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

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Patients were withdrawn from study when safety concerns were expressed by investigator.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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Research participants were be 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/m2 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
Arm title	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

Arm title	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 1	Femara	Nebido
Started	19	18
Completed	19	18

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

Arms	
Are arms mutually exclusive?	Yes
Arm title	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

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

median	83	82	
inter-quartile range (Q1-Q3)	78 to 94	76 to 88	-
Haemoglobin A1C			
Units: percentage			
median	6.3	6.1	
inter-quartile range (Q1-Q3)	5.9 to 7.6	6 to 6.3	-
Glucose			
Units: mmol/L			
median	6.4	5.2	
inter-quartile range (Q1-Q3)	5.7 to 8.8	4.9 to 5.7	-
Triglycerides			
Units: mmol/L			
median	1.31	1.31	
inter-quartile range (Q1-Q3)	1.17 to 1.9	1.08 to 1.96	-
Homeostatic Model Assessment of Insulin Resistance			
Units: score			
median	7.16	5.388	
inter-quartile range (Q1-Q3)	6.087 to 8.981	4.443 to 7.996	-
Haemoglobin			
Units: g/dL			
median	14.7	15	
inter-quartile range (Q1-Q3)	13.9 to 15.4	14.2 to 15.8	-
Creatinine			
Units: mmol/L			
median	67	68	
inter-quartile range (Q1-Q3)	60 to 75	63 to 79	-
Estimated glomerular filtration rate			
Units: mL/min/1.73 m²			
median	120.568	117.139	
inter-quartile range (Q1-Q3)	104.668 to 132.521	95.473 to 127.581	-
Alanine transaminase			
Units: U/L			
median	38	32	
inter-quartile range (Q1-Q3)	30 to 54	30 to 36	-
500 m walk			
Units: sec			
median	386	382	
inter-quartile range (Q1-Q3)	353 to 418	348 to 409	-
Average steps walked during previous 7 days			
Units: steps/day			
median	4216	6000	
inter-quartile range (Q1-Q3)	2523 to 6668	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

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	15	10		
Units: seconds				
arithmetic mean (standard error)	-18 (± 7)	-14 (± 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

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	18	18		
Units: mmHg				
arithmetic mean (standard error)	1 (± 2)	3 (± 2)		

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	= 0.4221
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

End point values	Femara	Nebido		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmHg				
arithmetic mean (standard error)	-2 (± 4)	3 (± 3)		

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	= 0.363
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 (± 0.1038)	0.0155 (± 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

Statistical analysis title	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 (± 0.1)	0.1 (± 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported