paget's	1	1%	0	0%	1	0%
Other	13	11%	12	11%	25	11%
WHO performance status (n, %):						
0	89	74%	89	79%	178	76%
1	27	22%	19	17%	46	20%
2	5	4%	5	4%	10	4%
Number of life-saving chemotherapy regimens (n, %):						
N	62		49		111	
1	42	68%	37	76%	79	71%
2	20	32%	12	24%	32	29%

Overall, the treatment groups were balanced for baseline characteristics with possible exception of the proportion of patients having received 2 life-saving chemotherapy regimens. Of the 234 randomized patients, 231 (99%) were confirmed as postmenopausal, and 233 (99.6%) as oestrogen receptor positive. 166 (71%) patients had measurable diseases (with an comparable number of patients in each treatment group), and a further 68 (29%) patients had non measurable diseases only. For 187 (80%) patients, infiltrating ductal carcinoma was the most frequently reported histology type. The vast majority of patients were either WHO performance 0 or 1 (ie, with normal or restricted activity), with 178 (76%) and 46 (20%) patients, respectively. In total, 111 (47%) patients had received life-saving chemotherapy. In the fulvestrant group, of the 62 patients who had received life-saving chemotherapy, 2 regimens were reported in about 1 tier of the cases (32%). Of the 49 patients who had received life-saving chemotherapy in the Arimidex group, 2 regimens were reported in 1 quarter of the cases (24%). This indicates that patients in the fulvestrant arm might be of worse prognosis.

Major deviations were determined on a blinded basis prior to database lock.

Efficacy results

The analysis was based on a data cut-off 10 July 2007. Table S3 summarizes the efficacy results.

Table S3 Summary of efficacy results

Variable	Result	Analysis
TTP (primary)	Median TTP from randomization to disease progression: 110 days in the fulvestrant group (N=121) 159 days in the Arimidex group (N=113)	Hazard ratio = 1.314; 95% CI: 0.948, 1.822; p=0.101
ORR[a]	Number of patient-responders (CR+PR combined) 8 (10%) patients in the fulvestrant group 12 (14%) patients in the Arimidex group	Odds ratio = 0.631; 95% CI: 0.244, 1.635; p=0.343
DoR[b]	Median duration of response from randomization to progression: 436 days in the fulvestrant group (N=8) 432 days in the Arimidex group (N=12)	Not applicable
CBR[c]	Number of patients with a response of CR, PR or SD ≥24 weeks: 30 (36%) in the fulvestrant group 40 (48%) in the Arimidex group	Odds ratio = 0.608; 95% CI: 0.327, 1.133; p=0.117
TTF	Median TTF from randomization to treatment failure: 110 days in the fulvestrant group (N=121) 147 days in the Arimidex group (N=113)	Hazard ratio = 1.307; 95% CI: 0.961, 1.778; p=0.088

TTP: time to progression; ORR: objective response rate; DoR: duration of response; CBR: clinical benefit rate; CR: complete response; PR: partial response; SD: stable disease; TTF: time to treatment failure

a For the patients with measurable lesion at the baseline.

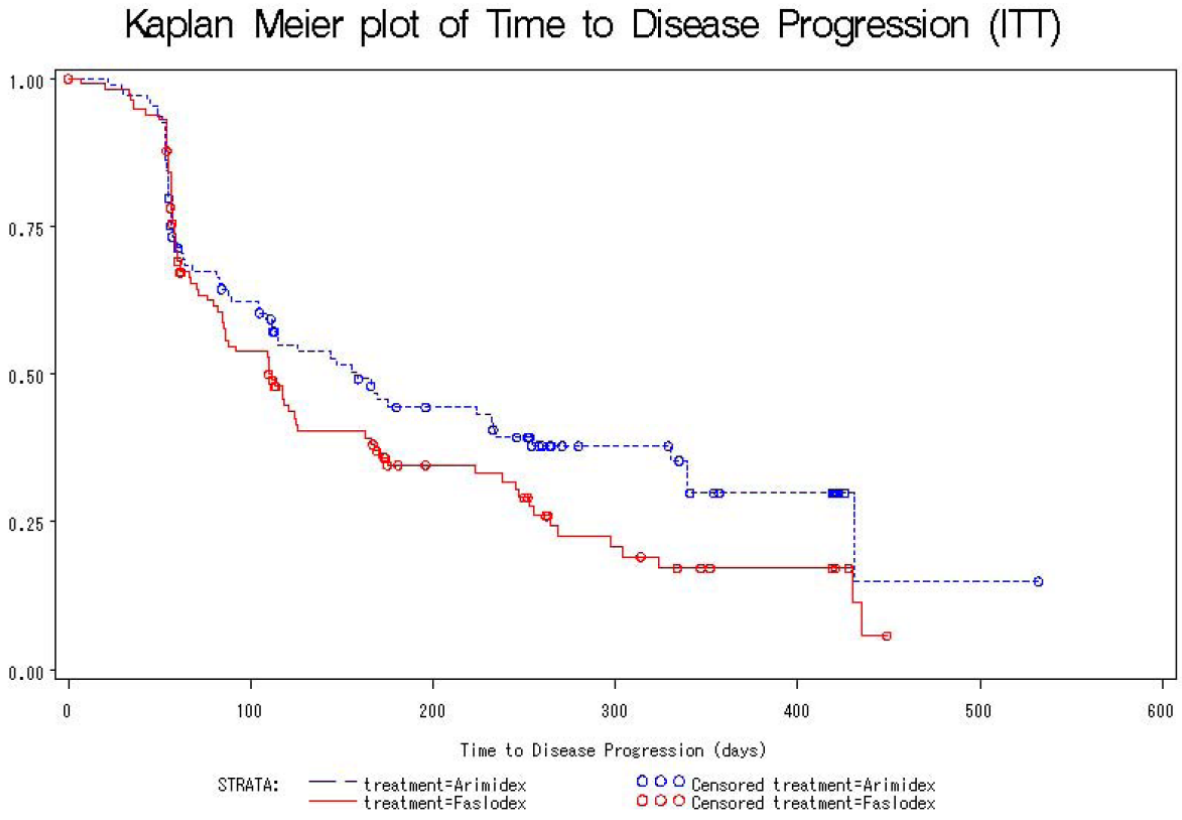
b For those patients who responded (CR+PR).

c For those patients with a response of CR, PR or SD (for at least 24 weeks).

Primary efficacy variable

There was no statistical difference between the treatments for TTP with a median time to progression of 110 days in the fulvestrant treatment group vs 159 days in the Arimidex treatment group (ITT analysis set); the hazard ratio from the primary analysis was 1.31 (HR=1.314; 95% CI: 0.948, 1.822; p=0.101) (Figure S1).

Figure S1 **Kaplan Meier plot of TTP, fulvestrant and Arimidex treatment groups (ITT analysis set)**



For subjects with no measurable disease at baseline, the median TTP was 124 days in the fulvestrant arm (N=38) vs 339 days in the Arimidex arm (N=30), (ITT analysis set); the hazard ratio was 1.852 (HR=1.852; 95% CI: 0.977, 3.898; p=0.058). In patients with measurable disease at baseline, median TTP was 110 days in the fulvestrant arm (N=83) vs 115 days in the Arimidex arm (N=83), (ITT analysis set); the hazard ratio was 1.161 (HR=1.161; 95% CI: 0.796, 1.693; p=0.438).

Secondary efficacy variables

ORR: There was no statistical difference between the treatments for ORR; the odds ratio from the primary analysis was 0.631 (OR=0.631; 95% CI: 0.244, 1.635; p=0.343). The number (%) of patient-responders (CR+PR combined) was slightly higher in the Arimidex arm than in the

fulvestrant arm: 12 (14%) vs 8 (10%). However, of these patients, the only CR as the best overall response was observed in the fulvestrant group.

DoR: For those patients who responded (CR+PR), the median duration of response from response to progression for those patients who responded (CR+PR) was 266 days in the fulvestrant treatment group (N=8) and 376 days in the Arimidex group (N=12). The median duration of response from randomization to progression in the fulvestrant treatment group was 436 days and 432 days in the Arimidex group.

CBR: there was no statistical difference between the treatments for CBR. The number (%) of patients with a response of CR, PR or SD (for at least 24 weeks), was slightly higher in the Arimidex arm than in the fulvestrant arm: 40 (48.2%) vs 30 (36.1%); the odds ratio from the primary analysis was 0.608 (OR=0.608; 95% CI: 0.327, 1.133; p=0.117).

TTF: There was no statistical difference between the treatments for TTF with a median of 110 days in the fulvestrant arm vs 147 days in the Arimidex arm (ITT analysis set); the hazard ratio from the primary analysis was 1.307 (HR=1.307; 95% CI: 0.961, 1.778; p=0.088).

Safety results

The 2 treatment groups were comparable in terms of duration of treatment (exposure) with an overall mean (SD) duration of 162.9 (123.1) days.

There were very few adverse events leading to death with 1 (1%) patient in the fulvestrant treatment group and 4 (4%) patients in the Arimidex group (Table S4). The events differed in each case. None of the adverse events leading to death were causally related to study treatment, as assessed by the investigator.

Overall, 7 (3%) patients experienced a total of 7 non-fatal SAEs during the treatment period. The number of patients with non-fatal SAEs in each treatment group was similar with 4 (3%) in the fulvestrant group and 3 (3%) in the Arimidex group (Table S4). Very few patients experienced treatment related non-fatal SAEs with 2 (2%) patients reporting endometrial hypertrophy in the fulvestrant treatment group. In total, 6 (3%) patients discontinued study treatment due to AEs, fewer patients in the fulvestrant group did so than in the Arimidex group (2 vs 4). No discontinuation due to treatment related SAEs was reported.

During the study period 332 AEs were reported by 89 (38%) of the 234 patients in the safety analysis set (Table S4). The number (%) of patients reporting any AE was similar for each treatment group with 48 (40%) in the fulvestrant group vs 41 (36%) in the Arimidex group.

The most commonly reported AEs in the fulvestrant and Arimidex groups were asthenia, nausea, and injection site pain with 14 (12%) vs 12 (11%), 8 (7%) vs 3 (3%) and 5 (4%) vs 9 (8%) patients, respectively (Table S5). Fewer patients experienced nausea in the Arimidex group whilst fewer reported injection site pain in the fulvestrant group. Further, injection site reaction were reported in similar frequency in the treatment arms with 8 (7%) patients in the

fulvestrant treatment group vs 10 (9%) in the Arimidex treatment group, all those were CTC Grade 1.

Other AEs were reported with similar frequency in each treatment group with the possible exception of arthralgia, back pain, hypoaesthesia, and anorexia; reported as follows (fulvestrant vs Arimidex): 5 (4%) vs 1 (1%), 1 (1%) vs 7 (6%), 5 (4%) vs 1 (1%) and 4 (3%) vs 0 (0%), respectively. The most commonly reported AEs in both treatment groups were typically CTC Grade 1 with few events of CTC Grade 2, furthermore, no events of CTC Grade 3 or 4 were recorded. Differences in distribution of severity for individual AEs were small and there was no trend toward more severe AEs in either group.

The most common treatment related AEs in the fulvestrant and Arimdex groups were asthenia, injection site pain and hot flush with 13 (11%) vs 11 (9%), 5 (4%) vs 9 (7%), and 5 (4%) vs 4 (3%) patients, respectively. Similar number (%) of patients experienced asthenia and hot flush in both treatment groups whilst fewer patients reported injection site pain in the fulvestrant group. Overall, treatment related AEs in both groups were typically CTC Grade 1 with few events of CTC Grade 2, only 1 patient in the Arimidex group reported 1 treatment related AE of CTC Grade 3, no CTC Grade 4, or 5 events were recorded.

There were no remarkable changes in hematology, clinical chemistry and urinalysis and no apparent differences for the within-group and between-group comparisons. There were no remarkable changes in vital signs, ECG and physical findings and no apparent differences for the within-group and between-group comparisons.

Table S4 Number (%) of subjects who had an adverse event in any category (safety analysis set)

Category of adverse event[a]	Number (%) of subjects who had an adverse event in each category[b]	
	Fulvestrant (N=121)	Arimidex (N=113)
Any AE	48 (40%)	41 (36%)
Any study treatment related AE	32 (26%)	25 (22%)
Any SAE	5 (4%)	6 (5%)
Any SAE leading to death	1 (1%)	4 (4%)
Any SAE not leading to death	4 (3%)	3 (3%)
Any study treatment related SAE	2 (2%)	0 (-)
Discontinuations of study treatment due to adverse events	2 (2%)	4 (4%)
Other significant adverse event	3 (2%)	0 (-)
	Total number of adverse events	
Any adverse events	169	163
Any study treatment related AE	106	111
Any SAE	5	7
Any SAE leading to death	1	4
Any SAE not leading to death	4	3
Any study treatment related SAE	2	0
Discontinuations of study treatment due to adverse events	2	4
Other significant adverse events	3	0

a AEs were collected during the study period - defined as the period from the first dose of study medication through to 8 weeks after last injection or 4 weeks after last tablet (whichever was longer).

b 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.

Table S5 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event					
	Fulvestrant (n=121)		Arimidex (n=113)		Total (n=234)	
Asthenia	14	(12%)	12	(11%)	26	(11%)
Injection site pain	5	(4%)	9	(8%)	14	(6%)
Nausea	8	(7%)	3	(3%)	11	(5%)

[a] Events with a total frequency of ≥4% across all treatment groups are included in this table.

Table S6 Number (%) of patients with serious adverse events, summarized by SOC and PT (Safety analysis set)

MedDRA System Organ Class[a] - Preferred Term	Fulvestrant (N=121)	Arimidex (N=113)
Respiratory, thoracic and mediastinal disorders		
- Asphyxia	0 (-)	1 (1%)
- Respiratory failure	1 (1%)	0 (-)
Gastrointestinal disorders		
- Pancreatitis acute	1 (1%)	0 (-)
Infections and infestations		
- Lung infection	0 (-)	1 (1%)
General disorders and administration site conditions		
- Death	0 (-)	1 (1%)
Injury, poisoning and procedural complications		
- Injury	0 (-)	1 (1%)
- Lower limb fracture	0 (-)	1 (1%)
Reproductive system and breast disorders		
- Endometrial hypertrophy	2 (2%)	0 (-)
Metabolism and nutrition disorders		
- Diabetes mellitus	1 (1%)	0 (-)
Cardiac disorders		
- Cardiac failure	0 (-)	1 (1%)
Renal and urinary disorders		
- Renal failure	0 (-)	1 (1%)

a AEs were collected during the treatment period - defined as the period from the first dose of study medication through to 8 weeks after last injection or 4 weeks after last tablet (whichever was longer).

Primary efficacy variable:

There was no statistical difference between the treatment groups for the primary variable time to disease progression (TTP).

Secondary efficacy variables:

ORR and CBR – there was no statistical difference between the treatment groups for ORR and CBR. No conclusions are possible for DoR due to the small number of patients who responded and because these results were obtained from a sub group of patients, defined post-randomization according to RECIST criteria (CR+PR).

TTF – There was no statistical difference between the treatment groups for time to treatment failure (TTF).

Safety:

Fulvestrant demonstrated a safety profile (AEs, safety laboratory tests and vital signs) that was generally similar to that of Arimidex, indicating that fulvestrant was well tolerated.