



## Clinical trial results:

### The Effects of Normalising Sex Hormone Levels in Obese Hypogonadal Men: A Prospective Randomized Comparator Controlled Parallel Arm Clinical Trial

#### Summary

EudraCT number	2010-021268-13
Trial protocol	IE
Global end of trial date	01 November 2013

#### Results information

Result version number	v1 (current)
This version publication date	04 March 2020
First version publication date	04 March 2020

#### Trial information

##### Trial identification

Sponsor protocol code	Letrozole2010-1
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##### Additional study identifiers

ISRCTN number	ISRCTN21665331
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Belfield, Dublin, Ireland,
Public contact	Rabia Hussain, University College Dublin, +353 017164593, rabia.hussain@ucd.ie
Scientific contact	Tomás Ahern, University College Dublin, +353 0878302939, TomasB.Ahern@hse.ie

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 February 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 November 2013
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the research project is to determine the effect of twelve weeks' treatment with an aromatase inhibitor (Femara®, 2.5mg weekly) on the change in the serum concentration of the pro-inflammatory cytokine, C Reactive Protein, as measured by the Roche® Cobas immuno-turbidimetric test and compare it to that of twelve weeks' treatment with a depot intramuscular formulation of testosterone undecanoate (Nebido®, 1g every 6 weeks) and to that of six weeks of no treatment.

Protection of trial subjects:

Patients were withdrawn from study when safety concerns were expressed by investigator. All research participants who withdraw early from the study were be advised to agree to attend the end of study visit for safety investigations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	34
From 65 to 84 years	3

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Research participants were recruited from two centres: St Columcille's Hospital, Loughlinstown, Co Dublin and St Vincent's University Hospital, Elm Park, Dublin 4. Men attending these units with a BMI greater than 30kg/m<sup>2</sup> and a serum total testosterone concentration measured at less than 8.0mmol/L were screened to be eligible.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Femara
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	Femara
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg tablet once weekly by oral ingestion for 12 weeks

<b>Arm title</b>	Nebido
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Arm description: -

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

Dosage and administration details:

1g injection every 6 weeks by intramuscular administration for 12 weeks

Number of subjects in period 1	Femara	Nebido
Started	19	18
Completed	19	18

<b>Period 2</b>	
Period 2 title	Outcome period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
<b>Arms</b>	
Are arms mutually exclusive?	Yes
<b>Arm title</b>	Femara
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	Femara
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
2.5mg tablet once weekly by oral ingestion for 12 weeks	
<b>Arm title</b>	Nebido
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Testosterone undecanoate
Investigational medicinal product code	
Other name	Nebido
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use
Dosage and administration details:	
1g injection every 6 weeks by intramuscular administration for 12 weeks	

Number of subjects in period 2	Femara	Nebido
Started	19	18
Completed	18	18
Not completed	1	0
Unknown	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Femara
Reporting group description: -	
Reporting group title	Nebido
Reporting group description: -	

Reporting group values	Femara	Nebido	Total
Number of subjects	19	18	37
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	48.0	49.1	
standard deviation	± 11.7	± 11.0	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	19	18	37
Type II diabetes Units: Subjects			
Yes	9	6	15
No	10	12	22
Obstructive sleep apnoea syndrome Units: Subjects			
Yes	9	7	16
No	10	11	21
Height Units: meter			
median	1.819	1.772	
inter-quartile range (Q1-Q3)	1.744 to 1.836	1.724 to 1.813	-
Weight Units: kg			
median	166.6	173	
inter-quartile range (Q1-Q3)	154.4 to 181.6	156.1 to 188.9	-
BMI Units: kg/m2			

median inter-quartile range (Q1-Q3)	53.3 46.4 to 56.7	53.6 48.7 to 59.6	-
C-reactive protein Units: mg/L median inter-quartile range (Q1-Q3)	8.2 5 to 13.1	10.3 4.9 to 13.7	-
Testosterone Units: nmol/L median inter-quartile range (Q1-Q3)	6.4 4.7 to 7.7	6.4 5.9 to 8	-
Oestradiol Units: pmol/L median inter-quartile range (Q1-Q3)	135 104 to 161	154 132 to 210	-
Sex hormone-binding globulin Units: nmol/L median inter-quartile range (Q1-Q3)	22.2 16.3 to 27.4	26.4 22.6 to 29.5	-
Luteinizing hormone Units: IU/L median inter-quartile range (Q1-Q3)	3.4 2.8 to 5.6	4.1 3.2 to 6.4	-
Haematocrit Units: percentage median inter-quartile range (Q1-Q3)	43.4 41.35 to 44.15	45.3 41.38 to 45.98	-
Cholesterol Units: mmol/L median inter-quartile range (Q1-Q3)	4.1 3.2 to 5.1	4.8 4.2 to 5.1	-
High-density lipoprotein Units: mmol/L median inter-quartile range (Q1-Q3)	1 0.9 to 1.25	1.06 0.95 to 1.13	-
Low-density lipoprotein Units: mmol/L median inter-quartile range (Q1-Q3)	2.21 1.72 to 3.22	2.86 2.38 to 3.43	-
Prostate-specific antigen Units: ng/mL median inter-quartile range (Q1-Q3)	0.58 0.28 to 1.19	0.63 0.42 to 0.85	-
Heart rate Units: bpm median inter-quartile range (Q1-Q3)	77 68 to 83	74 71 to 80	-
Systolic blood pressure Units: mmHg median inter-quartile range (Q1-Q3)	134 126 to 144	127 122 to 137	-
Diastolic blood pressure Units: mmHg			

median inter-quartile range (Q1-Q3)	83 78 to 94	82 76 to 88	-
Haemoglobin A1C Units: percentage median inter-quartile range (Q1-Q3)	6.3 5.9 to 7.6	6.1 6 to 6.3	-
Glucose Units: mmol/L median inter-quartile range (Q1-Q3)	6.4 5.7 to 8.8	5.2 4.9 to 5.7	-
Triglycerides Units: mmol/L median inter-quartile range (Q1-Q3)	1.31 1.17 to 1.9	1.31 1.08 to 1.96	-
Homeostatic Model Assessment of Insulin Resistance Units: score median inter-quartile range (Q1-Q3)	7.16 6.087 to 8.981	5.388 4.443 to 7.996	-
Haemoglobin Units: g/dL median inter-quartile range (Q1-Q3)	14.7 13.9 to 15.4	15 14.2 to 15.8	-
Creatinine Units: mmol/L median inter-quartile range (Q1-Q3)	67 60 to 75	68 63 to 79	-
Estimated glomerular filtration rate Units: mL/min/1.73 m <sup>2</sup> median inter-quartile range (Q1-Q3)	120.568 104.668 to 132.521	117.139 95.473 to 127.581	-
Alanine transaminase Units: U/L median inter-quartile range (Q1-Q3)	38 30 to 54	32 30 to 36	-
500 m walk Units: sec median inter-quartile range (Q1-Q3)	386 353 to 418	382 348 to 409	-
Average steps walked during previous 7 days Units: steps/day median inter-quartile range (Q1-Q3)	4216 2523 to 6668	6000 3162 to 6883	-



## End points

### End points reporting groups

Reporting group title	Femara
Reporting group description: -	
Reporting group title	Nebido
Reporting group description: -	
Reporting group title	Femara
Reporting group description: -	
Reporting group title	Nebido
Reporting group description: -	

### Primary: Change from baseline in serum concentration of C-reactive protein

End point title	Change from baseline in serum concentration of C-reactive protein
End point description:	
End point type	Primary
End point timeframe:	12 weeks

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	0.2 (-0.5 to 1.7)	-1.6 (-3.6 to 0.4)		

### Statistical analyses

Statistical analysis title	Difference in medians
Comparison groups	Femara v Nebido
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0327
Method	Wilcoxon (Mann-Whitney)

### Secondary: Change from baseline in time to walk 500 metres

End point title	Change from baseline in time to walk 500 metres
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End point description:

End point type	Secondary
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End point timeframe:

18 weeks

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: seconds				
arithmetic mean (standard error)	-18 ( $\pm$ 7)	-14 ( $\pm$ 16)		

### Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Femara v Nebido
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8217
Method	t-test, 2-sided

### Secondary: Change from baseline in diastolic blood pressure

End point title	Change from baseline in diastolic blood pressure
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End point description:

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmHg				
arithmetic mean (standard error)	1 ( $\pm$ 2)	3 ( $\pm$ 2)		

### Statistical analyses

<b>Statistical analysis title</b>	Difference in means
Comparison groups	Femara v Nebido
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4221
Method	t-test, 2-sided

### Secondary: Change from baseline in systolic blood pressure

End point title	Change from baseline in systolic blood pressure
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

<b>End point values</b>	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmHg				
arithmetic mean (standard error)	-2 ( $\pm$ 4)	3 ( $\pm$ 3)		

### Statistical analyses

<b>Statistical analysis title</b>	Difference in means
Comparison groups	Femara v Nebido
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363
Method	t-test, 2-sided

### Secondary: Change from baseline in HbA1C

End point title	Change from baseline in HbA1C
End point description:	
End point type	Secondary
End point timeframe:	
18 weeks	

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percentage				
arithmetic mean (standard error)	-0.0653 ( $\pm$ 0.1038)	0.0155 ( $\pm$ 0.1125)		

### Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Femara v Nebido
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.601
Method	t-test, 2-sided

### Secondary: Change from baseline in HOMA-IR

End point title	Change from baseline in HOMA-IR
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: score				
median (inter-quartile range (Q1-Q3))	-0.4 (-0.9 to 0)	1.3 (0.3 to 2.3)		

### Statistical analyses

Statistical analysis title	Difference in medians
Comparison groups	Femara v Nebido

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01448
Method	Wilcoxon (Mann-Whitney)

### Secondary: Change from baseline in HDL

End point title	Change from baseline in HDL
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: mmol/L				
arithmetic mean (standard error)	-0.1 (± 0)	0 (± 0)		

### Statistical analyses

<b>Statistical analysis title</b>	Difference in means
Comparison groups	Femara v Nebido
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002076
Method	t-test, 2-sided

### Secondary: Change from baseline in LDL

End point title	Change from baseline in LDL
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	18		
Units: mmol/L				
arithmetic mean (standard error)	0 ( $\pm$ 0.1)	0.1 ( $\pm$ 0.1)		

### Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Femara v Nebido
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4632
Method	t-test, 2-sided

### Secondary: Change from baseline in weight

End point title	Change from baseline in weight
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: kg				
median (inter-quartile range (Q1-Q3))	-0.8 (-2 to 0.8)	1.3 (-0.2 to 3.3)		

### Statistical analyses

Statistical analysis title	Difference in medians
Comparison groups	Femara v Nebido

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03189
Method	Wilcoxon (Mann-Whitney)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

26 weeks

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Femara
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Reporting group description: -

Reporting group title	Nebido
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Reporting group description: -

Serious adverse events	Femara	Nebido	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	2 / 18 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Hospitalisation	Additional description: Hospitalisation for three weeks for antibiotic treatment of cellulitis		
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Femara	Nebido	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)	6 / 18 (33.33%)	
Investigations			



Prostatic specific antigen increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Nervous system disorders			
Depressed mood subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Headache subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Hypersomnia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Lethargy subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 18 (16.67%) 3	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Somnolence subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Pyrexia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Gastrointestinal disorders			
Faeces hard subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Infrequent bowel movements subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	

Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Productive cough subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	2 / 18 (11.11%) 2	
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Psychiatric disorders			
Sleep disorder subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	2 / 18 (11.11%) 2	
Muscle strain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Myalgia			

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported