



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 | 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 (\pm 8.4) | 61.5 (\pm 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>