Clinical trial results:
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

Summary

EudraCT number	2004-000727-15
Trial protocol	HU
Global end of trial date	30 September 2016

Results information

Result version number	v1 (current)
This version publication date	05 August 2017
First version publication date	05 August 2017
Summary attachment (see zip file)	PDF of the article summarizing the results (Chia et al EFECT JCO 2008.pdf)

Trial information

Trial identification

Sponsor protocol code	D6697C00048 - 9238IL/0048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Alderley Park, Macclesfield, United Kingdom, SK10 4TG
Public contact	Jasmine Lichfield, AstraZeneca, 44 (0)7585404954, jasmine.lichfield@astrazeneca.com
Scientific contact	Jasmine Lichfield, AstraZeneca, 44 (0)7585404954, jasmine.lichfield@astrazeneca.com

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	30 June 2006
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2006
Global end of trial reached?	Yes
Global end of trial date	30 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of FASLODEX™ vs AROMASIN™ in postmenopausal women to see whether one drug will be more effective than the other in preventing the growth of cancer cells and also to see whether one drug will be better tolerated than the other.

Protection of trial subjects:

An IDMC was implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2003
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	Argentina: 53
Country: Number of subjects enrolled	Belgium: 51
Country: Number of subjects enrolled	Brazil: 88
Country: Number of subjects enrolled	Canada: 102
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	South Africa: 44
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 190
Worldwide total number of subjects	759
EEA total number of subjects	245

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)	424
From 65 to 84 years	322
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Recruitment occurred between 5th August 2003 and 10th November 2005 in hospitals, clinics and offices across several countries.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	759
Number of subjects completed	693

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screening failure - not randomised: 66

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fulvestrant

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	FASLODEX
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant 500mg (2 x 5mL IM injections) as a loading dose on Day 0, followed by 250mg (1 x 5 mL) on Day 14, Day 28 then monthy (28 +/- 3 days).

Arm title	Exemestane

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	AROMASIN
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25mg, once daily, po

Number of subjects in period 1[1]	Fulvestrant	Exemestane
Started	351	342
Completed	351	342

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number enrolled into the trial (759) is all patients enrolled into screening, whereas the baseline period number (693) is those who were enrolled and randomized. The 66 patients who failed screening due to ineligibility are removed from this period.

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Fulvestrant

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant 500mg (2 x 5mL IM injections) as a loading dose on Day 0, followed by 250mg (1 x 5 mL) on Day 14, Day 28 then monthy (28 +/- 3 days).

Arm title	Exemestane

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25mg, once daily, po

Number of subjects in period 2	Fulvestrant	Exemestane
Started	351	342
Completed	119	118
Not completed	232	224
information not collected	232	224

Baseline characteristics

Reporting groups	
Reporting group title	Fulvestrant
Reporting group description: -	
Reporting group title	Exemestane
Reporting group description: -	

Reporting group values	Fulvestrant	Exemestane	Total
Number of subjects	351	342	693
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	189	194	383
From 65-84 years	156	141	297
85 years and over	6	7	13
Age Continuous Units: years			
arithmetic mean	63.2	63	
standard deviation	± 10.96	± 11.03	-
Gender Categorical Units: Subjects			
Female	351	342	693
Race Units: Subjects			
Caucasian	313	312	625
Black	11	13	24
Oriental	4	4	8
Other	23	13	36

Subject analysis sets	
Subject analysis set title	Full Analysis Set (ITT population)
Subject analysis set type	Full analysis
Subject analysis set description: All randomised patients	

Reporting group values	Full Analysis Set (ITT population)		
Number of subjects	693		

Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	383		
From 65-84 years	297		
85 years and over	13		
Age Continuous Units: years			
arithmetic mean	63.1		
standard deviation	± 10.99		
Gender Categorical Units: Subjects			
Female	693		
Race Units: Subjects			
Caucasian	625		
Black	24		
Oriental	8		
Other	36		

End points

End points reporting groups

Reporting group title	Fulvestrant
Reporting group description: -	
Reporting group title	Exemestane
Reporting group description: -	
Reporting group title	Fulvestrant
Reporting group description: -	
Reporting group title	Exemestane
Reporting group description: -	
Subject analysis set title	Full Analysis Set (ITT population)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised patients	

Primary: Time to progression

End point title	Time to progression
End point description:	
Time from randomisation to the earliest evidence of disease progression, or death from any cause.	
End point type	Primary
End point timeframe:	
Time from randomisation to disease progression	

End point values	Fulvestrant	Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	342		
Units: Days				
median (not applicable)	112 (± 0)	112 (± 0)		

Statistical analyses

Statistical analysis title	Log rank test for time to progression
Statistical analysis description:	
Log rank test (fitting treatment only) for time from randomisation to objective disease progression or death from any cause	
Comparison groups	Fulvestrant v Exemestane
Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.6531
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.963

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.819
upper limit	1.133

Notes:

[1] - HR < 1 favours fulvestrant

Secondary: Objective response rate

End point title	Objective response rate

End point description:

The number of patients with measurable disease at baseline who had a complete or partial objective response during the study.

End point type	Secondary

End point timeframe:

Between randomisation and data cut off

End point values	Fulvestrant	Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[2]	270[3]		
Units: Patients	20	18		

Notes:

[2] - Patients evaluable for response (measurable disease at baseline)

[3] - Patients evaluable for response (measurable disease at baseline)

Statistical analyses

Statistical analysis title	Logistic regression of objective response rate

Statistical analysis description:

Logisitic regression adjusting for treatment only

Comparison groups	Fulvestrant v Exemestane
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.7364
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.578
upper limit	2.186

Notes:

[4] - OR >1 favours fulvestrant

Secondary: Clinical benefit rate

End point title	Clinical benefit rate

End point description:

The number of patients with measurable disease who had a complete or partial objective response or stable disease for at least 24 weeks during the study

End point type	Secondary

End point timeframe:

Between randomisation and data cut off

End point values	Fulvestrant	Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[5]	270[6]		
Units: patients	87	85		

Notes:

[5] - Patients evaulable for response (measurable disease at baseline)

[6] - Patients evaulable for response (measurable disease at baseline)

Statistical analyses

Statistical analysis title	Logisitic regression of clinical benefit rate

Statistical analysis description:

Logistic regression adjusting for treatment only

Comparison groups	Fulvestrant v Exemestane
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.8534
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.487

Notes:

[7] - OR > 1 favours fulvestrant

Secondary: Quality of Life - Trial Outcome Index (TOI)

End point title	Quality of Life - Trial Outcome Index (TOI)

End point description:

TOI measured at baseline and month 12 are summarised.

End point type	Secondary

End point timeframe:

From randomisation to data cut off

End point values	Fulvestrant	Fulvestrant	Exemestane	Exemestane
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	290[8]	290[9]	280	280[10]
Units: none				
arithmetic mean (standard deviation)	52.1 (± 10.67)	51.4 (± 7.98)	53.1 (± 9.99)	54 (± 10.31)

Notes:

[8] - number at baseline was 291

[9] - number at month 12 was 40

[10] - number at month 12 was 42

Statistical analyses

Statistical analysis title	Repeated measures analysis of TOI over time

Statistical analysis description:

A linear mixed model using baseline score as a covariate.

Comparison groups	Fulvestrant v Exemestane
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.322
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5506
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5405
upper limit	1.6417

Notes:

[11] - A positive treatment difference favours fulvestrant.

Secondary: Functional Assessment of Cancer Therapy - Endocrine system (FACT-ES)

End point title	Functional Assessment of Cancer Therapy - Endocrine system (FACT-ES)

End point description:

Baseline and month 12 data shown.

End point type	Secondary

End point timeframe:

From randomisation to data cut off

End point values	Fulvestrant	Fulvestrant	Exemestane	Exemestane
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	286[12]	286[13]	281	281[14]
Units: none				
arithmetic mean (standard deviation)	138.1 (± 20.44)	141 (± 20.86)	140.6 (± 20.93)	143.9 (± 19.58)

Notes:
[12] - number at baseline was 287
[13] - number at month 12 was 42
[14] - number at month 12 was 44

Statistical analyses

Statistical analysis title	Repeated measures analysis of FACT-ES over time
Statistical analysis description:	
A linear mixed model using baseline score as a covariate	
Comparison groups	Fulvestrant v Exemestane
Number of subjects included in analysis	567
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	= 0.7772
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2795
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6597
upper limit	2.2187

Notes:
[15] - A positive treament difference favours fulvestrant

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to 8 weeks after the last study treatment injection was administered or 30 days after the last study treament capsule was taken, whichever was longer.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Exemestane

Reporting group description:

Exemestane

Reporting group title	Fulvestrant

Reporting group description:

Fulvestrant

Serious adverse events	Exemestane	Fulvestrant	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 340 (12.35%)	40 / 351 (11.40%)	
number of deaths (all causes)	117	119	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			

subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 340 (0.59%)	2 / 351 (0.57%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (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 exacerbated			
subjects affected / exposed	2 / 340 (0.59%)	2 / 351 (0.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 340 (0.59%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	3 / 340 (0.88%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 340 (0.29%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticipatory anxiety			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	2 / 340 (0.59%)	2 / 351 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ankle fracture			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 340 (0.29%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischemia			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Palpitations			

subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningeal disorder			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 340 (0.59%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 340 (0.00%)	3 / 351 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 340 (0.29%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 340 (0.00%)	2 / 351 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen tongue			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (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			

Rash			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 340 (0.59%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	3 / 340 (0.88%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 340 (0.29%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 340 (0.29%)	2 / 351 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 340 (0.00%)	2 / 351 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 340 (0.29%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 340 (0.59%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Actinomycosis			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 340 (0.29%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 340 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 340 (0.29%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Exemestane	Fulvestrant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	298 / 340 (87.65%)	307 / 351 (87.46%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	49 / 340 (14.41%)	37 / 351 (10.54%)	
occurrences (all)	71	48	
Nervous system disorders			
Headache			
subjects affected / exposed	41 / 340 (12.06%)	42 / 351 (11.97%)	
occurrences (all)	66	72	
Dizziness			
subjects affected / exposed	27 / 340 (7.94%)	22 / 351 (6.27%)	
occurrences (all)	37	27	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	79 / 340 (23.24%)	56 / 351 (15.95%)	
occurrences (all)	115	85	
Asthenia			
subjects affected / exposed	28 / 340 (8.24%)	41 / 351 (11.68%)	
occurrences (all)	40	60	

Injection site pain			
subjects affected / exposed	31 / 340 (9.12%)	33 / 351 (9.40%)	
occurrences (all)	52	62	
Oedema peripheral			
subjects affected / exposed	23 / 340 (6.76%)	19 / 351 (5.41%)	
occurrences (all)	30	26	
Pyrexia			
subjects affected / exposed	15 / 340 (4.41%)	19 / 351 (5.41%)	
occurrences (all)	18	23	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	74 / 340 (21.76%)	69 / 351 (19.66%)	
occurrences (all)	107	112	
Diarrhoea			
subjects affected / exposed	44 / 340 (12.94%)	46 / 351 (13.11%)	
occurrences (all)	55	63	
Vomiting			
subjects affected / exposed	37 / 340 (10.88%)	34 / 351 (9.69%)	
occurrences (all)	43	48	
Constipation			
subjects affected / exposed	28 / 340 (8.24%)	31 / 351 (8.83%)	
occurrences (all)	33	46	
Abdominal pain			
subjects affected / exposed	13 / 340 (3.82%)	20 / 351 (5.70%)	
occurrences (all)	16	28	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 340 (11.47%)	33 / 351 (9.40%)	
occurrences (all)	53	48	
Dyspnoea			
subjects affected / exposed	28 / 340 (8.24%)	30 / 351 (8.55%)	
occurrences (all)	33	41	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	28 / 340 (8.24%)	21 / 351 (5.98%)	
occurrences (all)	33	26	

Anxiety			
subjects affected / exposed	19 / 340 (5.59%)	19 / 351 (5.41%)	
occurrences (all)	26	27	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	49 / 340 (14.41%)	49 / 351 (13.96%)	
occurrences (all)	85	75	
Pain in extremity			
subjects affected / exposed	43 / 340 (12.65%)	30 / 351 (8.55%)	
occurrences (all)	63	47	
Back pain			
subjects affected / exposed	34 / 340 (10.00%)	28 / 351 (7.98%)	
occurrences (all)	42	42	
Bone pain			
subjects affected / exposed	23 / 340 (6.76%)	22 / 351 (6.27%)	
occurrences (all)	31	41	
Myalgia			
subjects affected / exposed	20 / 340 (5.88%)	21 / 351 (5.98%)	
occurrences (all)	35	28	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 340 (4.71%)	19 / 351 (5.41%)	
occurrences (all)	21	27	
Urinary tract infection			
subjects affected / exposed	12 / 340 (3.53%)	19 / 351 (5.41%)	
occurrences (all)	20	20	
Influenza			
subjects affected / exposed	8 / 340 (2.35%)	18 / 351 (5.13%)	
occurrences (all)	13	22	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	32 / 340 (9.41%)	33 / 351 (9.40%)	
occurrences (all)	36	50	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2004	Patients with bone lesions, lytic or mixed (lytic + sclerotic), in the absence of measurable disease per RECIST criteria, were made eligible to participate in the study. Clarification of following: - That either bone scans or skeletal surveys were to be performed at baseline for all patients, then every 4 months until progression for patients with any metastatic bone lesions at baseline. - Exclusion of patients with known brain or CNS metastases (Exclusion # 12). - Tumor assessments in accordance with RECIST criteria. - Addition of safety info for fulvestrant & exemestane. - Concomitant treatments permitted and prohibited. - Exclusion of intercurrent systemic anti cancer therapy after prior non-steroidal AI therapy. - Tumor assessment schedule for patients who withdrew for reasons other than progression. - QoL completion & removal of the 1-month post progression QoL completion time point. - Health care resource completion and timing of health care resource collection. - Exclusion laboratory values for ALT or AST (Exclusion #6). - Timing of AE collection. - AE reporting including serious adverse events. - Change to details of hormone assessments. - Timing of PK assessments
31 July 2007	To allow patients who were on study drug therapy at the time of final survival analysis to continue on their assigned study therapy and go into an open label extension phase. The extension phase allowed patients who are receiving benefit from study therapy to continue to receive study therapy after the time of final survival analysis. During the extension AstraZeneca only collected safety assessments (i.e. SAE's and drug accountability data). Radiological assessments, haematology & clinical chemistry assessments were continued to be followed as normal standard level of care but data were not collected on the CRF.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported