Clinical trial results:
Constitutional Delay of Growth and Puberty: towards evidence-based treatment

Summary

EudraCT number	2012-002477-59
Trial protocol	FI
Global end of trial date	05 February 2018

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020
Summary attachment (see zip file)	abstract (Lancet_child_adolescent_accepted.pdf)

Trial information

Trial identification

Sponsor protocol code	CDGP1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01797718
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Helsinki University Hospital
Sponsor organisation address	Tukholmankatu 8 C, 6. krs LKL tutkijat, Helsinki, Finland, 00029
Public contact	Pediatric Endocrinology outpatient clinic, Helsinki Univ. Hospital, Helsinki University Hospital, matti.hero@hus.fi
Scientific contact	Pediatric Endocrinology outpatient clinic, Helsinki Univ. Hospital, Helsinki University Hospital, matti.hero@hus.fi

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	01 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2018
Global end of trial reached?	Yes
Global end of trial date	05 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study in boys with constitutional delay of puberty, showing the first signs of puberty initiation, whether 6 months treatment with the aromatase inhibitor letrozole promotes the progression puberty more efficiently than the current standard of care, low-dose testosterone therapy. The primary outcomes were changes in testicular volume and hormonal markers of puberty at 6 months after treatment initiation.

Protection of trial subjects:

The participants were evaluated at pediatric outpatient clinic at 0,3,6, and 12 months visit. Blood samples were taken at each visit. Anesthetic cream were offered before blood sampling to minimize pain. Clinical examination did not cause any pain to the participants.

Background therapy:

No background therapy were included.

Evidence for comparator:

Intramuscular low-dose testosterone has been used to induct pubertal development in boys with constitutional delay of growth and puberty (CDGP) for decades. Although treatment with testosterone promotes androgenic signs of puberty, it might initially suppress, rather than activate, the hypothalamic–pituitary–gonadal (HPG) axis and its puberty-promoting effects on gonadotropin secretion and testicular growth emerge later after the treatment. Peroral aromatase inhibitor letrozole which inhibits the conversion of androstenedione to estrone and testosterone to estradiol, which results in the activation of the HPG axis and induce testicular growth. Letrozole has been used before in adolescents, but not in a similar randomized controlled setting. Letrozole appears to be a safe treatment modality at least in short term.

Actual start date of recruitment	03 October 2013
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	Finland: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	35
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted between August 1st, 2013, and January 30th, 2017, at the paediatric endocrinology outpatient clinics of Helsinki University Hospital, Turku University Hospital, Kuopio University Hospital, and Kymenlaakso Central Hospital in Finland. The total population covered was approximately 2 million.

Pre-assignment

Screening details:

Eligible boys were > 14 years old ; had presented with delayed puberty, and had a mean testicular volume of at least 2.5 mL but less than 4 mL and serum testosterone concentration of less than 5 nmol/L (or serum testosterone concentration ≥1 nmol/L even if the mean testicular volume was <2.5). Chronic illnesses were screened and excluded.

Period 1

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

Blinding implementation details:

Letrozole was administered perorally, whereas testosterone was given in intramuscular injections. Thus, no blinding was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Letrozole

Arm description:

Letrozole group received aromatase inhibitor letrozole 2.5mg/day for 6 months.

Arm type	Active comparator
Investigational medicinal product name	letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg per day for 6 months

Arm title	Testosterone

Arm description:

Testosterone arm received intramuscular low dose testosterone 1mg/kg every 4 weeks for 6 months.

Arm type	Active comparator
Investigational medicinal product name	Sustanon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

1mg/kg every 4 weeks for 6 months

Arm title	follow-up group

Arm description:

boys with delayed puberty who did not want any treatment but wished to participate in the trial were followed up within the trial protocol but they did not receive any puberty inducting treatment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Letrozole	Testosterone	follow-up group
Started	15	15	5
Completed	15	15	4
Not completed	0	0	1
Lack of efficacy	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Letrozole
Reporting group description:	
Letrozole group received aromatase inhibitor letrozole 2.5mg/day for 6 months.	
Reporting group title	Testosterone
Reporting group description:	
Testosterone arm received intramuscular low dose testosterone 1mg/kg every 4 weeks for 6 months.	
Reporting group title	follow-up group
Reporting group description:	
boys with delayed puberty who did not want any treatment but wished to participate in the trial were followed up within the trial protocol but they did not receive any puberty inducting treatment.	

Reporting group values	Letrozole	Testosterone	follow-up group
Number of subjects	15	15	5
Age categorical			
Boys aged over 14 years who presented with constitutional delay of growth and puberty			
Units: Subjects			
Adolescents	15	15	5
Age continuous			
Units: years			
arithmetic mean	14.6	14.8	14.9
standard deviation	± 0.7	± 0.5	± 0.4
Gender categorical			
Units: Subjects			
Male	15	15	5

Reporting group values	Total		
Number of subjects	35		
Age categorical			
Boys aged over 14 years who presented with constitutional delay of growth and puberty			
Units: Subjects			
Adolescents	35		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Male	35		

End points

End points reporting groups

Reporting group title	Letrozole
Reporting group description:	
Letrozole group received aromatase inhibitor letrozole 2.5mg/day for 6 months.	
Reporting group title	Testosterone
Reporting group description:	
Testosterone arm received intramuscular low dose testosterone 1mg/kg every 4 weeks for 6 months.	
Reporting group title	follow-up group
Reporting group description:	
boys with delayed puberty who did not want any treatment but wished to participate in the trial were followed up within the trial protocol but they did not receive any puberty inducting treatment.	

Primary: Testicular volume

End point title	Testicular volume[1]
End point description:	
Testicular size was measured with a ruler, and testicular volume (ml) was calculated by using the formula length x width x width x 0.52.	
End point type	Primary
End point timeframe:	
Change in testicular volume between 0 and 6 months and between 0 and 12 months	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie	

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: millilitre(s)				
arithmetic mean (confidence interval 95%)	7.2 (5.2 to 9.3)	2.2 (1.4 to 2.9)		

Attachments (see zip file)	Testicular size increase between groups/Figure 3_16_10.tif

Statistical analyses

Statistical analysis title	Mixed-model analysis of testicular volume growth
Comparison groups	Letrozole v Testosterone

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.2
Variability estimate	Standard deviation

Primary: Testosterone 3 mo

End point title	Testosterone 3 mo[2]

End point description:

End point type	Primary

End point timeframe:

At 3 months

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specified.

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: nanomole(s)/millilitre				
arithmetic mean (standard deviation)	21.0 (± 18.6)	9.7 (± 6.1)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.033
Method	t-test, 2-sided

Primary: Testosterone 6 mo

End point title	Testosterone 6 mo[3]

End point description:

End point type	Primary

End point timeframe:

at 6 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: nanomole(s)/millilitre				
arithmetic mean (standard deviation)	30.2 (± 18.4)	5.7 (± 2.7)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	t-test, 2-sided

Primary: testosterone 12mo

End point title	testosterone 12mo[4]

End point description:

End point type	Primary

End point timeframe:

At 12 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: nanomole(s)/millilitre				
arithmetic mean (standard deviation)	10.2 (± 4.3)	11.9 (± 3.1)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.22
Method	t-test, 2-sided

Primary: LH 3mo

End point title	LH 3mo[5]

End point description:

End point type	Primary

End point timeframe:

At 3 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: international unit(s)/litre				
arithmetic mean (standard deviation)	7.1 (± 3.6)	0.2 (± 0.2)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	t-test, 2-sided

Primary: LH 6mo

End point title	LH 6mo[6]

End point description:

End point type	Primary

End point timeframe:

At 6 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: international unit(s)/millilitre				
arithmetic mean (standard deviation)	7.6 (± 4.0)	2.2 (± 1.4)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	t-test, 2-sided

Primary: LH 12 mo

End point title	LH 12 mo[7]

End point description:

End point type	Primary

End point timeframe:

At 12 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: international unit(s)/litre				
arithmetic mean (standard deviation)	2.9 (± 1.3)	3.3 (± 1.1)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.45
Method	t-test, 2-sided

Primary: Inhibin B 3 mo

End point title	Inhibin B 3 mo[8]

End point description:

End point type	Primary

End point timeframe:

At 3 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: nanogram(s)				
arithmetic mean (standard deviation)	198 (± 62)	112 (± 65)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	t-test, 2-sided

Primary: Inhibin B 6 mo

End point title	Inhibin B 6 mo[9]

End point description:

End point type	Primary

End point timeframe:

At 6 months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: nanogram(s)				
arithmetic mean (standard deviation)	211 (± 57)	166 (± 96)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.13
Method	t-test, 2-sided

Primary: Inhibin B 12 mo

End point title	Inhibin B 12 mo[10]

End point description:

End point type	Primary

End point timeframe:

At 12 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: nanogram(s)				
arithmetic mean (standard deviation)	223 (± 73)	212 (± 96)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Testosterone v Letrozole
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.73
Method	t-test, 2-sided

Primary: Growth velocity 0-6mo

End point title	Growth velocity 0-6mo[11]

End point description:

End point type	Primary

End point timeframe:

Between 0 and 6months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: millimeter(s)				
arithmetic mean (standard deviation)	6.3 (± 2.4)	8.2 (± 2.1)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.032
Method	t-test, 2-sided

Primary: Growth velocity 0-12mo

End point title	Growth velocity 0-12mo[12]

End point description:

End point type	Primary

End point timeframe:

Between 0 and 12 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: millimeter(s)				
arithmetic mean (standard deviation)	7.0 (± 2.2)	7.9 (± 1.5)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.17
Method	t-test, 2-sided

Primary: Genital Stage 6 mo

End point title	Genital Stage 6 mo[13]

End point description:

End point type	Primary

End point timeframe:

At 6 months

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
G1	0	0		
G2	7	4		
G3	6	10		
G4	2	1		
G5	0	0		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2
Method	Fisher exact

Primary: Pubic hair stage 6 mo

End point title	Pubic hair stage 6 mo[14]

End point description:

End point type	Primary

End point timeframe:

Between 0 and 12 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
P1	3	0		
P2	5	5		
P3	6	9		
P4	1	1		
P5	0	0		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3
Method	Fisher exact

Primary: Genital stage 12 mo

End point title	Genital stage 12 mo[15]

End point description:

End point type	Primary

End point timeframe:

At 12 months

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
G1	0	0		
G2	2	0		
G3	6	8		
G4	7	7		
G5	0	0		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4
Method	Fisher exact

Primary: GnRH stimulated LH 0 mo

End point title	GnRH stimulated LH 0 mo[16]

End point description:

End point type	Primary

End point timeframe:

At 0 months

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: international unit(s)/litre				
arithmetic mean (standard deviation)	14.6 (± 5.3)	15.1 (± 6.7)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5
Method	t-test, 2-sided

Primary: GnRH stimulated LH 12 mo

End point title	GnRH stimulated LH 12 mo[17]

End point description:

End point type	Primary

End point timeframe:

At 12 months

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: international unit(s)/litre				
arithmetic mean (standard deviation)	19.6 (± 7.1)	20.1 (± 9.2)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.34
Method	t-test, 2-sided

Primary: Pubic hair stage 12 mo

End point title	Pubic hair stage 12 mo[18]

End point description:

End point type	Primary

End point timeframe:

At 12 months

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
P1	1	0		
P2	3	0		
P3	7	7		
P4	4	8		
P5	0	0		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4
Method	Fisher exact

Secondary: Change in lumbar spine BMD 0-6mo

End point title	Change in lumbar spine BMD 0-6mo[19]

End point description:

End point type	Secondary

End point timeframe:

Between 0 and 6 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: gram(s)/cubic meter				
arithmetic mean (standard deviation)	0.004 (± 0.02)	0.029 (± 0.03)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.011
Method	t-test, 2-sided

Secondary: Change in lumbar spine BMD 0-12

End point title	Change in lumbar spine BMD 0-12[20]

End point description:

End point type	Secondary

End point timeframe:

Between 0 and 12 months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: gram(s)/cubic meter				
arithmetic mean (standard deviation)	0.04 (± 0.05)	0.08 (± 0.05)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.038
Method	t-test, 2-sided

Secondary: Change in BMAD 0-6 mo

End point title	Change in BMAD 0-6 mo[21]

End point description:

Bone mineral apparent density (g/m3).

End point type	Secondary

End point timeframe:

Between 0 and 6 months.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: gram(s)/cubic meter				
arithmetic mean (standard deviation)	-0.002 (± 0.006)	-0.0006 (± 0.008)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.55
Method	t-test, 2-sided

Secondary: Change in BMAD 0-12mo

End point title	Change in BMAD 0-12mo[22]
End point description:	
Bone mineral apparent density g/m3	
End point type	Secondary
End point timeframe:	
Change between 0 and 12 months	

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only treatment groups were compared, and follow-up group was used as background data. This decision was pre-specifie

End point values	Letrozole	Testosterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: gram(s)/cubic meter				
arithmetic mean (standard deviation)	-0.003 (± 0.01)	0.004 (± 0.01)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Letrozole v Testosterone

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.093
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed at 0, 3, 6 and 12 months visits

Adverse event reporting additional description:

Adverse events were asked from the participants and their parents. Additionally, a structured adverse event questionnaire was used, which included all major symptoms of major organ systems.

Assessment type	Systematic

Dictionary used

Dictionary name	NA
Dictionary version	1

Reporting groups

Reporting group title	Letrozole

Reporting group description: -

Reporting group title	Testosterone

Reporting group description: -

Serious adverse events	Letrozole	Testosterone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Letrozole	Testosterone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)	6 / 15 (40.00%)	
Nervous system disorders			
Migraine			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Nausea			

subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Enzyme abnormality			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 15 (20.00%)	3 / 15 (20.00%)	
occurrences (all)	3	3	
Fracture			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Infections and infestations			
Myocarditis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30612946