EU Clinical Trials Register

Clinical trial results:

An Open-label, Non-Comparative Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of FASLODEX™ (fulvestrant) in Girls with Progressive Precocious Puberty Associated with McCune-Albright Syndrome

Summary

EudraCT number	2005-004893-26
Trial protocol	GB ES DE IT
Global end of trial date	20 July 2023

Results information

Result version number	v1
This version publication date	07 January 2024
First version publication date	07 January 2024

Trial information

Trial identification

Sponsor protocol code	D6992C00044

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00278915
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Clinical study Information Center
Sponsor organisation address	One MedImmune Way, Gaithersburg, Maryland, United States, 20878
Public contact	Global Clinical Lead, AstraZeneca Clinical study Information Center, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical study Information Center, +1 8772409479, information.center@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 September 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study included:
1. Safety component: The safety of study treatment will be evaluated by assessments of adverse events, withdrawals, laboratory data, ovarian volume as assessed by ultrasound, including the number of ovarian cysts and size of the largest cyst, and uterine volume.
2. Efficacy component: The efficacy of study treatment will be based on change in frequency of vaginal bleeding days, rate of increase in bone age, and growth rate.
3. Pharmacokinetics (PK) component: PK of fulvestrant in girls with progressive precocious puberty (PPP) associated with McCune-Albright syndrome (MAS).

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	30
EEA total number of subjects	11

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)	30
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at study sites located in France, Germany, Italy, Russian Federation, United Kingdom, and the United States of America.

Pre-assignment

Screening details:

A total of 30 participants were enrolled in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Fulvestrant

Arm description:

Participants received intramuscular injection of fulvestrant 2 mg/kg or 4 mg/kg (First 10 participants were dosed at 2 mg/kg then increased to 4 mg/kg. All subsequent participants were dosed at 4 mg/kg) into the buttock or thigh monthly for 12 months or until the participant demonstrates lack of efficacy based upon one or more of the primary endpoints or experiences a serious drug-related toxicity requiring treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received intramuscular injection of fulvestrant 2 mg/kg or 4 mg/kg (First 10 participants were dosed at 2 mg/kg then increased to 4 mg/kg. All subsequent participants were dosed at 4 mg/kg) into the buttock or thigh monthly for 12 months or until the participant demonstrates lack of efficacy based upon one or more of the primary endpoints or experiences a serious drug-related toxicity requiring treatment discontinuation.

Number of subjects in period 1	Fulvestrant
Started	30
Completed	29
Not completed	1
Disease progression	1

Baseline characteristics

Reporting groups

Reporting group title	Fulvestrant

Reporting group description:

Participants received intramuscular injection of fulvestrant 2 mg/kg or 4 mg/kg (First 10 participants were dosed at 2 mg/kg then increased to 4 mg/kg. All subsequent participants were dosed at 4 mg/kg) into the buttock or thigh monthly for 12 months or until the participant demonstrates lack of efficacy based upon one or more of the primary endpoints or experiences a serious drug-related toxicity requiring treatment discontinuation.

Reporting group values	Fulvestrant	Total	
Number of subjects	30	30	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	30	30	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	5.86		
standard deviation	± 1.846	-	
Gender, Male/Female			
Units: Participants			
Female	30	30	
Male	0	0	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	26	26	
More than one race	2	2	
Unknown or Not Reported	1	1	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	4	4	
Unknown or Not Reported	23	23	

End points

End points reporting groups

Reporting group title	Fulvestrant

Reporting group description:

Participants received intramuscular injection of fulvestrant 2 mg/kg or 4 mg/kg (First 10 participants were dosed at 2 mg/kg then increased to 4 mg/kg. All subsequent participants were dosed at 4 mg/kg) into the buttock or thigh monthly for 12 months or until the participant demonstrates lack of efficacy based upon one or more of the primary endpoints or experiences a serious drug-related toxicity requiring treatment discontinuation.

Primary: Percentage of Participants With Baseline Vaginal Bleeding Who Experienced Cessation of Vaginal Bleeding Over the Whole 12-month Treatment Period

End point title	Percentage of Participants With Baseline Vaginal Bleeding Who Experienced Cessation of Vaginal Bleeding Over the Whole 12-month Treatment Period[1]

End point description:

Percentage of participants with baseline vaginal bleeding who experienced cessation of vaginal bleeding days over a 12-month treatment period based on a worst-case approach (ie, missing diary card days counted as bleeding days) are reported. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who had bleeding during the 6 month baseline period.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 12 treatment period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (confidence interval 95%)	34.8 (16.4 to 57.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Frequency of Annualised Days of Vaginal Bleeding on Treatment Compared to Baseline

End point title	Change in Frequency of Annualised Days of Vaginal Bleeding on Treatment Compared to Baseline[2]

End point description:

Vaginal bleeding days are defined as the number of days in which vaginal bleeding, (including spotting) occurred. In order to annualise, a 12 month period is defined as 360 days and a 6 month period is defined as 180 days. Frequency of annualised vaginal bleeding days = [(number of vaginal bleeding

days)/(total number of days of the time interval under consideration)] multiplied by 360. Change in frequency is equal to the on treatment frequency minus the baseline frequency. Diary cards will capture days of vaginal bleeding during the 12-month treatment period. Change in the frequency of annualised days of vaginal bleeding during the 12 month treatment period compared to the 6 month baseline period, based on a worst-case scenario calculation (ie, missing diary card days counted as bleeding days) are reported. The full-analysis set (FAS) population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 12 treatment period

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Days per year				
median (full range (min-max))	-3.6 (-42 to 185)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Baseline Vaginal Bleeding Who Experienced ≥ 50% Reduction in the Number of Vaginal Bleeding Days on Treatment Compared to Baseline

End point title	Percentage of Participants With Baseline Vaginal Bleeding Who Experienced ≥ 50% Reduction in the Number of Vaginal Bleeding Days on Treatment Compared to Baseline[3]

End point description:

The percentage change in frequency is defined as 100% times the difference (the on-treatment period frequency minus the baseline period frequency), divided by the baseline period frequency. The percentage of participants with baseline vaginal bleeding days who experienced ≥ 50% reduction in the number of vaginal bleeding days during the 12 month treatment period compared to the 6 month baseline period based on a worst-case approach (ie, missing diary card days counted as bleeding days) are reported. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who had bleeding during the 6 month baseline period.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 12 treatment period

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (confidence interval 95%)	73.9 (51.6 to 89.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Baseline Vaginal Bleeding Who Experienced Cessation of Vaginal Bleeding Over a 6-month Treatment Period

End point title	Percentage of Participants With Baseline Vaginal Bleeding Who Experienced Cessation of Vaginal Bleeding Over a 6-month Treatment Period[4]

End point description:

Percentage of participants with baseline vaginal bleeding who experienced cessation of vaginal bleeding days over a 6-month treatment period based on a worst-case approach (ie, missing diary card days counted as bleeding days) are reported. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who had bleeding during the 6 month baseline period.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 12 treatment period

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (confidence interval 95%)	78.3 (56.3 to 92.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Growth Velocity (Annualised Growth Velocity in cm/year) Over Second 6-month Treatment Period Compared to Baseline

End point title	Change in Growth Velocity (Annualised Growth Velocity in cm/year) Over Second 6-month Treatment Period Compared to Baseline[5]

End point description:

Change in growth velocity (annualized growth velocity in cm/year) from the baseline (pre-treatment period) to second 6-month treatment period is reported. Growth velocity for a particular time period was calculated as the increase in height over that time period divided by the length of that time period

(expressed in cm/year). Baseline growth velocity was calculated from 6-month observational/retrospective period of the study. Change in growth velocity was calculated as growth velocity on treatment minus change in growth velocity during baseline. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through 12-month treatment period

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: cm/year				
arithmetic mean (standard deviation)	-0.8 (± 4.49)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Growth Velocity (Annualized Growth Velocity in cm/year) Over Whole 12-month Treatment Period Compared to Baseline

End point title	Change in Growth Velocity (Annualized Growth Velocity in cm/year) Over Whole 12-month Treatment Period Compared to Baseline[6]

End point description:

Change in growth velocity (annualized growth velocity in cm/year) from the baseline (pre-treatment period) to the 12-month treatment period is reported. Growth velocity for a particular time period was calculated as the increase in height over that time period divided by the length of that time period (expressed in cm/year). Baseline growth velocity was calculated from 6-month observational/retrospective period of the study. Change in growth velocity was calculated as growth velocity on treatment minus change in growth velocity during baseline. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 12 of treatment period

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: cm/year				
arithmetic mean (standard deviation)	-1.4 (± 3.69)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Growth Velocity (Z-Score) Over the First 6-month Treatment Period Compared to Baseline

End point title	Change in Growth Velocity (Z-Score) Over the First 6-month Treatment Period Compared to Baseline[7]

End point description:

Change in growth velocity (Z-score) from baseline period to the first 6 months of treatment period is reported. The Z-score is defined as [(growth velocity from the previous visit to the current visit minus mean growth velocity) divided by standard deviation (SD)], where the mean and SD are the age- and gender-specific statistics for growth velocity from the National Center for Health Statistics, Fels study and age is the age at the current visit. Baseline growth velocity was calculated from 6-month observational/retrospective period of the study. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through first 6-month treatment period

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Unit on a score				
arithmetic mean (standard deviation)	-1.60 (± 4.616)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Growth Velocity (Z-Score) Over the Second 6-month Treatment Period Compared to Baseline

End point title	Change in Growth Velocity (Z-Score) Over the Second 6-month Treatment Period Compared to Baseline[8]

End point description:

Change in growth velocity (Z-score) from baseline period to the second 6 months of treatment period is reported. The Z-score is defined as [(growth velocity from the previous visit to the current visit minus mean growth velocity) divided by SD], where the mean and SD are the age- and gender-specific statistics for growth velocity from the National Center for Health Statistics, Fels study and age is the age at the current visit. Baseline growth velocity was calculated from 6-month observational/retrospective period of the study. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through second 6-month treatment period

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Unit on a score				
arithmetic mean (standard deviation)	-0.64 (± 4.606)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Growth Velocity (Annualized Growth Velocity in cm/year) Over First 6-month Treatment Period Compared to Baseline

End point title	Change in Growth Velocity (Annualized Growth Velocity in cm/year) Over First 6-month Treatment Period Compared to Baseline[9]

End point description:

Change in growth velocity (annualized growth velocity in cm/year) from the baseline (pre-treatment period) to first 6-month treatment period is reported. Growth velocity for a particular time period was calculated as the increase in height over that time period divided by the length of that time period (expressed in cm/year). Baseline growth velocity was calculated from 6-month observational/retrospective period of the study. Change in growth velocity was calculated as growth velocity on treatment minus change in growth velocity during baseline. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through first 6-month of treatment period

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: cm/year				
arithmetic mean (standard deviation)	-1.7 (± 4.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Growth Velocity (Z-Score) Over the Whole 12-month Treatment Period Compared to Baseline

End point title	Change in Growth Velocity (Z-Score) Over the Whole 12-month Treatment Period Compared to Baseline[10]

End point description:

Change in growth velocity (Z-score) from baseline period to 12 months of treatment period is reported. The Z-score is defined as [(growth velocity from the previous visit to the current visit minus mean growth velocity) divided by SD)], where the mean and SD are the age- and gender-specific statistics for

growth velocity from the National Center for Health Statistics, Fels study and age is the age at the current visit. Baseline growth velocity was calculated from 6-month observational/retrospective period of the study. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 12 of treatment period

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Unit on a score				
arithmetic mean (standard deviation)	-1.14 (± 4.078)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Rate of BA Advancement Over Second 6-month Treatment Period Compared to Baseline

End point title	Change in Rate of BA Advancement Over Second 6-month Treatment Period Compared to Baseline[11]

End point description:

Change in rate of BA advancement over second 6-month treatment period compared to baseline (6 month pre-treatment observation period) is reported. Increase in BA is defined as BA (expressed as fractional years) at end of time period minus BA at beginning of time period (unit: years). Rate of increase in BA for a particular time interval is increase in BA during this time interval adjusted (ie, normalized) for the length of this time interval. Rate of BA advancement is change in BA (years) divided by change in CA (years). Change in rate of increase in BA from baseline period to on-treatment period is defined as increase in BA divided by change in CA (in fractional years) between the BA radiograph dates. It is calculated as $[(BA6 - BA0)/(CA6 - CA0)] - [(BA0 - BA*)/(CA0 - CA*)]$, where 6, 0, * stands for second Month 6 Visit, Month 0 Visit, and the 6 month retrospective visit, respectively. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through second Month 6 of treatment period

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Ratio				
arithmetic mean (standard deviation)	-1.10 (± 1.383)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Rate of Bone Age (BA) Advancement Over First 6-month Treatment Period Compared to Baseline

End point title	Change in Rate of Bone Age (BA) Advancement Over First 6-month Treatment Period Compared to Baseline[12]

End point description:

Change in rate of BA advancement over first 6-month treatment period compared to baseline (6 month pre-treatment observation period) is reported. Increase in BA is defined as BA (expressed as fractional years) at end of time period minus BA at beginning of time period (unit: years). Rate of increase in BA for a particular time interval is increase in BA during this time interval adjusted (ie, normalized) for the length of this time interval. Rate of BA advancement is change in BA (years) divided by change in chronological age (CA) (years). Change in rate of increase in BA from baseline period to on-treatment period is defined as increase in BA divided by change in CA (in fractional years) between BA radiograph dates. It is calculated as $[(BA6 - BA0)/(CA6 - CA0)] - [(BA0 - BA*)/(CA0 - CA*)]$, where 6, 0, * stands for first Month 6 Visit, Month 0 Visit, and the 6 month retrospective visit, respectively. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 6 of treatment period

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Ratio				
arithmetic mean (standard deviation)	-0.83 (± 1.507)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Rate of BA Advancement Over the Whole 12-month Treatment Period Compared to Baseline

End point title	Change in Rate of BA Advancement Over the Whole 12-month Treatment Period Compared to Baseline[13]

End point description:

Change in rate of BA advancement over whole 12-month treatment period compared to baseline (6 month pre-treatment observation period) is reported. Increase in BA is defined as BA (expressed as fractional years) at end of time period minus BA at beginning of time period (unit: years). Rate of increase in BA for a particular time interval is increase in BA during this time interval adjusted (ie,

normalized) for the length of this time interval. Rate of BA advancement is change in BA (years) divided by change in CA (years). Change in rate of increase in BA from baseline period to on-treatment period is defined as increase in BA divided by change in CA (in fractional years) between the BA radiograph dates. It is calculated as [(BA12 – BA0) / (CA12 – CA0)] – [(BA0 – BA*) / (CA0 – CA*)], where 12, 0, * stands for Month 12 Visit, Month 0 Visit, and the 6 month retrospective visit, respectively. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (6 month pre-treatment observation period) through Month 12 of treatment period

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Ratio				
arithmetic mean (standard deviation)	-0.93 (± 1.343)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Uterine Volume From Baseline to Month 12/Final Visit as Assessed by Ultrasound

End point title	Change in Uterine Volume From Baseline to Month 12/Final Visit as Assessed by Ultrasound[14]

End point description:

Uterine volume was calculated via ultrasound using the formula: 0.5 multiplied by (longitudinal multiplied by anteroposterior multiplied by transverse), if all 3 linear dimensions were recorded. If all 3 linear dimensions were not recorded, uterine volume was not calculated. Change in uterine volume from baseline to Month 12/final visit was calculated as End of Study volume (by ultrasound) minus Screening Visit volume (by ultrasound). Baseline (screening visit) is the pre-treatment baseline visit. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants with data at both time points.

End point type	Primary

End point timeframe:

Baseline (pre-treatment screening visit) and Month 12 treatment period

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Cubic centimeters				
median (full range (min-max))	-2.44 (-10.20 to 6.56)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Uterine Volume From Month 6 to Month 12/Final Visit as Assessed by Ultrasound

End point title	Change in Uterine Volume From Month 6 to Month 12/Final Visit as Assessed by Ultrasound[15]

End point description:

Uterine volume was calculated via ultrasound using the formula: 0.5 multiplied by (longitudinal multiplied by anteroposterior multiplied by transverse), if all 3 linear dimensions were recorded. If all 3 linear dimensions were not recorded, uterine volume was not calculated. Change in uterine volume from Month 6 to Month 12/final visit was calculated as Month 12/finial visit volume (by ultrasound) minus Month 6 volume (by ultrasound). The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants with data at both time points.

End point type	Primary

End point timeframe:

At Month 6 and Month 12/final visit treatment period

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Cubic centimetres				
median (full range (min-max))	-0.13 (-11.84 to 4.48)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Uterine Volume From Baseline to Month 6 as Assessed by Ultrasound

End point title	Change in Uterine Volume From Baseline to Month 6 as Assessed by Ultrasound[16]

End point description:

Uterine volume was calculated via ultrasound using the formula: 0.5 multiplied by (longitudinal multiplied by anteroposterior multiplied by transverse), if all 3 linear dimensions were recorded. If all 3 linear dimensions were not recorded, uterine volume was not calculated. Change in uterine volume from baseline to Month 6 was calculated as Month 6 volume (by ultrasound) minus screening visit volume (by ultrasound). Baseline (screening visit) is the pre-treatment baseline visit. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants with data at both time points.

End point type	Primary

End point timeframe:

Baseline (pre-treatment baseline visit) and Month 6 of treatment period

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Cubic centimeters				
median (full range (min-max))	-1.10 (-15.10 to 6.04)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Mean Ovarian Volume From Baseline to Month 6 as Assessed by Ultrasound

End point title	Change in Mean Ovarian Volume From Baseline to Month 6 as Assessed by Ultrasound[17]

End point description:

The mean ovarian volume was the average of both ovaries. Average volume was calculated as 0.5 multiplied by (volume of left ovary plus volume of right ovary) if both volumes were calculated; otherwise, average ovarian volume was considered missing. The volume of each ovary was calculated via ultrasound using the formula: 0.5 multiplied by longitudinal dimension multiplied by anterior-posterior dimension multiplied by transverse dimension. Change in mean ovarian volume from baseline to Month 6 was calculated as Month 6 mean volume minus Screening Visit mean volume. Baseline (screening visit) is the pre-treatment baseline visit. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants with data at both time points.

End point type	Primary

End point timeframe:

Baseline (pre-treatment screening visit) and Month 6 of treatment period

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Cubic centimetres				
median (full range (min-max))	0.10 (-27.62 to 7.96)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Volume of Distribution (V2/F) of Fulvestrant

End point title	Mean Volume of Distribution (V2/F) of Fulvestrant[18]

End point description:

Total apparent volume of distribution (Vss/F) is the total apparent volume in the body into which Fulvestrant distributes at equilibrium. Vss/F = V1/F + V2/F. V1/F is the volume of the first compartment and V2/F is the volume of the second compartment. V2/F of fulvestrant is reported. The measure of variability presented is the inter-individual error. Population PK analysis set included all participants who received at least 1 dose of study drug and have evaluable PK data.

End point type	Primary

End point timeframe:

Post-dose: Weeks 1, 2, 3, and pre-dose: Week 4 of Month 1 for first 6 participants, then pre-dose steady state samples on 2 occasions between Month 6 and 12 with at least 1 month in between wherein first sample drawn at least 30 days following sixth dose

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Litres				
arithmetic mean (standard error)	32700 (± 0.296)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Volume of Distribution (V1/F) of Fulvestrant

End point title	Mean Volume of Distribution (V1/F) of Fulvestrant[19]

End point description:

Total apparent volume of distribution (Vss/F) is the total apparent volume in the body into which Fulvestrant distributes at equilibrium. Vss/F = V1/F + V2/F. V1/F is the volume of the first compartment and V2/F is the volume of the second compartment. V1/F of fulvestrant is reported. The measure of variability presented is the inter-individual error. Population PK analysis set included all participants who received at least 1 dose of study drug and have evaluable PK data.

End point type	Primary

End point timeframe:

Post-dose: Weeks 1, 2, 3, and pre-dose: Week 4 of Month 1 for first 6 participants, then pre-dose steady state samples on 2 occasions between Month 6 and 12 with at least 1 month in between wherein first sample drawn at least 30 days following sixth dose

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Litres				
arithmetic mean (standard error)	33000 (± 0.492)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Clearance of Fulvestrant

End point title	Mean Clearance of Fulvestrant[20]

End point description:

Mean clearance of fulvestrant is reported. Population pharmacokinetic (PK) analysis set included all participants who received at least 1 dose of study drug and have evaluable PK data.

End point type	Primary

End point timeframe:

Post-dose: Weeks 1, 2, 3, and pre-dose: Week 4 of Month 1 for first 6 participants, then pre-dose steady state samples on 2 occasions between Month 6 and 12 with at least 1 month in between wherein first sample drawn at least 30 days following sixth dose

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Litres/hour				
arithmetic mean (standard deviation)	38.4 (± 11.56)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Mean Ovarian Volume From Baseline to Month 12/Final Visit as Assessed by Ultrasound

End point title	Change in Mean Ovarian Volume From Baseline to Month 12/Final Visit as Assessed by Ultrasound[21]

End point description:

The mean ovarian volume was the average of both ovaries. Average ovarian volume was calculated as 0.5 multiplied by (volume of left ovary plus volume of right ovary) if both volumes were calculated; otherwise, average ovarian volume was considered missing. The volume of each ovary was calculated via ultrasound using the formula: 0.5 multiplied by longitudinal dimension multiplied by anterior-posterior dimension multiplied by transverse dimension. Change in mean ovarian volume from baseline to the end of the study was calculated as end of study mean volume minus screening visit mean volume. Baseline (screening visit) is the pre-treatment baseline visit. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants with data at both time points.

End point type	Primary

End point timeframe:

Baseline (pre-treatment baseline visit) and Month 12/final visit treatment period

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Cubic centimetres				
median (full range (min-max))	1.01 (-22.25 to 10.36)			

Statistical analyses

No statistical analyses for this end point

Primary: Change Mean in Ovarian Volume From Month 6 to Month 12/Final Visit as Assessed by Ultrasound

End point title	Change Mean in Ovarian Volume From Month 6 to Month 12/Final Visit as Assessed by Ultrasound[22]

End point description:

The mean ovarian volume was the average of both ovaries. Average volume was calculated as 0.5 multiplied by (volume of left ovary plus volume of right ovary) if both volumes were calculated; otherwise, average ovarian volume was considered missing. The volume of each ovary was calculated via ultrasound using the formula: 0.5 multiplied by longitudinal dimension multiplied by anterior-posterior dimension multiplied by transverse dimension. Change in mean ovarian volume from Month 6 to Month 12/final visit was calculated as Month 12/final visit mean volume minus Month 6 mean volume. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants with data at both time points.

End point type	Primary

End point timeframe:

At Month 6 and Month 12/final visit treatment period

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Cubic centimetres				
median (full range (min-max))	0.76 (-4.08 to 9.97)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)[23]

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Day 1 through 68.7 weeks (maximum observed duration)

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Participants				
Any TEAEs	27			
Any TESAEs	9			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs

End point title	Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs[24]

End point description:

Number of participants with abnormal clinical laboratory parameters reported as TEAEs are reported. Clinical laboratory parameter analysis included hematology and clinical chemistry. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Day 1 through 68.7 weeks (maximum observed duration)

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Participants				
Anemia	1			
Vitamin D Deficiency	1			

Statistical analyses

No statistical analyses for this end point

Primary: Hormone Assay: Serum Follicle-stimulating Hormone (FSH) Level

End point title	Hormone Assay: Serum Follicle-stimulating Hormone (FSH) Level[25]

End point description:

Serum FSH level collected at Month 12 (final visit) is reported. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who were evaluable at the specified time point.

End point type	Primary

End point timeframe:

Month 12 (final visit) of treatment period

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: IU/L				
arithmetic mean (standard deviation)	1.13 (± 1.024)			

Statistical analyses

No statistical analyses for this end point

Primary: Hormone Assay: Serum Luteinizing Hormone (LH) Level

End point title	Hormone Assay: Serum Luteinizing Hormone (LH) Level[26]

End point description:

Serum LH level collected at Month 12 (final visit) is reported. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who were evaluable at the specified time point.

End point type	Primary

End point timeframe:

Month 12 (final visit) of treatment period

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: IU/L				
arithmetic mean (standard deviation)	0.11 (± 0.042)			

Statistical analyses

No statistical analyses for this end point

Primary: Hormone Assay: Serum Oestradiol Level

End point title	Hormone Assay: Serum Oestradiol Level[27]

End point description:

Serum oestradiol level at Month 12 (final visit) is reported. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who were evaluable at the specified time point.

End point type	Primary

End point timeframe:

Month 12 (final visit) of treatment period

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: pmol/L				
arithmetic mean (standard deviation)	25.95 (± 30.718)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Withdrawals from Study Treatment due to TEAE

End point title	Number of Participants With Withdrawals from Study Treatment due to TEAE[28]

End point description:

Number of participants with withdrawals from study treatment due to TEAE are reported. The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Day 1 through 68.7 weeks (maximum observed duration)

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Compliance to Study Treatment

End point title	Number of Participants With Compliance to Study Treatment[29]

End point description:

Compliance with study treatment for the 12-month treatment period is total number of injections divided by number of visits between first injection (month 0) and last injection (at month 11). The FAS population included participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Day 1 through 68.7 weeks (maximum observed duration)

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Participants	30			

Statistical analyses

No statistical analyses for this end point

Primary: Hormone Assay: Serum Testosterone Level

End point title	Hormone Assay: Serum Testosterone Level[30]

End point description:

Serum testosterone level at Month 12 (final visit) is reported. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who were evaluable at the specified time point.

End point type	Primary

End point timeframe:

Month 12 (final visit) of treatment period

Notes:

[30] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: nmol/L				
arithmetic mean (standard deviation)	0.65 (± 0.273)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Tanner Stage of Breast From Baseline to Month 12/Final Visit

End point title	Change in Tanner Stage of Breast From Baseline to Month 12/Final Visit

End point description:

Change in Tanner stage (measure of pubertal progression) of breast from baseline to Month 12/last visit is reported. Tanner stage (breast) is a score of range 1-5 where 1=no development and 5=adult breast. The FAS population included participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Baseline (Month 0) through Month 12 treatment period

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Unit on a scale				
median (full range (min-max))	0.0 (-3 to 2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Tanner Stage of Pubic Hair From Baseline to Month 12/Final Visit

End point title	Change in Tanner Stage of Pubic Hair From Baseline to Month 12/Final Visit

End point description:

Change in Tanner stage (measure of pubertal progression) of pubic hair from baseline to Month 12/final visit is reported. Tanner stage (pubic hair) is a score of range 1-5 where 1=no development and 5=adult

pubic hair. The FAS population included participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Baseline (Month 0) through Month 12 treatment period

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Unit on a scale				
median (full range (min-max))	0.0 (-2 to 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Predicted Adult Height (PAH) From Baseline to Month 12/Final Visit

End point title	Change in Predicted Adult Height (PAH) From Baseline to Month 12/Final Visit

End point description:

Change in PAH for children over age 6 is reported. Bone age radiographs were collected retrospectively. PAH equals the current height divided by a factor (the fraction of final adult height) based on current bone age (central read) and current bone age relative to chronological age, classified as retarded, average or advanced. Retarded is defined as current bone age (years) < chronological age (years) minus 1; advanced is defined as current bone age (years) > chronological age (years) plus 1; otherwise, bone age is classified as average. The PAH was summarized using the Bayley and Pinneau method. The FAS population included participants who received at least 1 dose of study drug. Here, number of subjects analyzed denotes those participants who were analyzed for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline (screening visit) through Month 12 treatment period

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Centimeter				
arithmetic mean (standard deviation)	0.5 (± 4.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With McCune-Albright Syndrome (MAS)

Associated G Protein α-subunit (Gsα) Mutation

End point title	Percentage of Participants With McCune-Albright Syndrome (MAS) Associated G Protein α-subunit (Gsα) Mutation

End point description:

The MAS is caused by an activating mutation in the gene coding for the stimulatory subunit of the G protein, Gsα. The altered Gsα causes autonomous activation of G-protein stimulated cAMP formation, which in the gonads, results in episodic uncontrolled sex steroid production and subsequent pubertal development. For participants who provided separate specific informed consent, the percentage of participants with a Gsα mutation at screening was assessed by molecular analysis of peripheral blood. The FAS population included participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline (screening)

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Percentage of participants				
number (not applicable)	23.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through 68.7 weeks (maximum observed duration)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Fulvestrant

Reporting group description:

Participants received intramuscular injection of fulvestrant 2 mg/kg or 4 mg/kg (First 10 participants were dosed at 2 mg/kg then increased to 4 mg/kg. All subsequent participants were dosed at 4 mg/kg) into the buttock or thigh monthly for 12 months or until the participant demonstrates lack of efficacy based upon one or more of the primary endpoints or experiences a serious drug-related toxicity requiring treatment discontinuation.

Serious adverse events	Fulvestrant		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 30 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Femur Fracture			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuromyopathy			
alternative dictionary used: MedDRA 12.1			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions

Pyrexia

alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders

Ovarian Cyst

alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders

Wheezing

alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders

Tic

alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders

Pain in extremity

alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Bone Pain			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral Infection			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fulvestrant		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 30 (83.33%)		
Vascular disorders			

Hot Flush			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

Nervous system disorders			
Lethargy			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Headache			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	20		

General disorders and administration site conditions			
Pyrexia			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	14 / 30 (46.67%)		
occurrences (all)	32		
Injection Site Inflammation			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Injection Site Pain			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	6		
Fatigue			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Injection site reaction			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	5		

Ear and labyrinth disorders			

Ear Pain			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	9		
Gastrointestinal disorders			
Abdominal Pain Upper			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	7		
Diarrhoea			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Abdominal Pain			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	21		
Toothache			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	6		
Vomiting			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	12		
Nausea			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	6		
Cough			

alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	10		
Productive Cough			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Eczema			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Rash			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Bone Pain			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Arthralgia			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pain in Extremity			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	18		
Neck Pain			
alternative dictionary used: MedDRA 12.1			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Infections and infestations			

Otitis Media

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   2 / 30 (6.67%)

    occurrences (all)   8

Gastroenteritis

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   3 / 30 (10.00%)

    occurrences (all)   3

Ear Infection

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   3 / 30 (10.00%)

    occurrences (all)   5

Bronchitis

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   2 / 30 (6.67%)

    occurrences (all)   2

Rhinitis

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   6 / 30 (20.00%)

    occurrences (all)   14

Pharyngitis

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   2 / 30 (6.67%)

    occurrences (all)   3

Varicella

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   2 / 30 (6.67%)

    occurrences (all)   3

Vaginal Infection

    alternative dictionary used: MedDRA 12.1

    subjects affected / exposed   2 / 30 (6.67%)

    occurrences (all)   2

Upper Respiratory Tract Infection

    alternative dictionary used: MedDRA 12.1

subjects affected / exposed	5 / 30 (16.67%)
occurrences (all)	8
Tonsillitis	
alternative dictionary used: MedDRA 12.1	
subjects affected / exposed	3 / 30 (10.00%)
occurrences (all)	3
H1N1 influenza	
alternative dictionary used: MedDRA 12.1	
subjects affected / exposed	2 / 30 (6.67%)
occurrences (all)	4
Sinusitis	
alternative dictionary used: MedDRA 12.1	
subjects affected / exposed	2 / 30 (6.67%)
occurrences (all)	2
Pharyngitis Streptococcal	
alternative dictionary used: MedDRA 12.1	
subjects affected / exposed	2 / 30 (6.67%)
occurrences (all)	3
Nasopharyngitis	
subjects affected / exposed	4 / 30 (13.33%)
occurrences (all)	6
Urinary Tract Infection	
alternative dictionary used: MedDRA 12.1	
subjects affected / exposed	3 / 30 (10.00%)
occurrences (all)	3
Metabolism and nutrition disorders	
Decreased Appetite	
alternative dictionary used: MedDRA 12.1	
subjects affected / exposed	3 / 30 (10.00%)
occurrences (all)	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2008	Various sections throughout the original Clinical Study Protocol (CSP): Text revised to reflect the fact that separate consent was not required for the Five-Year Safety Surveillance period. Text revised to clarify that first month blood samples were only required for the first 6 participants. The collection period for steady state samples was revised to include Month 10, 11 and 12. Text in Sections 3.4.1.1 and 3.4.2 revised to clarify syringes provided in the Unites States and Rest of World. Text in Section 3.4.2 also revised to indicate that injection could be given in the buttock or thigh. Section 4.2, Screening and demographic measurements; text removed to make it clear that retrospective data was available for some participants prior to written informed consent. Various sections throughout the original CSP: Text revised for to clarify that full physical exams, including Tanner stage, were performed at Month 0, 3, 6 and 12 only. Height and weight were collected at each study visit. Text added to indicate that for Months 0 to 12, radiographs were read both locally and centrally. In the extension period only, local radiographs were collected. Additional text added to indicate that a telephone visit or participant office visit was required 60 days following the last injection of study drug to collect any post treatment AEs. Text was added to clarify that the genetic specimens will be analyzed at an independent institute. Section 5, Data management: text edited to include the possibility that case report forms would be sent to an AstraZeneca designee.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Data for exploration on body weight and race effect on fulvestrant PK is not available due to small sample size. Data for number and size of ovarian cysts at different time-point were too sparse to produce a meaningful summary, hence not reported.

Notes: