



Clinical trial results:

A randomised, open-label, parallel group, multicentre, phase II study to compare the efficacy and tolerability of fulvestrant (FASLODEX) 500mg with anastrozole (ARIMIDEX) 1mg as first line hormonal treatment for postmenopausal women with hormone receptor positive advanced breast cancer.

Summary

EudraCT number	2005-002868-28
Trial protocol	CZ ES GB IT
Global end of trial date	15 July 2014

Results information

Result version number	v1 (current)
This version publication date	26 January 2018
First version publication date	26 January 2018

Trial information

Trial identification

Sponsor protocol code	D6995C00006
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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 07585404954, jasmine.lichfield@astrazeneca.com
Scientific contact	Jasmine Lichfield, AstraZeneca, 44 07585404954, 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	31 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2008
Global end of trial reached?	Yes
Global end of trial date	15 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the clinical benefit rate in patients treated with fulvestrant 500mg with patients treated with anastrozole 1mg

Protection of trial subjects:

The protocol, relevant consent forms and patient information sheet were submitted for review to a recognised Independent Ethics Committee (IEC), covering each study site. Written approval identifying the Study Protocol version and consent document was obtained before patient recruitment commenced. Amendments to the Study Protocol were also submitted for written IEC approval before implementation.

In North America this study was conducted under a Food and Drug Administration (FDA) investigational new drug (IND) application. In centres in North America the principal investigator provided an Institutional Review Board (IRB) with reports of any serious adverse drug reactions from any other study conducted with the investigational product.

Progress reports and notifications of serious adverse drug reactions were provided to the IRB or IEC according to local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Brazil: 35
Country: Number of subjects enrolled	Czech Republic: 54
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	233
EEA total number of subjects	183

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)	93
From 65 to 84 years	134
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	233
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Number of subjects completed	205
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	death: 1
Reason: Number of subjects	unknown: 2
Reason: Number of subjects	Consent withdrawn by subject: 4
Reason: Number of subjects	Protocol deviation: 20
Reason: Number of subjects	Adverse event, non-fatal: 1

Period 1

Period 1 title	Randomisation
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Is this the baseline period?	Yes
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Allocation method	Randomised - controlled
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Blinding used	Not blinded
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Arms

Are arms mutually exclusive?	Yes
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Arm title	Fulvestrant 500mg
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	FASLODEX
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
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Routes of administration	Intramuscular use
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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 monthly (28 +/- 3 days).

Arm title	Anastrozole 1mg
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Arm description: -

Arm type	Active comparator
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Investigational medicinal product name	ARIMIDEX
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Coated tablet
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Routes of administration	Oral use
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Dosage and administration details:

Anastrozole 1mg, once daily PO

Number of subjects in period 1 ^[1]	Fulvestrant 500mg	Anastrozole 1mg
Started	102	103
Completed	102	103

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 baseline period doesn't contain data for patients not randomised so the numbers won't match the world wide enrolment numbers

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fulvestrant 500mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	FASLODEX
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 monthly (28 +/- 3 days).

Arm title	Anastrozole 1mg
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Arm description: -

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

Dosage and administration details:

Anastrozole 1mg, once daily PO

Number of subjects in period 2	Fulvestrant 500mg	Anastrozole 1mg
Started	102	103
Completed	23	10
Not completed	79	93
Consent withdrawn by subject	16	19
death	63	74

Baseline characteristics

Reporting groups

Reporting group title	Fulvestrant 500mg
Reporting group description: -	
Reporting group title	Anastrozole 1mg
Reporting group description: -	

Reporting group values	Fulvestrant 500mg	Anastrozole 1mg	Total
Number of subjects	102	103	205
Age Categorical Units: Subjects			
Adults (18-64 years)	45	40	85
From 65-84 years	54	60	114
85 years and over	3	3	6
Age Continuous Units: years			
median	66	68	
full range (min-max)	40 to 89	48 to 87	-
Gender Categorical Units: Subjects			
Female	102	103	205

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All randomised patients	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: All randomised patients with no major protocol deviation	
Subject analysis set title	Evaluable for response Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All randomised patients with measurable disease at baseline	

Reporting group values	Full Analysis Set	Per Protocol Analysis Set	Evaluable for response Set
Number of subjects	205	198	182
Age Categorical Units: Subjects			
Adults (18-64 years)	85		
From 65-84 years	114		
85 years and over	6		
Age Continuous Units: years			
median	67		

full range (min-max)	40 to 89		
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Gender Categorical Units: Subjects			
Female	205	198	182

End points

End points reporting groups

Reporting group title	Fulvestrant 500mg
Reporting group description: -	
Reporting group title	Anastrozole 1mg
Reporting group description: -	
Reporting group title	Fulvestrant 500mg
Reporting group description: -	
Reporting group title	Anastrozole 1mg
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All randomised patients	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: All randomised patients with no major protocol deviation	
Subject analysis set title	Evaluable for response Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All randomised patients with measurable disease at baseline	

Primary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)
End point description: Patients with complete response, partial response or stable disease for at least 24 weeks.	
End point type	Primary
End point timeframe: Randomisation to data cut off for primary analysis	

End point values	Fulvestrant 500mg	Anastrozole 1mg	Full Analysis Set	Per Protocol Analysis Set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	102	103	205	198
Units: patients	74	69	143	139

Statistical analyses

Statistical analysis title	Logistic regression analysis of CBR
Statistical analysis description: Logistic regression controlling for treatment only	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.386
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.302
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.717
upper limit	2.38

Notes:

[1] - OR > 1 favours fulvestrant

Statistical analysis title	Logistic regression analysis of CBR
Statistical analysis description:	
Logistics regression analysis of CBR controlling for treatment only	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Per Protocol Analysis Set
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	= 0.276
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.404
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.763
upper limit	2.605

Notes:

[2] - OR > 1 favours fulvestrant

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description:	
patients with complete or partial response	
End point type	Secondary
End point timeframe:	
randomisation to data cut off for the primary analysis	

End point values	Fulvestrant 500mg	Anastrozole 1mg	Evaluable for response Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	89	93	182	
Units: patients	32	33	65	

Statistical analyses

Statistical analysis title	Logistic regression of ORR
Statistical analysis description: Logistic regression analysis of ORR controlling for treatment only.	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Evaluable for response Set
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.947
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.556
upper limit	1.874

Notes:

[3] - OR > 1 favours fulvestrant

Secondary: Time to Objective Disease Progression (TTP)

End point title	Time to Objective Disease Progression (TTP)
End point description: time to objective disease progression or death from any cause	
End point type	Secondary
End point timeframe: TTP from randomisation to data cut off for primary analysis	

End point values	Fulvestrant 500mg	Anastrozole 1mg	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102 ^[4]	103	205	
Units: days				
median (full range (min-max))	999999999 (999999999 to 999999999)	381 (0 to 602)	433 (0 to 604)	

Notes:

[4] - Median not reached

Statistical analyses

Statistical analysis title	Log rank analysis of TTP
Statistical analysis description: Log Rank analysis of TTP controlling for treatment only	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0496
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6266
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3929
upper limit	0.9991

Notes:

[5] - HR < 1 favours fulvestrant

Secondary: Time to treatment failure (TTTF)

End point title	Time to treatment failure (TTTF)
End point description: Time from randomisation to treatment discontinuation	
End point type	Secondary
End point timeframe: Randomisation to data cut off for 75% treatment failure	

End point values	Fulvestrant 500mg	Anastrozole 1mg	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	103	205	
Units: days				
median (full range (min-max))	536 (14 to 1401)	387 (16 to 1369)	457 (14 to 1401)	

Statistical analyses

Statistical analysis title	Log Rank Analysis of TTTF
Statistical analysis description: Log Rank analysis of TTTF controlling for treatment only	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.05
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1

Notes:

[6] - HR < 1 favours fulvestrant

Statistical analysis title	Cox regression analysis of TTF
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Statistical analysis description:

Cox regression analysis of TTF adjusting for baseline covariates

Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.04
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.98

Notes:

[7] - HR < 1 favours fulvestrant

Secondary: Time to Progression (investigator assessed) (TTP)

End point title	Time to Progression (investigator assessed) (TTP)
End point description:	
Time from randomisation to disease progression (investigator assessed) or death from any cause	
End point type	Secondary
End point timeframe:	
Randomisation to data cut off for 75% TTF analysis	

End point values	Fulvestrant 500mg	Anastrozole 1mg	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	103	205	
Units: days				
median (full range (min-max))	712 (0 to 1387)	400 (0 to 1369)	518 (0 to 1387)	

Statistical analyses

Statistical analysis title	Log Rank analysis of TTP
Statistical analysis description:	
Log rank analysis of TTP (investigator assessed) controlling for treatment only	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.92

Notes:

[8] - HR < 1 favours fulvestrant

Statistical analysis title	Cox regression analysis of TTP
Statistical analysis description:	
Cox regression analysis of TTP (investigator assessed)controlling for baseline covariates	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.01
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.9

Notes:

[9] - HR < 1 favours fulvestrant

Post-hoc: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: time from randomisation to death (any cause)	
End point type	Post-hoc
End point timeframe: randomisation to data cut off for 65% OS analysis	

End point values	Fulvestrant 500mg	Anastrozole 1mg	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	103	205	
Units: days				
median (full range (min-max))	1647 (8 to 3060)	1472 (16 to 2994)	1519 (8 to 3060)	

Statistical analyses

Statistical analysis title	Log Rank analysis of overall survival
Statistical analysis description: Log Rank analysis overall survival controlling for treatment only	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Post-hoc
Analysis type	superiority ^[10]
P-value	= 0.041
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.98

Notes:

[10] - HR < 1 favours fulvestrant

Statistical analysis title	Cox regression analysis of OS
Statistical analysis description: Cox regression analysis of OS controlling for baseline covariates	
Comparison groups	Fulvestrant 500mg v Anastrozole 1mg v Full Analysis Set

Number of subjects included in analysis	410
Analysis specification	Post-hoc
Analysis type	superiority ^[11]
P-value	= 0.126
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.08

Notes:

[11] - HR < 1 favours fulvestrant

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events = randomisation upto the point of data cut off for the primary efficacy analysis.

Serious adverse events = randomisation up to the point of data cut off for the 65% overall survival analysis

Adverse event reporting additional description:

Non-serious adverse events are reported from randomisation upto the point of data cut off for the primary efficacy analysis (56 days after last injection and 30 days after last tablet).

Serious adverse events are reported from randomisation up to the point of data cut off for the 65% overall survival analysis

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Fulvestrant 500mg
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Reporting group description:

Fulvestrant 500mg

Reporting group title	Anastrozole 1mg
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Reporting group description:

Anastrozole 1mg

Serious adverse events	Fulvestrant 500mg	Anastrozole 1mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 101 (23.76%)	22 / 103 (21.36%)	
number of deaths (all causes)	63	74	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to thorax			

subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 101 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Asthenia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 101 (0.99%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (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 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
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	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary ostial stenosis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuralgia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 101 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (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			

Febrile neutropenia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphadenopathy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacrimal disorder			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (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	1 / 101 (0.99%)	0 / 103 (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			
Angioedema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (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			
Decreased appetite			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (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	Fulvestrant 500mg	Anastrozole 1mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 101 (70.30%)	70 / 103 (67.96%)	
Vascular disorders			
Hot flush			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	8 / 101 (7.92%)	14 / 103 (13.59%)	
occurrences (all)	8	15	
Hypertension			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	6 / 101 (5.94%)	2 / 103 (1.94%)	
occurrences (all)	6	5	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	4 / 101 (3.96%)	13 / 103 (12.62%)	
occurrences (all)	26	16	
Dizziness			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	4 / 101 (3.96%)	6 / 103 (5.83%)	
occurrences (all)	4	6	
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	8 / 101 (7.92%)	8 / 103 (7.77%)	
occurrences (all)	14	9	
Fatigue			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	1 / 101 (0.99%)	8 / 103 (7.77%)	
occurrences (all)	1	8	
Injection site pain			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	6 / 101 (5.94%)	0 / 103 (0.00%)	
occurrences (all)	14	0	
Gastrointestinal disorders			

<p>Constipation</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 101 (9.90%)</p> <p>12</p>	<p>5 / 103 (4.85%)</p> <p>5</p>	
<p>Diarrhoea</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 101 (5.94%)</p> <p>7</p>	<p>7 / 103 (6.80%)</p> <p>7</p>	
<p>Vomiting</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 101 (7.92%)</p> <p>10</p>	<p>3 / 103 (2.91%)</p> <p>4</p>	
<p>Nausea</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 101 (9.90%)</p> <p>10</p>	<p>7 / 103 (6.80%)</p> <p>8</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Dyspnoea</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 101 (6.93%)</p> <p>8</p> <p>5 / 101 (4.95%)</p> <p>6</p>	<p>7 / 103 (6.80%)</p> <p>7</p> <p>8 / 103 (7.77%)</p> <p>9</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Bone pain</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>alternative dictionary used: MedDRA 10.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 101 (13.86%)</p> <p>19</p> <p>10 / 101 (9.90%)</p> <p>14</p>	<p>10 / 103 (9.71%)</p> <p>23</p> <p>8 / 103 (7.77%)</p> <p>8</p>	

Myalgia alternative dictionary used: MedDRA 10.1 subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 3	9 / 103 (8.74%) 10	
Infections and infestations Influenza alternative dictionary used: MedDRA 10.1 subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	6 / 103 (5.83%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2006	<p>Additional detail added regarding the exclusion of previously irradiated lesions from the analysis, as the effects of radiotherapy on tumours may manifest more than 6 weeks after completion of radiotherapy. Therefore inclusion of previously irradiated lesions in the analysis may have impacted the primary outcome variable of CBR.</p> <p>Also added further detail around concomitant use of vaginal creams and vaginal rings during the study. New evidence had come to light regarding the significance of the systemic absorption of oestrogens from topical vaginal preparations used in the treatment of menopausal symptoms (atrophic vaginitis) in patients taking AIs (Kendall et al 2006). The authors were of the opinion that the use of topical vaginal oestrogen-containing creams is contraindicated in patients taking AIs. On this basis, and also because the use of these creams had the potential to bias the study against the AI arm, the study restrictions were clarified to specifically preclude the use of oestrogen-containing vaginal creams or other oestrogen containing topical preparations. However given the distressing nature of atrophic vaginitis, it was felt necessary from an ethical point of view to allow the use of controlled-release oestrogen containing vaginal rings (e.g., Estrin®), as a last resort only, pending any updated advice, and only at the discretion of the investigator.</p>
12 April 2010	<p>At the DCO for the primary analysis, patients on fulvestrant 500 mg had a 60% longer TTP compared to patients on anastrozole 1 mg. The data maturity in terms of the proportion of patients with progression events was approximately 30%. A more mature analysis, planned for when approximately 75% of patients had discontinued study treatment, allowed a more meaningful interpretation of this secondary endpoint. Since patients were not followed within the study according to formal scheduled RECIST assessments from the time of primary DCO onwards, a "time to treatment failure" (TTF) analysis was planned where treatment failure was determined according to the investigator's opinion.</p> <p>This amendment also clarified the timing for the final analysis, and also documented that, for subjects still on study treatment, only serious adverse event data would be collected following the final analysis.</p>
07 February 2011	<p>Following a statistically significant benefit (time to progression hazard ratio = 0.66, 95% confidence interval (0.47, 0.92), $p=0.01$) in favour of fulvestrant, seen in the follow-up analysis of time to progression (TTP), it was decided to amend the protocol to investigate if the benefit observed for TTP translates into an overall survival (OS) benefit.</p> <p>The amendment covered the collection of OS data and detailed the performance of an OS analysis. It clarified that the "time to treatment failure analysis" (TTF) was not the final analysis for this study.</p>

03 December 2013	<p>The amendment covered the collection of overall survival (OS) data and described the change in timing for the final OS analysis.</p> <p>Significant decline in rate of death had been observed during the later stages of overall survival follow-up. This rate had become very unpredictable as the CSP amendment 3 was looking for events in a small group of patients. It was possible that 75% deaths would not be reached for several years, which was not considered a reasonable timeframe for obtaining information on OS. Performing the analysis at approximately 65% rather than 75% maturity did not make a large difference to the outcome, in terms of the largest observed HR which would achieve statistical significance ($p < 0.05$); 0.71 and 0.73 for 65% and 75% respectively.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported