Clinical trial results:
Testosterone therapy of men with type 2 diabetes mellitus
Summary

EudraCT number	2011-002102-73
Trial protocol	DK
Global end of trial date	05 November 2013

Results information

Result version number	v1 (current)
This version publication date	02 December 2020
First version publication date	02 December 2020

Trial information

Trial identification

Sponsor protocol code	171178

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01560546
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	Kløvervænget 6, Odense C, Denmark, 5000
Public contact	Marianne Andersen, Odense University Hospital, department of Endocrinology, +45 65412502, msa@rsyd.dk
Scientific contact	Marianne Andersen, Odense University Hospital, department of Endocrinology, +45 65412502, msa@rsyd.dk

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	29 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to investigate if treatment with testosterone in men with low to normal bioavailable testosterone levels (<7.3 nmol/l) and T2DM will increase lean body mass

Protection of trial subjects:

Measurement of hematocrit was chosen as increase in this is a well-described side effect of the treatment and as high levels increase the risk of blood clots.
Due to the Danish Urological Society's report from 2005 regarding androgen replacement and the risk of prostate cancer, the inclusion criterion for prostate-specific antigen (PSA) in the study was set at PSA<3 µg/L

Background therapy:

Metformin and concomitant medication: The use of metformin was equally distributed with regard to low and maximum dosage between the two groups. Totals of 69.2% (27/39), 84.6% (33/39), 33.3% (13/39), 7.7% (3/39), and 7.7% (3/39) of patients were on antihypertensive drugs, cholesterol-lowering drugs, antithrombotic drugs, inhalation steroids and antidepressants, respectively. The concomitant medication was equally distributed between the two groups. No cholesterol-lowering drugs were introduced during the study. All patients took their usual medication on the morning they attended the clinic. Any antithrombotic agents were stopped 3-7 days before the clamp and muscle biopsy.

Evidence for comparator: -

Actual start date of recruitment	02 April 2012
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	Denmark: 43
Worldwide total number of subjects	43
EEA total number of subjects	43

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)	31
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited using advertisements in local newspapers, magazines, at local general practitioners in Odense, and through written invitations to patients with newly diagnosed T2D, who were referred to our department at Odense University Hospital. The recruitment period started in April 2012 and ended in May 2013.

Pre-assignment

Screening details:

Screening (n=59). Screening failure (n=16). White men, aged 50–70 years, with BioT levels <7.3 nmol/L, a diagnosis of T2D within the preceding 3 months to 10 years, and receiving metformin for >3 months were eligible for inclusion.

Period 1

Period 1 title	Intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Trial investigators and patients were blinded to the intervention allocation. Dose titration and safety monitoring were externally handled to ensure continued blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Testosterone

Arm description:

Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing 50 mg testosterone (Testim; TRT, n = 22).

Arm type	Experimental
Investigational medicinal product name	testim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Transdermal use

Dosage and administration details:

Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing testim (testosterone) (n = 21). After 3 weeks of treatment, 16/21 patients were increased to 10 g gel daily.

Arm title	Placebo

Arm description:

Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing placebo (n = 21)

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Transdermal use

Dosage and administration details:

Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing placebo (n = 21). After 3 weeks of treatment, all patients in the placebo group were increased to 10 g gel daily,

Number of subjects in period 1	Testosterone	Placebo
Started	22	21
Completed	20	19
Not completed	2	2
Physician decision	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Testosterone
Reporting group description:	
Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing 50 mg testosterone (Testim; TRT, n = 22).	
Reporting group title	Placebo
Reporting group description:	
Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing placebo (n = 21)	

Reporting group values	Testosterone	Placebo	Total
Number of subjects	22	21	43
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	19	39
From 65-84 years	2	2	4
85 years and over	0	0	0
50-70	0	0	0
Not recorded	0	0	0
Age continuous			
Units: years			
arithmetic mean	61	59	
standard deviation	± 6	± 6	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	22	21	43

Subject analysis sets	
Subject analysis set title	Total lean body mass (muscle mass) testosterone
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol analyses were performed. Differences in baseline values were analyzed using an unpaired t-test on normally distributed data. Multiple linear regression analysis, controlled for baseline values, were conducted on normally distributed data for the placebo-controlled mean effect of intervention between groups. The models were checked with residual plots and Box-Cox analysis. Nonparametric Wilcoxon rank-sum tests were conducted on baseline values and Δ-values (24 weeks - baseline) if data could not be transformed to normally distributed data using natural logarithm. The Kruskal–Wallis test was used to compare and test for differences in Δ-value frequencies between the groups. Spearman's rank correlation analysis was performed to test correlations. All tests were two-sided, and results with p values <0.05 were considered statistically significant. Results are expressed as arithmetic mean standard deviation, geometric mean (95% CI), or median [interquartile range (IQR)].

Subject analysis set title	Total lean body mass (muscle mass) placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol analyses were performed. Differences in baseline values were analysed using an unpaired t-test on normally distributed data. Multiple linear regression analysis, controlled for baseline values, were conducted on normally distributed data for the placebocontrolled mean effect of intervention between groups. The models were checked with residual plots and Box-Cox analysis. Nonparametric Wilcoxon rank-sum tests were conducted on baseline values and Δ-values (24 weeks - baseline) if data could not be transformed to normally distributed data using natural logarithm. The Kruskal–Wallis test was used to compare and test for differences in Δ-value frequencies between the three groups of sample data. Spearman's rank correlation analysis was performed to test correlations. All tests were two-sided, and results with p values <0.05 were considered statistically significant.

Reporting group values	Total lean body mass (muscle mass) testosterone	Total lean body mass (muscle mass) placebo	
Number of subjects	20	19	
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)	0	0	
Adolescents (12-17 years)		0	
Adults (18-64 years)	18	17	
From 65-84 years	2	2	
85 years and over	0	0	
50-70	0	0	
Not recorded	0	0	
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical			
Units: Subjects			
Female	0		
Male	39		

End points

End points reporting groups

Reporting group title	Testosterone
Reporting group description:	
Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing 50 mg testosterone (Testim; TRT, n = 22).	
Reporting group title	Placebo
Reporting group description:	
Patients were assigned to 5 g gel daily, dispensed in visually identical tubes, containing placebo (n = 21)	
Subject analysis set title	Total lean body mass (muscle mass) testosterone
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol analyses were performed. Differences in baseline values were analyzed using an unpaired t-test on normally distributed data. Multiple linear regression analysis, controlled for baseline values, were conducted on normally distributed data for the placebo-controlled mean effect of intervention between groups. The models were checked with residual plots and Box-Cox analysis. Nonparametric Wilcoxon rank-sum tests were conducted on baseline values and Δ-values (24 weeks - baseline) if data could not be transformed to normally distributed data using natural logarithm. The Kruskal–Wallis test was used to compare and test for differences in Δ-value frequencies between the groups. Spearman's rank correlation analysis was performed to test correlations. All tests were two-sided, and results with p values <0.05 were considered statistically significant. Results are expressed as arithmetic mean standard deviation, geometric mean (95% CI), or median [interquartile range (IQR)].	
Subject analysis set title	Total lean body mass (muscle mass) placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol analyses were performed. Differences in baseline values were analysed using an unpaired t-test on normally distributed data. Multiple linear regression analysis, controlled for baseline values, were conducted on normally distributed data for the placebocontrolled mean effect of intervention between groups. The models were checked with residual plots and Box-Cox analysis. Nonparametric Wilcoxon rank-sum tests were conducted on baseline values and Δ-values (24 weeks - baseline) if data could not be transformed to normally distributed data using natural logarithm. The Kruskal–Wallis test was used to compare and test for differences in Δ-value frequencies between the three groups of sample data. Spearman's rank correlation analysis was performed to test correlations. All tests were two-sided, and results with p values <0.05 were considered statistically significant.	

Primary: Lean body mass (muscle mass)

End point title	Lean body mass (muscle mass)
End point description:	
End point type	Primary
End point timeframe:	
Data were analyzed in 2015 and published in 2016.	

End point values	Testosterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: kilogram(s)				
arithmetic mean (standard deviation)	63.6 (± 8.4)	61.5 (± 8.0)		

Statistical analyses

Statistical analysis title	Lean body mass
Comparison groups	Testosterone v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	placebocontr mean effect of intervention
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	97.5
Variability estimate	Standard deviation

Notes:

[1] - Per-protocol analyses were performed. Differences in baseline values were analysed using an unpaired t-test on normally distributed data. Multiple linear regression analysis, controlled for baseline values, were conducted on normally distributed data for the placebocontrolled mean effect of intervention between groups. Nonparametric Wilcoxon rank-sum tests were conducted on baseline values and Δ-values if data could not be transformed to normally distributed data using natural log

Secondary: Total fat mass

End point title	Total fat mass

End point description:

End point type	Secondary

End point timeframe:

Analyzed in 2015. Published in 2016.

End point values	Testosterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: kilogram(s)				
geometric mean (confidence interval 95%)	27.1 (23.3 to 31.6)	27.2 (23.9 to 30.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events and serious adverse events were recorded throughout the study in the time period 2012-2013.

Adverse event reporting additional description:

Two serious adverse events occurred in the study. As a result of gallstones, one patient (placebo) developed pancreatitis complicated with sepsis and multiple organ failure but made a full recovery. One patient (TRT) required a pacemaker as a result of arrhythmia. Both patients were discontinued from the study and excluded from statistics.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Testosterone
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported.

Serious adverse events	Testosterone	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Arrhythmia	Additional description: One patient (TRT) required a pacemaker as a result of arrhythmia. Both patients were discontinued from the study and excluded from statistics.		
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Pancreatitis acute	Additional description: As a result of gallstones, one patient (placebo) developed pancreatitis complicated with sepsis and multiple organ failure but made a full recovery.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
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: 0.05 %

Non-serious adverse events	Testosterone	placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	

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/28914503

http://www.ncbi.nlm.nih.gov/pubmed/28522646

http://www.ncbi.nlm.nih.gov/pubmed/27265844

http://www.ncbi.nlm.nih.gov/pubmed/28673384