Drug product	FASLODEX	**SYNOPSIS**	
Drug substance(s)	Fulvestrant		
Study code	D6997C00048		
Date	19 December 2006		

A Randomized, Double Blind, Multi-center Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEX™) vs Exemestane (AROMASIN™) in Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer with Disease Progression after Prior Non-Steroidal Aromatase Inhibitor (AI) Therapy

International coordinating investigators

Study center(s)

This was a randomized, double blind, multi-center study involving 138 study sites in 15 countries (Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Hungary, Israel, Russia, South Africa, Spain, Sweden, the UK and the USA).

Publications

None.

Study dates		**Phase of development**
First patient enrolled	5 August 2003	Therapeutic confirmatory (III)
Last patient enrolled	10 November 2005	

Objectives

The primary objective of the study was:

- To assess the efficacy of AstraZeneca ZD9238 (fulvestrant, FASLODEX™) vs exemestane (AROMASIN™, Pfizer Inc.) in hormone receptor-positive postmenopausal women with breast cancer progression after prior non-steroidal aromatase inhibitor (AI) therapy, by evaluation of time to disease progression (TTP).

The secondary objectives of the study were:

- To compare objective response (OR) rates (complete response [CR] + partial response [PR]), duration of response (DoR), time to response (TTR)[1], clinical benefit (CB) rate, overall survival (OS), tolerability, quality of life (QoL), and health care resource use between the patients described above on fulvestrant and those on exemestane.

The pharmacokinetic (PK) objectives[2] of the study were to characterize exposure to fulvestrant during a loading dose regimen in the following way:

- Primary: to assess the PK profile and accumulation to steady state (C_{ss}) of fulvestrant in 30 patients receiving fulvestrant.

- Secondary: to measure the maximum plasma concentration (C_{max}) of fulvestrant in 30 patients receiving fulvestrant.

Study design

This was a randomized, double-blind, double-dummy, parallel group, multinational, multi-center, Phase III study to compare the efficacy and tolerability of the fulvestrant loading dose regimen versus exemestane in postmenopausal women with hormone receptor-positive advanced breast cancer whose disease had progressed after prior non-steroidal AI therapy. Patients were treated until disease progression or death, or until the investigator had determined that treatment was not in the best interest of the patient; whichever occurred first. Approximately 660 patients with advanced breast cancer who have progressed after prior

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[1] TTR was an additional endpoint included in the statistical analysis plan (SAP) before unblinding of the data, (see Appendix 12.1.9).

[2] The study protocol did not include any objectives assessing the relationship of PK to efficacy and safety. However, an unplanned analysis was undertaken to assess the PK/PD relationship of fulvestrant using the efficacy variable TTP, and the following safety (AE) variables: 'joint disorders', 'nausea/vomiting' and 'asthenia/fatigue'. The decision to assess the PK/PD relationship using the efficacy variable TTP was made prior to unblinding the data. The safety (AE) variables were identified following unblinding of the data.

treatment with a non-steroidal AI (anastrozole [ARIMIDEX™, AstraZeneca] or letrozole [FEMARA™, Novartis]) were to be recruited from hospitals, clinics and offices across several countries (including Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Hungary, Israel, Russia, South Africa, Spain, Sweden, the UK and the USA).

Target patient population and sample size

Eligible patients were postmenopausal women receiving treatment with a non-steroidal AI for locally advanced or metastatic breast cancer, whose disease had progressed, or those women whose disease had recurred, while receiving (or within 6 months of discontinuation of) a non-steroidal AI as adjuvant therapy.

The primary endpoint of this study (TTP) was used to determine the sample size by assuming exponential survival times. In order to detect a hazard ratio ≤ 0.76 (or ≥ 1.31) for fulvestrant compared to exemestane, at a 2-sided significance level of 5%, with 90% power, approximately 580 events were required to have occurred in the study (ie, 580 patients were to have progressed or died). For patients whose disease had recurred or progressed following 1 prior hormonal therapy, the hazard rate for fulvestrant was estimated to be 0.0041756 per day, corresponding to a median TTP of 23.7 weeks (AstraZeneca Clinical Study Reports 9238IL/0020, 17 January 2001 and 9238IL/0021, 7 February 2001; combined). For patients whose disease had progressed following 2 prior hormonal therapies, the hazard rate for exemestane was estimated to be 0.0077016 per day, corresponding to a median TTP of 12.9 weeks (Lonning *et al* 2000). A hazard ratio of 0.76 would, therefore, equate to a prolongation of median TTP for fulvestrant over exemestane of 5.6 weeks for patients receiving 1 prior hormonal therapy and 4.0 weeks for patients receiving 2 prior therapies.

For purposes of sample size estimation, it was assumed that the proportion of patients whose disease had recurred or progressed following 1 prior hormonal therapy would be approximately 60%, and the proportion of patients whose disease progressed following 2 prior hormonal therapies would be approximately 40%. Using an estimated accrual time of 21 months and minimum follow-up of 6 months, approximately 330 patients were required per treatment group. Among them, approximately 60 patients (30 per treatment group) were to be recruited for PK sampling and analysis.

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

Fulvestrant was provided as a single-dose in a pre-filled syringe. Each active pre-filled syringe contained 250 mg of fulvestrant at a concentration of 50 mg/mL in a volume of 5 mL, designated a fulvestrant 5% weight/volume (w/v) injection. The placebo pre-filled syringe was identical in appearance to the active pre-filled syringe with a volume of 5 mL.

Exemestane 25 mg tablet, produced by Pfizer Inc., was encapsulated into a white opaque hard gelatin capsule and overfilled with mannitol. The placebo capsule was a white opaque hard gelatin capsule filled with mannitol and identical in appearance to the encapsulated exemestane 25 mg tablet.

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

Duration of treatment

Fulvestrant 500 mg (2 x 5 mL, im injections) was administered as a loading dose on Day 0, followed by 250 mg (1 x 5 mL) on Day 14, Day 28 and monthly (ie, 28 ± 3 days) thereafter. Exemestane 25 mg was administered once daily by mouth (po) from Day 0. All patients received the corresponding placebo medication, either an im injection or an oral placebo capsule following the appropriate schedule. All active and placebo medication were to be administered until disease progression or death or until considered by the investigator not in the best interest of the patient, whichever occurred first.

Criteria for evaluation (main variables)

Efficacy

- Primary variable:
  - Time to disease progression (TTP)
- Secondary variables:
  - Objective response rate (ORR)
  - Duration of response (DoR)
  - Time to response (TTR)
  - Clinical benefit rate (CBR)
  - Overall survival (OS)

Patient reported outcomes (PROs); Quality of Life

- Functional assessment of cancer therapy – endocrine symptoms (FACT-ES)
- Trial Outcome Index (TOI)[3]
- EuroQol (EQ-5D)

Health economics (health care resource use)

- Inpatient days, outpatient visits, lab tests, doctor home visits, nurse home visits.

[3] The FACT-ES instrument was scored in terms of Trial Outcome Index (TOI), which is a summary score of the following subscales: Physical well-being (PWB), Functional well-being (FWB) and Breast cancer subscale (BCS).

Pharmacokinetic (PK) measurement and variables[4]

The PK objectives of the study were to characterize exposure to fulvestrant during a loading dose regimen in the following way:

- Primary PK variable:
  - PK profile and accumulation to steady state (C_{ss}) of fulvestrant by analysis of the plasma clearance and volume of distribution using population PK techniques in 30 patients receiving fulvestrant.
- Secondary PK variable:
  - Maximum plasma concentration (C_{max}) using either compartmental analysis or simulation taking the individual PK parameters from the population model.

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 injection or 30 days after ingestion of the last capsule (whichever was longer) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Serious adverse events (SAEs) were to be followed until resolution. An Independent Data Monitoring Committee (IDMC) was established to review the safety aspects of the study.

Statistical methods

The primary statistical analyses of the efficacy endpoints, QoL data and health care resource use data were performed by randomized study treatment for the 'Intention-to-treat ' (ITT) population. In addition, secondary analyses for TTP and QoL data were carried out for the 'Per-protocol' (PP) population. Analyses on safety endpoints were performed by study treatment actually received. The "treatment actually received" was the same as the randomized treatment in this study, except in a small number of patients (and only for a short period of time) due to errors in dispensing. Such exceptions have been examined case by case and were not considered to justify a change to the analysis.

TTP was analyzed using the log-rank test. Supporting analyses were performed using the Cox proportional hazards model to investigate any impact of baseline covariates. OR and CB rates were analyzed using a logistic regression model with treatment factor only. DoR and TTR were summarized. QoL data was analyzed using a longitudinal analysis. Health care resource use (health economic) data were summarized. An inferential formal comparison for treatment

[4] An unplanned analysis was undertaken to assess the PK/PD relationship of fulvestrant using TTP, and the AE variables: 'joint disorders', 'nausea/vomiting' and 'asthenia/fatigue'. The decision to assess the PK/PD relationship using the efficacy variable TTP was made prior to unblinding the data. The safety (AE) variables were identified following unblinding of the data.

differences was performed for the pre-specified categories of AEs. No interim analysis was carried out in this study. The decision on whether or not the primary study objective has been achieved was made upon the superiority test for TTP using the log-rank test in the ITT population.

Patient population

Table S1 summarizes the details of patient disposition, the analysis sets and demography. Key patient characteristics at baseline are summarized in Table S2.

Table S1 Summary of patient disposition, analysis sets, demographic characteristics

			Fulvestrant	Exemestane	All patients
Disposition					
Patients enrolled and randomized			351	342	693
Patients who received study treatment			351	340	691
Patients who discontinued study treatment			314	312	626
Patients who completed the study[a]			119	118	237
Patients who were on study treatment at data cut-off			37	28	65
Analysis sets					
ITT analysis			351	342	693
Safety analysis			351	340	691
Per-protocol analysis			312	313	625
PK analysis			44	31	75
Demographic characteristics (ITT analysis set)			(N= 351)	(N= 342)	(N= 693)
Age (years)	Mean (SD)		63.2 (11.0)	63.0 (11.0)	63.1 (11.0)
	Range		38 to 88	32 to 91	32 to 91
	Age group (n, %):	>16 to <65 years	189 (53.8)	194 (56.7)	383 (55.3)
		≥65 years	162 (46.2)	148 (43.3)	310 (44.7)
Race, n (%):	Caucasian		313 (89.2)	312 (91.2)	625 (90.2)
	Black		11 (3.1)	13 (3.8)	24 (3.5)
	Oriental		4 (1.1)	4 (1.2)	8 (1.2)
	Other		23 (6.6)	13 (3.8)	36 (5.2)

a Patients who completed the study were those patients who died (ie, have a non-missing date of death)

In total, 693 patients were enrolled and randomized with 351 patients in the fulvestrant treatment group and 342 in the exemestane group. Of these, 691 received study treatment. In total, 626 discontinued study treatment primarily due to reaching a study endpoint, and 65 patients were ongoing at data cut off (30 June 2006).

The 2 treatment groups were comparable with respect to demographic characteristics. The studied population was predominantly Caucasian (90.2%), with a mean (SD) age of 63.1 (11.0) years (age distribution: 55.3% of patients were >16 to <65 years and 44.7% of patients were ≥65 years of age).

Table S2 Summary of patient characteristics at baseline (ITT analysis set)

		Fulvestrant (N=351)		Exemestane (N=342)		All patients (N=693)	
Post-menopausal status (n, %):	Yes	350	(99.7)	342	(100.0)	692	(99.9)
	No	1	(0.3)	0	(-)	1	(0.001)
Hormone receptor status (ER+, PgR+ combined) (n, %):							
	Positive, positive	237	(67.5)	193	(56.4)	430	(62.0)
	Positive, negative	77	(21.9)	97	(28.4)	174	(25.1)
	Positive, unknown	20	(5.7)	30	(8.8)	50	(7.2)
	Negative, positive	9	(2.6)	16	(4.7)	25	(3.6)
	Unknown, positive	2	(0.6)	0	(-)	2	(0.3)
	Both receptors either unknown or negative	6	(1.7)	6	(1.8)	12	(1.7)
Tumor evaluation (n, %):							
	Target lesion(s) present	270	(76.9)	270	(78.9)	540	(77.9)
	No target lesion(s) present, bone non-target lesion(s) present	74	(21.1)	70	(20.5)	144	(20.8)
	No target or bone non-target lesion(s), but other non-target lesions present	5	(1.4)	2	(0.6)	7	(1.0)
	No lesions recorded	2	(0.6)	0	(-)	2	(0.3)
Histology type (n, %):							
	Adenocarcinoma	44	(12.5)	44	(12.9)	88	(12.7)
	Undifferentiated carcinoma	3	(0.9)	3	(0.9)	6	(0.9)
	Infiltrating ductal carcinoma	223	(63.5)	231	(67.5)	454	(65.5)
	Infiltrating lobular carcinoma	50	(14.2)	33	(9.6)	83	(12.0)
	Other	30	(8.5)	30	(8.8)	60	(8.7)
	Not recorded	1	(0.3)	1	(0.3)	2	(0.3)
Tumor grade (n, %):							
	Well differentiated - G1	30	(8.5)	22	(6.4)	52	(7.5)
	Moderately differentiated - G2	121	(34.5)	139	(40.6)	260	(37.5)
	Poorly differentiated - G3	103	(29.3)	85	(24.9)	188	(27.1)
	Undifferentiated - G4	3	(0.9)	3	(0.9)	6	(0.9)
	Unassessable - GX	14	(4.0)	8	(2.3)	22	(3.2)
	Not recorded	80	(22.8)	85	(24.9)	165	(23.8)
Visceral involvement[a] (n, %):							
	Yes	197	(56.1)	198	(57.9)	395	(57.0)
	No	154	(43.9)	144	(42.1)	298	(43.0)
WHO performance status (n, %):							
	0	194	(55.3)	181	(52.9)	375	(54.1)
	1	133	(37.9)	149	(43.6)	282	(40.7)
	2	24	(6.8)	12	(3.5)	36	(5.2)
Prior hormonal therapy (n, %):							
	1	145	(41.3)	147	(43.0)	292	(42.1)
	≥2	206	(58.7)	195	(57.0)	401	(57.9)
Disease stage (n, %):							
	Locally advanced disease	8	(2.3)	10	(2.9)	18	(2.6)
	Metastatic	342	(97.4)	332	(97.1)	674	(97.3)
	Not recorded	1	(0.3)	0	(-)	1	(0.3)

a Visceral involvement: life-threatening hepatic or pulmonary spread of disease.

Overall, the treatment groups were balanced for baseline patient characteristics and were representative of the target population.

Of the 693 randomized patients, 692 (99.9%) were confirmed as postmenopausal. In total, 430 (62.0%) were hormone receptor positive for both ER and PgR. Of the remaining patients, 251 (36.2%) were positive for ER or PgR and 12 (1.7%) patients were either negative at

baseline for both receptors, or the results were unknown. Of this latter group, 3 patients had an earlier positive result and 3 patients with missing results, were later confirmed as hormone receptor positive; all 6 were considered eligible for the study.

Five hundred and forty (77.9%) patients had target lesions (with an equal number of patients in each treatment group), and a further 144 (20.8%) patients had non-target lesions only (including bone); accounting for 98.7% of the studied population. For 454 (65.5%) patients, infiltrating ductal carcinoma was the most frequently reported histology type. Where tumor grade was known, moderately or poorly differentiated tumors accounted for 260 (37.5%) and 188 (27.1%) patients, respectively. Disease stage at baseline was identified as metastatic for 674 (97.3%) patients, and was locally advanced for 18 (2.6%) patients. Visceral involvement (non-life-threatening hepatic or pulmonary spread of disease) was reported for 395 (57.0%) patients vs 298 (43.0%) who were negative for visceral involvement. The vast majority of patients were either WHO performance 0 or 1 (ie, with normal or restricted activity), with 375 (54.1%) and 282 (40.7%) patients, respectively. In total, 292 (42.1%) patients reported 1 prior hormonal therapy at randomization and 401 (57.9%) patients reported 2 or more.

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

Efficacy and pharmacokinetic results

The analysis was based on a data cut-off 30 June 2006. Table S3 summarizes the efficacy results.

Table S3 Summary of efficacy results

Variable	Result	Analysis
TTP (primary)	The median was 112 days in both groups	Hazard ratio = 0.96; 95% CI: 0.82, 1.13; p=0.6531
ORR[a]	Number of patient-responders (CR+PR combined) 20 (7.4%) patients in the fulvestrant treatment group 18 (6.7%) patients in the exemestane group	Odds ratio = 1.12; 95% CI: 0.58, 2.19; p=0.7364
DoR[b]	Median duration of response from response to progression: 228 days in the fulvestrant treatment group (N=20) 168 days in the exemestane group (N=18)	Not applicable
TTR[b]	Median time to response from response: 162 days in the fulvestrant treatment group (N=20) 113 days in the exemestane group (N=18)	Not applicable
CBR[c]	Number of patients with a response of CR, PR or StD ≥24 weeks: 87 (32.2%) in the fulvestrant treatment group 85 (31.5%) in the exemestane group	Odds ratio = 1.04; 95% CI: 0.72, 1.49; p=0.8534).
OS	Number of deaths in the period to data cut-off (30 June 2006): 119 (33.9%) in the fulvestrant treatment group 118 (34.5%) in the exemestane group	Not applicable

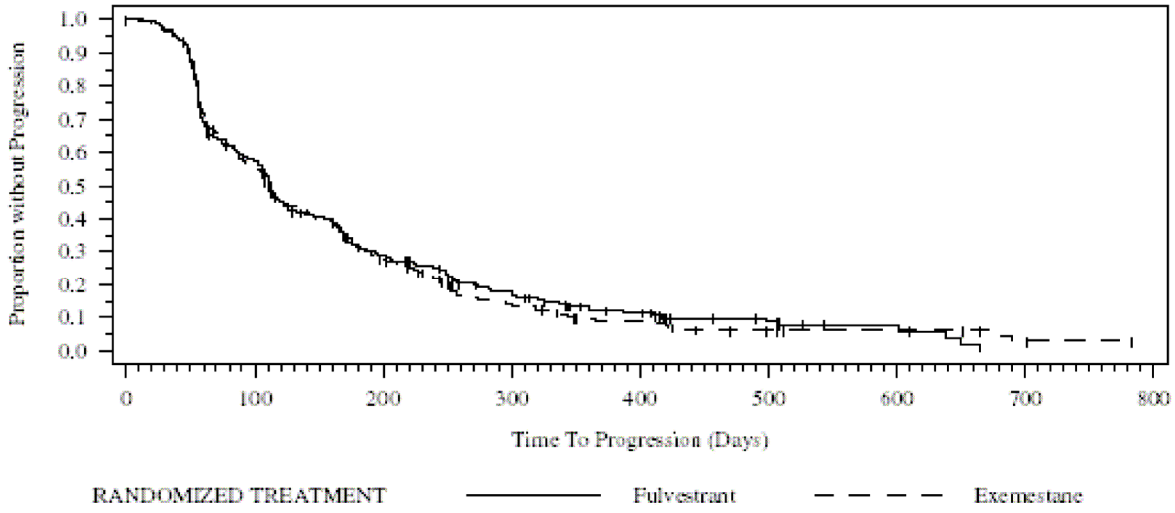
TTP: time to progression; ORR: objective response rate; DoR: duration of response; TTR: time to response; CBR: clinical benefit rate; OS: overall survival; CR: complete response; PR: partial response; StD: stable disease

a For the evaluable for response population.
b For those patients who responded (CR+PR).
c For those patients with a response of CR, PR or StD (for at least 24 weeks).

Primary efficacy variable

- There was no difference between the treatments for TTP with a median time to disease progression of 112 days in both groups (ITT analysis set); the hazard ratio from the primary analysis was 0.96 (HR=0.96; 95% CI: 0.82, 1.13; p=0.6531). The Kaplan Meier plot for time to disease progression for both treatment groups is illustrated in Figure S1.

Figure S1 Kaplan Meier plot of time to disease progression, fulvestrant and exemestane treatment groups (ITT analysis set)



Days	0	50	100	150	200	250	300	350	400	450	500	550	600	650	700
Fulvestrant at Risk	351	301	191	127	89	67	46	29	23	13	10	4	4	2	0
Exemestane at Risk	342	305	184	130	80	56	37	24	21	13	10	8	8	6	2

Tick marks are used to indicate censored observations.

Secondary efficacy variables

- ORR: for those patients who were evaluable (the evaluable for response population) the number (%) of patient-responders (CR+PR combined) was similar in both treatments groups with 20 (7.4%) patients in the fulvestrant treatment group, and 18 (6.7%) patients in the exemestane group. Of these patients, PR was the best overall response for all but one patient in the fulvestrant group; the odds ratio from the primary analysis was 1.12 (OR=1.12; 95% CI: 0.58, 2.19; p=0.7364).

- DoR: for those patients who responded (CR+PR), the median duration of response from response to progression in the fulvestrant treatment group (N=20) was 228 days and 168 days in the exemestane group (N=18). The median duration of response from randomization to progression in the fulvestrant treatment group was 410 days and 299 days in the exemestane group.

- TTR: for those patients who responded (CR+PR), the median time from randomization to response in the fulvestrant treatment group (N=20) was 162 days and 113 days in the exemestane group (N=18).

- CBR: the number (%) of patients with a response of CR, PR or StD (for at least 24 weeks), was similar in both treatments groups with 87 (32.2%) patients in the fulvestrant treatment group and 85 (31.5%) patients in the exemestane group, 1.04 (OR=1.04; 95% CI: 0.72, 1.49; p=0.8534).

- OS: in the period to data cut-off, the number of deaths in each group was similar with 119 (33.9%) in the fulvestrant treatment group vs 118 (34.5%) in the exemestane group.

Patient reported outcomes and health economics

- There were no differences between the treatment groups for the FACT-ES and TOI analyses in either the 'All patients evaluable for QoL' or 'Per-protocol' analyses. Therefore, it appears that on-treatment QoL, as defined by the FACT-ES and TOI, was similar between groups. There were no apparent major differences between the groups in mean utility scores derived from the EQ-5D questionnaire.

- There were no apparent major differences between the treatment groups for health care resource utilization.

Pharmacokinetics

- The mean (±SD) clearance from the studied patients in the fulvestrant treatment group was estimated at 32.3 ± 5.24 L/hr (range 15.2 to 41.6). AUC during the first month of dosing was estimated at 9131 ± 5753 ng.hr/mL (range 2932 to 34760), approximately 21% higher than the steady state exposure (7530 ng.hr/mL) achieved with the standard monthly administration of the intramuscular (im) formulation (AstraZeneca Clinical Study Reports 9238IL/0020, 17 January 2001 and 9238IL/0021, 7 February 2001). The mean (±SD) maximum concentration (C_{max}) during month 1 was 19.7 ± 18.5 ng/mL that was reached (t_{max}) approximately 12.2 ± 7.1 days following commencement of the loading dose regimen. The mean (±SD) minimum concentration (C_{min}) during month 1 was 9.62 ± 2.91 ng/mL. The mean (±SD) AUC_{ss} was estimated at 8011 ± 1847 ng.hr/mL (range 6005 to 16458). The C_{max} and C_{min} overall were 16.7 ± 8.74 ng/mL and 7.71 ± 1.62 ng/mL, respectively.

Safety results

- The 2 treatment groups were comparable in terms of duration of treatment (exposure) with an overall mean (SD) duration of 159 (131) days.

- In total, there were 6 (0.9%) fatal SAEs involving 3 (0.9%) patients in each treatment group. In the fulvestrant group the fatal SAEs (by preferred term) were pulmonary embolism, myocardial ischemia and intestinal perforation. In the

exemestane group, the events were coma, encephalitis and pulmonary embolism. It was later established that the primary cause of death was breast cancer for the patient with a fatal SAE of coma. None of these SAEs were causally related to study treatment, as assessed by the investigator (Table S4).

- Overall, 77 (11.1%) patients experienced a total of 99 non-fatal SAEs during the treatment period. The number of patients with non-fatal SAEs in each group was similar with 37 (10.5%) in the fulvestrant group and 40 (11.8%) in the exemestane group. However, the total number of SAEs reported in the fulvestrant group was smaller versus exemestane, 42 vs 57. Few patients experienced DAEs in either group with 7 (2.0%) in the fulvestrant group and 9 (2.6%) in the exemestane group. There were no patients identified with OAEs (Table S4 and Table S5). The reporting of pre-specified AEs (irrespective of CTC Grade) was similar in each treatment group.

- During the treatment period 3752 AEs were reported by 614 (88.9%) of the 691 patients in the safety analysis set. The number (%) of patients reporting any AE was similar for each treatment group with 312 (88.9%) in the fulvestrant group vs 302 (88.8%) in the exemestane group. The most commonly reported AEs in the fulvestrant and exemestane groups were nausea, fatigue and arthralgia with 70 (19.9%) vs 74 (21.8%), 56 (16.0%) vs 79 (23.2%) and 49 (14.0%) vs 49 (14.4%) patients, respectively. The number of patients reporting AEs for these preferred terms was similar with the exception of fatigue; fewer patients reported fatigue in the fulvestrant group. Within the "General disorders and administration site conditions" all other AEs were reported with similar frequency other than asthenia; in the fulvestrant group 41 (11.7%) patients reported asthenia vs 28 (8.2%) in the exemestane group.

- Other AEs were reported with similar frequency in each treatment group with the possible exception of hot flush, pain in extremity, urinary tract infection and influenza; reported as follows (fulvestrant vs exemestane): 37 (10.5%) vs 49 (14.4%), 30 (8.5%) vs 43 (12.6%), 21 (6.0%) vs 13 (3.8%) and 18 (5.1%) vs 8 (2.4%), respectively. The most commonly reported AEs in both treatment groups were typically CTC Grade 1 or 2 with relatively few events of CTC Grade 3 or 4. 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 AE was hot flush with 31 (8.8%) patients in the fulvestrant treatment group versus 39 (11.5%) in the exemestane group; injection site pain followed with 33 (9.4%) patients vs 28 (8.2%), respectively. Overall, treatment related AEs were typically CTC Grade 1 or 2 with a few events of CTC Grade 3 (fatigue). There were no CTC Grade 4 or 5 treatment related AEs.

- There were no remarkable changes in hematology and clinical chemistry and no apparent differences for the within-group and between-group comparisons. There

were no remarkable changes in vital signs and no apparent differences for the within-group and between-group comparisons.

Table S4 Overview of safety (Safety analysis set)

Category of adverse event[a]	Number (%) of patients who had an adverse event in each category[b]	
	Fulvestrant (N=351)	Exemestane (N=340)
Any adverse events	312 (88.9%)	302 (88.8%)
Serious adverse events	40 (11.4%)	42 (12.4%)
Serious adverse events leading to death	3 (0.9%)	3 (0.9%)
Serious adverse events not leading to death	37 (10.5%)	40 (11.8%)
Discontinuations of study treatment due to adverse events	7 (2.0%)	9 (2.6%)
Other significant adverse event	0 (-)	0 (-)

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 30 days after last capsule (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 patients with serious adverse events (≥0.5% cut-off), summarized by SOC and PT (Safety analysis set)

MedDRA System Organ Class - Preferred Term	Fulvestrant (N=351)	Exemestane (N=340)
Respiratory, thoracic and mediastinal disorders		
- Dyspnea exacerbated	2 (0.6%)	2 (0.6%)
- Pleural effusion	0 (-)	3 (0.9%)
- Dyspnea	0 (-)	2 (0.6%)
Gastrointestinal disorders		
- Vomiting	3 (0.9%)	0 (-)
- Small intestine obstruction	2 (0.6%)	0 (-)
Infections and infestations		
- Urinary tract infection	2 (0.6%)	1 (0.3%)
- Cellulitis	2 (0.6%)	0 (-)
- Pneumonia	0 (-)	2 (0.6%)
Injury, poisoning and procedural complications		
- Hip fracture	2 (0.6%)	2 (0.6%)
Vascular disorders		
- Deep vein thrombosis	2 (0.6%)	2 (0.6%)
Musculoskeletal and connective tissue disorders		
- Bone pain	1 (0.3%)	3 (0.9%)
Blood and lymphatic system disorders		
- Anemia	1 (0.3%)	2 (0.6%)
Renal and urinary disorders		
- Renal failure acute	0 (-)	2 (0.6%)