Clinical trial results:
Ensayo fase III aleatorizado, multicéntrico, abierto, de grupos paralelos para comparar la eficacia y tolerabilidad de Fulvestrant (Faslodex®) durante tres años en combinación con Anastrozol (Arimidex®) durante 5 años versus Anastrozol durante 5 años como tratamiento hormonal adyuvante en mujeres posmenopáusicas con cáncer de mama temprano y receptores hormonales positivos.

A randomized, multicentral, phase III study of parallel groups to compare the efficiency and tolerance of Fulvestrant (Faslodex) administered for three years in combination with Anastrozol (Arimidex) for 5 years versus Anastrozol for 5 years as adjuvant hormonotherapy in postmenopausal women with early breast cancer and positive hormonal receptors.

Summary

EudraCT number	2007-003417-14
Trial protocol	ES
Global end of trial date	09 July 2016
Results information	
Result version number	v1 (current)
This version publication date	26 March 2020
First version publication date	26 March 2020

Trial information

Trial identification	
Sponsor protocol code	GEICAM 2006-10
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00543127
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA)
Sponsor organisation address	Avenida de los Pirineos 7, San Sebastián de los Reyes / Madrid, Spain, 28703
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 July 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare free disease survival of patients treated with Fulvestrant for 3 years and anastrozol for 5 years vesus free disease survival of patients treated with anastrozol for 5 years.

Protection of trial subjects:

Not applicable. It was not necessary to applied extra measures for protection of the subjects out of the good clinical practice environment.

Background therapy:

Radiotherapy was allowed, and could be concomitantly administered within the study.
The following restrictions applyed:
1. Concomitant treatments against cancer were not allowed.
2. Use of bisphosphonates to treat osteoporosis was allowed.
3. Administration of drugs containing sex hormones were not allowed. Use of a vaginal ring with estrogens or other topical preparations was allowed.
Use of hormone antagonists or related drugs was not allowed.
Use of topical applications, inhaled aerosols, eye drops, local injections, and mouthwashes (if not swallowed) containing corticosteroids or ketoconazole was allowed.
4. Patients receiving long-term anticoagulant treatment with warfarin could not participate
5. Patients who required anticoagulant treatment while receiving the trial treatment may receive low molecular weight heparin (LMWH) at the investigator’s discretion.
6. Patients who received anti-platelet agregants may have an increased bleeding risk from intramuscular injection.
Any drug that was considered necessary for patient safety and wellbeing could be administered at the investigator’s discretion.

Evidence for comparator:

Based on the results of multiple randomised studies, adjuvant treatment for hormone receptor positive breast cancer in postmenopausal women should include an aromatase inhibitor in order to decrease the risk of disease recurrence. Anastrozol for 5 years had shown to be superior in terms of efficacy and

tolerability as compared to tamoxifen becoming a standard treatment in this group of patients (by the time of this study).

Actual start date of recruitment	28 January 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 870
Worldwide total number of subjects	870
EEA total number of subjects	870

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	538
From 65 to 84 years	328
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

From January 2008 to June 2010, 872 patients were recruited in 53 Spanish sites belonging to GEICAM, Spanish Breast Cancer Group. For 2 patients the informed consent document could not be found and were not included in the analysis that was finally performed with 870 patients.

Pre-assignment

Screening details:

872 patients were recruited. For 2 patients the informed consent document could not be found and were not included in the analysis that was finally performed with 870 patients. 437 to control arm (Anastrozole) and 433 to experimental arm (Fulvestrant + Anastrozole). 18 patients (3 control arm + 15 experimental arm) never received treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fulvestrant + Anastrozole

Arm description:

Fulvestrant loading dose regimen consisted of two 5 ml intramuscular injections on day 0 (500 mg), 250 mg single injection on days 14 and 28, and 250 mg single injection every 28 days thereafter for 3 years plus
Anastrozole 1 mg PO once daily for 5 years

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant loading dose regimen consisted of two 5 ml intramuscular injections on day 0 (500 mg), 250 mg single injection on days 14 and 28, and 250 mg single injection every 28 days thereafter for 3 years. Fulvestrant was supplied in a concentration of 250 mg in 5 ml in a prefilled syringe. Each fulvestrant dose was administered as a 250 mg dose, i.e. a 5 ml IM injection.
Injections were administered by the IM route in the upper lateral quadrant of the buttock using an aseptic parenteral technique. The injection was administered slowly over approximately 1-2 minutes. After administration, investigator examined injection sites for local reactions. Patients was instructed to report to the investigator any complications that may occur.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Anastrozol 1 mg once daily orally for 5 years

Arm title	Anastrozole

Arm description:

Anastrozole 1 mg will be administered orally as one tablet daily for 5 years.

Arm type	Active comparator

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Anastrozol 1 mg once daily orally for 5 years

Number of subjects in period 1	Fulvestrant + Anastrozole	Anastrozole
Started	433	434
Completed	288	319
Not completed	145	118
Consent withdrawn by subject	48	20
Physician decision	1	-
Adverse event, non-fatal	21	23
Death	3	4
Other	12	15
Transferred to other arm/group	3	-
Breast Cancer Relapse	20	25
Second primary malignacy	12	9
Lost to follow-up	8	18
Protocol deviation	2	4
Patients not treated	15	-
Joined	0	3
Transferred in from other group/arm	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Fulvestrant + Anastrozole
Reporting group description:	
Fulvestrant loading dose regimen consisted of two 5 ml intramuscular injections on day 0 (500 mg), 250 mg single injection on days 14 and 28, and 250 mg single injection every 28 days thereafter for 3 years plus Anastrozole 1 mg PO once daily for 5 years	
Reporting group title	Anastrozole
Reporting group description:	
Anastrozole 1 mg will be administered orally as one tablet daily for 5 years.	

Reporting group values	Fulvestrant + Anastrozole	Anastrozole	Total
Number of subjects	433	437	870
Age categorical Units: Subjects			
Adults (18-64 years)	267	271	538
From 65-84 years	164	164	328
85 years and over	2	2	4
Age continuous Units: years			
median	62	62	
full range (min-max)	40 to 86	44 to 86	-
Gender categorical Units: Subjects			
Female	433	437	870
Male	0	0	0
Breast Surgery Units: Subjects			
Conservative	303	310	613
Mastectomy	130	127	257
Axillary surgery Units: Subjects			
Axillary dissection	258	281	539
Sentinel Node Biopsy	174	155	329
Unknown	1	1	2
Previous chemotherapy Units: Subjects			
Adjuvant	256	261	517
Neoadjuvant	37	34	71
Neoadjuvant + Adjuvant	3	2	5
None	137	140	277
Previous radiotherapy Units: Subjects			
Yes	348	347	695
No	85	90	175
Histopathologic type Units: Subjects			

Invasive Ductal Carcinoma	337	346	683
Invasive Lobular Carcinoma	71	71	142
Other	25	20	45
Histologic grade			
The grade of a breast cancer is a prognostic factor and is representative of the "aggressive potential" of the tumor. In a broad generalization, "low grade" cancers tend to be less aggressive than "high grade" cancers. There are 3 grades: Grade I tumors have a total score of 3-5, Grade II tumors have a total score of 6-7 and Grade III tumors have a total score of 8-9. Grade X is unknown result.			
Units: Subjects			
Grade 1	88	82	170
Grade 2	216	235	451
Grade 3	94	83	177
Grade X	35	37	72
Final diagnosis tumor size			
Using the Tumour Node Metastasis staging system (TNM) after surgery, the "T" plus a number (0 to 4) is used to describe the size of the tumor. The T0 means the lower size, and the T4 means the higher size. TX means unknown.			
Units: Subjects			
T1	220	243	463
T2	189	179	368
T3-T4	22	14	36
TX	2	1	3
Nodal status			
The "N" in the TNM staging stands for lymph nodes. NX: not evaluated. N0: No cancer was found / Only areas of cancer smaller than 0.2 mm. N1: The cancer has spread to 1 to 3 axillary lymph nodes and/or the internal mammary lymph nodes. N2: The cancer has spread to 4 to 9 axillary lymph nodes, or it has spread to the internal mammary lymph nodes, but not the axillary lymph nodes. N3: The cancer has spread to 10 or more axillary lymph nodes, or it has spread to the lymph nodes located under the clavicle, or collarbone. It may have also spread to the internal mammary lymph nodes.			
Units: Subjects			
N0	214	200	414
N1	157	164	321
N2	42	52	94
N3	14	18	32
NX	6	3	9
Tumor size			
Units: cm			
median	2	2	
full range (min-max)	0.08 to 10	0.0 to 15	-

End points

End points reporting groups

Reporting group title	Fulvestrant + Anastrozole

Reporting group description:

Fulvestrant loading dose regimen consisted of two 5 ml intramuscular injections on day 0 (500 mg), 250 mg single injection on days 14 and 28, and 250 mg single injection every 28 days thereafter for 3 years plus
Anastrozole 1 mg PO once daily for 5 years

Reporting group title	Anastrozole

Reporting group description:

Anastrozole 1 mg will be administered orally as one tablet daily for 5 years.

Primary: Disease Free Survival (DFS) Events

End point title	Disease Free Survival (DFS) Events

End point description:

Disease-free survival (DFS) has been evaluated in patients treated with Fulvestrant for 3 years and Anastrozole for 5 years as compared to DFS in patients treated with anastrozole for 5 years.
DFS event is defined as the evidence of local and/or distant recurrence, new primary breast tumour, or death from any cause.

End point type	Primary

End point timeframe:

Up to 5 years

End point values	Fulvestrant + Anastrozole	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	437		
Units: Count of participants				
Breast Cancer Relapse	35	43		
Second primary breast cancer	1	3		
Death without evidence of relapse	13	16		
No DFS event	384	375		

Attachments (see zip file)	DFS Kaplan-Meier/2006-10 KM DFS.docx

Statistical analyses

Statistical analysis title	Kaplan–Meier and log rank test

Statistical analysis description:

Kaplan–Meier methods and log rank test

Comparison groups	Fulvestrant + Anastrozole v Anastrozole

Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.351
Method	Logrank

Statistical analysis title	Cox's proportional Hazard Ratio
Statistical analysis description:	
Cox's proportional hazards model	
Comparison groups	Fulvestrant + Anastrozole v Anastrozole
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.352
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.22

Secondary: Breast Cancer Specific Survival (BCsS)	
End point title	Breast Cancer Specific Survival (BCsS)
End point description:	
BCsS events has been evaluated in patients treated with Fulvestrant for 3 years and Anastrozole for 5 years as compared to BCsS in patients treated with anastrozole for 5 years. BCsS event is defined as the time to death for breast cancer.	
End point type	Secondary
End point timeframe:	
Up to 5 years	

End point values	Fulvestrant + Anastrozole	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	437		
Units: Events	17	18		

Attachments (see zip file)	BCsS KM/2006-10 KM BCsS.docx

Statistical analyses

Statistical analysis title	Kaplan–Meier and log rank test
Statistical analysis description:	
Kaplan–Meier methods and log rank test	
Comparison groups	Anastrozole v Fulvestrant + Anastrozole
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.966
Method	Logrank

Statistical analysis title	Cox's proportional Hazard Ratio
Statistical analysis description:	
Cox's proportional hazards model	
Comparison groups	Fulvestrant + Anastrozole v Anastrozole
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.966
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.91

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS event has been evaluated in patients treated with Fulvestrant for 3 years and Anastrozole for 5 years as compared to DFS in patients treated with anastrozole for 5 years. OS event is defined as the death from any cause.	
End point type	Secondary
End point timeframe:	
Up to 5 years	

End point values	Fulvestrant + Anastrozole	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	437		
Units: Events	28	34		

Attachments (see zip file)	OS KM/2006-10 KM OS.docx

Statistical analyses

Statistical analysis title	Kaplan–Meier and log rank test

Statistical analysis description:

Kaplan–Meier methods and log rank test

Comparison groups	Fulvestrant + Anastrozole v Anastrozole
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.558
Method	Logrank

Statistical analysis title	Cox's proportional Hazard Ratio

Statistical analysis description:

Cox's proportional hazards model.

Comparison groups	Fulvestrant + Anastrozole v Anastrozole
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.559
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.42

Secondary: Time to Recurrence (TR)

End point title	Time to Recurrence (TR)

End point description:

TR event has been evaluated in patients treated with Fulvestrant for 3 years and Anastrozole for 5 years as compared to DFS in patients treated with anastrozole for 5 years.
TR event is defined as the evidence of breast cancer recurrence (local and/or distant recurrence of breast cancer, does not include second primary malignancies or deaths from any cause).

End point type	Secondary
End point timeframe:	
Up to 5 years	

End point values	Fulvestrant + Anastrozole	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	437		
Units: Events	36	46		

Attachments (see zip file)	TTR KM/2006-10 KM TTR.docx

Statistical analyses

Statistical analysis title	Kaplan–Meier and log rank test
Statistical analysis description:	
Kaplan–Meier methods and log rank test	
Comparison groups	Fulvestrant + Anastrozole v Anastrozole
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.406
Method	Logrank

Statistical analysis title	Cox's proportional Hazard Ratio
Statistical analysis description:	
Cox's proportional hazards model.	
Comparison groups	Fulvestrant + Anastrozole v Anastrozole
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.407
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.29

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) and Serious Adverse Events (SAEs) were recorded from the date informed consent was signed, during treatment period, and for up to 8 weeks after the last injection or up to 30 days after the last tablet.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTC
Dictionary version	3.0

Reporting groups

Reporting group title	Fulvestrant + Anastrozole

Reporting group description:

Fulvestrant loading dose regimen consisted of two 5 ml intramuscular injections on day 0 (500 mg), 250 mg single injection on days 14 and 28, and 250 mg single injection every 28 days thereafter for 3 years plus Anastrozole 1 mg PO once daily for 5 years

Reporting group title	Anastrozole

Reporting group description:

Anastrozole 1 mg will be administered orally as one tablet daily for 5 years.

Serious adverse events	Fulvestrant + Anastrozole	Anastrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 415 (9.64%)	61 / 437 (13.96%)	
number of deaths (all causes)	28	34	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
Thrombosis/embolism (vascular access-related)			
subjects affected / exposed	0 / 415 (0.00%)	3 / 437 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever)			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Traffic accident			

subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcalcification in breast			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary malignancy - possibly related to cancer treatment: uterine cervix cancer			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea (shortness of breath)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis/pulmonary infiltrates			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary/upper respiratory chest/thorax NOS pain			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angor			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac ischemia/infarction			
subjects affected / exposed	2 / 415 (0.48%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Conduction abnormality/atrioventricular heart block - av block-second degree mobitz type II			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular and nodal arrhythmia - atrial fibrilation			

subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular and nodal arrhythmia - sinus tachycardia			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Valvular heart disease			
subjects affected / exposed	0 / 415 (0.00%)	2 / 437 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilated cardiomyopathy			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS Cerebrovascular ischemia			
subjects affected / exposed	1 / 415 (0.24%)	4 / 437 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy: craneal - CN VI downward, inward movement of eye			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			

Hematoma			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemoglobin			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, CNS			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI - colon			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemorrhage GI - stomach			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage/bleeding associated with surgery, intra-operative or post-operative			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lymphoblastic leukemia			

subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	4 / 415 (0.96%)	4 / 437 (0.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhoea			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric diffuse			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis (including bile reflux gastritis)			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal abdomen NOS pain			
subjects affected / exposed	0 / 415 (0.00%)	2 / 437 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus, GI (functional obstruction of bowel)			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation, GI - appendix			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer, GI - duodenum			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu-like syndrome			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 415 (0.48%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver dysfunction/failure (clinical)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 415 (0.24%)	3 / 437 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreas cancer			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Induration/fibrosis (skin and subcutaneous tissue)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction/extravasation changes			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanoma			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Cystocele			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 415 (0.00%)	2 / 437 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary malignancy - possiby related to cancer treatment, specify: kidney cancer			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	2 / 415 (0.48%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	3 / 415 (0.72%)	5 / 437 (1.14%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint pain			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthrosis			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection with grade 3 or 4 neutrophils (ANC <1.0 x 109/l) - upper respiratory - lung (pneumonia)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC or grade 1 or 2 neutrophils - pulmonary/upper respiratory bronchus			

subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC or grade 1 or 2 neutrophils - pulmonary/upper respiratory lung (pneumonia)			
subjects affected / exposed	3 / 415 (0.72%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC or grade 1 or 2 neutrophils - pulmonary/upper respiratory upper airway nos			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC or grade 1 or 2 neutrophils - renal/genitourinary kidney			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC or grade 1 or 2 neutrophils - renal/genitourinary urinary tract nos			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC or grade 1 or 2 neutrophils - sexual/reproductive function vagina, vulva			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC or grade 1 or 2 neutrophils dermatology/skin skin (cellulitis)			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection with unknown ANC - cardiovascular heart (endocarditis)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC - gastrointestinal appendix			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC - gastrointestinal dental-tooth			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC - pulmonary/upper respiratory lung (pneumonia)			
subjects affected / exposed	1 / 415 (0.24%)	2 / 437 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC - renal/genitourinary urinary tract nos			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Fulvestrant + Anastrozole	Anastrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	192 / 415 (46.27%)	197 / 437 (45.08%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary malignancy - possiby related to cancer treatment, specify: uterine cervix cancer			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	

Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Thrombosis/embolism (vascular access-related)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue (asthenia, lethargy, malaise)			
subjects affected / exposed	30 / 415 (7.23%)	11 / 437 (2.52%)	
occurrences (all)	30	11	
Insomnia			
subjects affected / exposed	3 / 415 (0.72%)	0 / 437 (0.00%)	
occurrences (all)	3	0	
Obesity			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Drug intolerance			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Sweating (diaphoresis)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Weight gain			
subjects affected / exposed	12 / 415 (2.89%)	8 / 437 (1.83%)	
occurrences (all)	12	8	
Weight loss			
subjects affected / exposed	1 / 415 (0.24%)	4 / 437 (0.92%)	
occurrences (all)	1	4	
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever)			
subjects affected / exposed	2 / 415 (0.48%)	0 / 437 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			

Vaginal dryness			
subjects affected / exposed	2 / 415 (0.48%)	1 / 437 (0.23%)	
occurrences (all)	2	1	
Investigations			
Albumin, serum-low (hypoalbuminemia)			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
ALT, SGPT (Serum Glutamic Pyruvic Transaminase)			
subjects affected / exposed	3 / 415 (0.72%)	3 / 437 (0.69%)	
occurrences (all)	3	3	
AST, SGOT (Serum Glutamic Oxaloacetic Transaminase)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Bilirubin (hyperbilirubinemia)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Cholesterol, serum-high (hypercholesterolemia)			
subjects affected / exposed	9 / 415 (2.17%)	10 / 437 (2.29%)	
occurrences (all)	9	10	
GGT (Gamma-Glutamyl Transpeptidase)			
subjects affected / exposed	1 / 415 (0.24%)	4 / 437 (0.92%)	
occurrences (all)	1	4	
Lactate dehydrogenase serum increased			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
LDL-cholesterol high			
subjects affected / exposed	10 / 415 (2.41%)	15 / 437 (3.43%)	
occurrences (all)	10	15	
Triglyceride, serum-high (hypertriglyceridemia)			
subjects affected / exposed	2 / 415 (0.48%)	1 / 437 (0.23%)	
occurrences (all)	2	1	
Cardiac disorders			

Supraventricular and nodal arrhythmia - atrial tachycardia/paroxysmal atrial tachycardia			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	4 / 415 (0.96%)	8 / 437 (1.83%)	
occurrences (all)	4	8	
Dilated cardiomyopathy			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences (all)	1	1	
Mood alteration - depression			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences (all)	1	1	
Neuropathy: sensory			
subjects affected / exposed	1 / 415 (0.24%)	2 / 437 (0.46%)	
occurrences (all)	1	2	
Syncope (fainting)			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
General pain NOS			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	3 / 415 (0.72%)	3 / 437 (0.69%)	
occurrences (all)	3	3	
Restless legs syndrome			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Haemoglobin			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	

Leukocytes count decreased			
subjects affected / exposed	1 / 415 (0.24%)	4 / 437 (0.92%)	
occurrences (all)	1	4	
Neutrophil/granulocyte count decreased			
subjects affected / exposed	6 / 415 (1.45%)	4 / 437 (0.92%)	
occurrences (all)	6	4	
Platelet count decreased			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Anorexia nervosa			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Dry mouth/salivary gland (xerostomia)			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Mucositis/stomatitis (clinical exam) - oral cavity			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 415 (0.96%)	0 / 437 (0.00%)	
occurrences (all)	4	0	
Vomiting			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal abdomen NOS			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	

Flushing			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	2 / 415 (0.48%)	1 / 437 (0.23%)	
occurrences (all)	2	1	
Injection site reaction/extravasation changes			
subjects affected / exposed	2 / 415 (0.48%)	1 / 437 (0.23%)	
occurrences (all)	2	1	
Nail changes			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Pruritus/itching			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Rash/desquamation			
subjects affected / exposed	1 / 415 (0.24%)	2 / 437 (0.46%)	
occurrences (all)	1	2	
Rash: dermatitis associated with radiation - chemoradiation			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Endocrine disorders			
Hot flush			
subjects affected / exposed	21 / 415 (5.06%)	15 / 437 (3.43%)	
occurrences (all)	21	15	
Masculinization of female			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Pancreatic endocrine: glucose			

intolerance			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthritis (non-septic)			
subjects affected / exposed	0 / 415 (0.00%)	5 / 437 (1.14%)	
occurrences (all)	0	5	
Fracture			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences (all)	1	1	
Joint-function			
subjects affected / exposed	0 / 415 (0.00%)	2 / 437 (0.46%)	
occurrences (all)	0	2	
Muscle weakness, generalized or specific area (not due to neuropathy) - whole body/generalized			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Myositis (inflamation/damage of muscle)			
subjects affected / exposed	1 / 415 (0.24%)	1 / 437 (0.23%)	
occurrences (all)	1	1	
Osteoporosis			
subjects affected / exposed	16 / 415 (3.86%)	18 / 437 (4.12%)	
occurrences (all)	16	18	
Arthrosis			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Dupuytren's contracture			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	2 / 415 (0.48%)	2 / 437 (0.46%)	
occurrences (all)	2	2	
Bone pain			
subjects affected / exposed	27 / 415 (6.51%)	13 / 437 (2.97%)	
occurrences (all)	27	13	

Extremity-limb pain			
subjects affected / exposed	2 / 415 (0.48%)	3 / 437 (0.69%)	
occurrences (all)	2	3	
Joint pain			
subjects affected / exposed	57 / 415 (13.73%)	64 / 437 (14.65%)	
occurrences (all)	57	64	
Muscle pain			
subjects affected / exposed	21 / 415 (5.06%)	12 / 437 (2.75%)	
occurrences (all)	21	12	
Neck pain			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infection with normal ANC or grade 1 or 2 neutrophils - gastrointestinal dental-tooth			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Infection with normal ANC or grade 1 or 2 neutrophils - pulmonary/upper respiratory bronchus			
subjects affected / exposed	0 / 415 (0.00%)	1 / 437 (0.23%)	
occurrences (all)	0	1	
Infection with unknown ANC - gastrointestinal oral cavity-gums (gingivitis)			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Infection with unknown ANC - musculoskeletal muscle (infection myositis)			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	
Infection with unknown ANC - sexual/reproductive function vagina			
subjects affected / exposed	2 / 415 (0.48%)	0 / 437 (0.00%)	
occurrences (all)	2	0	
Breast			
subjects affected / exposed	1 / 415 (0.24%)	0 / 437 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2008	Relevant Modification #1 dated 18/Sep/2008: Protocol Version 2 dated 13/Aug/2007 with amendment #1 dated 18/Sep/2008; the amendment was relevant because the inclusion criteria number 3 was updated to allow patients without node involvement (negative node) with a tumour size more than 1cm to be included, approved on 05/Nov/2008 by reference IRB and on 23/Nov/2008 by AEMPs.
07 September 2009	Relevant Modification #2 dated 15/Jun/2009: Protocol Version 2 dated 13/Aug/2007 with amendment #1 dated 18/Sep/2008 and amendment#2 dated 15/Jun/2009; the amendment was relevant because the inclusion criteria number 3 was updated to allow patients with stage IIIC invasive breast cancer (except patients with metastasis in infraclavicular nodes) to be included approved on 07/Sep/2009 by reference IRB and on 25/Sep/2009 by AEMPs.
04 April 2011	Relevant Modification #3 dated 03/May/2011: Protocol Version 2 dated 13/Aug/2007 with amendment #1 dated 18/Sep/2008, amendment #2 dated 15/Jun/2009 and amendment #3 dated 21/Feb/2011; the amendment was relevant because the recruitment was finished early and the justification was recorded in the new protocol version and an Adenda to Inform Consent Form (ICF) was generated to inform to all patient who were on treatment in that moment (Adenda Main ICF dated 21/Feb/2011) approved on 04/Apr/2011 by reference IRB and on 03/May/2011 by AEMPs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 June 2010	On 29/Jun/2010 the recruitment was early interrupted with 872 enrolled patients because new information was published of other clinical trial about the treatment with fulvestrant in combination with anastrozole (FACT trial), and the financer decided to stop the study support.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No firm conclusions can be drawn because of the limited sample size achieved, due to the early stop of the trial.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31152327