Clinical trial results:
Testosterone Replacement in Young Male cancer Survivors (TRYMS)

Summary

EudraCT number	2011-000677-31
Trial protocol	GB
Global end of trial date	06 December 2015

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	STH15216

Additional study identifiers

ISRCTN number	ISRCTN70274195
ClinicalTrials.gov id (NCT number)	NCT99999999
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sheffield Teaching Hospitals NHS Foundation Trust
Sponsor organisation address	11 Broomfield Road, Sheffield, United Kingdom, S10 2SE
Public contact	Clinical Trials Research Unit (CTRU), University of Leeds, +44 01133431477, a.f.smith@leeds.ac.uk
Scientific contact	Clinical Trials Research Unit (CTRU), University of Leeds, +44 01133431477, a.f.smith@leeds.ac.uk

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	26 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2015
Global end of trial reached?	Yes
Global end of trial date	06 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is to find out whether testosterone replacement therapy can reduce body fat and improve quality of life in young male cancer survivors who have a borderline low level of testosterone. This question is split in to two principal research objectives which are: • To assess the effect of 26 weeks of testosterone treatment on levels of fat within the body • To assess the effect of 26 weeks of testosterone treatment on the participants' physical functioning. This information is collected using questionnaires that are completed by the participant.

Protection of trial subjects:

Testosterone gel is a drug that is widely used and has a robust safety profile. It is accepted as being a low risk drug with serious side effects occurring very rarely. As such the risk to the participant of using a drug that they may not have otherwise received is believed to be very low. As all participants were expected to receive testosterone gel for at least 13 weeks all participants should receive some benefit to outweigh the minimal risk.

Participants received 2 whole body scans called DXAs which involved a very low dose of radiation, about the same as you would get from the Earth’s atmosphere in a few days, and less than you would get from taking a flight to America. The Xray exposure in the study has been assessed and approved by a radiation expert. The Health Protection Agency Radiation Protection Division describes a few days natural background radiation as ‘negligible risk’ and participants are unlikely to experience any health problems from these scans.

Throughout the study participants were asked to have 6 additional blood tests which were the same as normal blood tests that participants will have had them before during cancer treatment. As with any blood test, there was a small risk of bruising and discomfort, and very rarely infections. These tests were performed in hospitals by appropriately trained members of staff.

Tostran gel may cause skin irritation such as a rash. Less commonly it can cause an increase in the participants' number of red blood cells, increased hair growth, enlargement of the male breast tissue, soft tissue swelling and an increase in PSA (Prostate Specific Antigen) levels. To minimise these risks red blood cell count and PSA were tested regularly during the study, and if the participants' doctor thought they were having significant side effects they could withdraw them from the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 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	United Kingdom: 136
Worldwide total number of subjects	136
EEA total number of subjects	136

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)	136
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between May 2012 and March 2015, 1407 patients were screened for the TRYMS trial, of which 304 were registered and 136 were randomised to the TRYMS trial.

Pre-assignment

Screening details:

1407 patients screened. 1103 were not registered because: they did not want to participate (N=399), clinically ineligible (N=610), too ill to consent (N=2), Other (N=46), no reason given (N=46). 168 were registered but not randomised because: ineligible (N=152), other (N=16). 136 patients were randomised.

Period 1

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

Blinding implementation details:

Treatment/placebo gels and canisters identical in appearance and identified by unique code assigned at random by Statistician to maintain the blind of patients and site staff (except in the case of emergency unblinding). All CTRU staff remained blind apart from key personnel incl. Statisticians and safety team for SUSAR reporting and independent endocrinologist for escalation of out-of-range testosterone levels after 2W. Testosterone samples taken at baseline and 26W analysed centrally.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tostran 2% Gel

Arm description:

- One gram of gel contains 20mg testosterone. One press of the canister piston delivers 0.5g of gel containing 10mg testosterone.
- Supplied by ProStrakan

Arm type	Active comparator
Investigational medicinal product name	Tostran 2% gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

3g gel (containing 60mg testosterone)/day applied cutaneously. At 2 weeks the dose may be adjusted based on the participants serum testosterone levels. If serum testosterone is lower than 11nmol/l the daily dose will be increased by 20mg, if serum testosterone is between 11 and 15nmol/l the daily dose will be increased by 10mg. If the testosterone level is greater than 15 but lower than 35 the daily dose will remain the same and if the level is between 35nmol and 40nmol/l then the daily dose will be reduced by 20mg. If the
testosterone level is greater than 40nmol/l the unblinded endocrinologist will determine an appropriate dose.

Arm title	Placebo

Arm description:

- Composition: Propylene glycol, ethanol anhydrous, isopropylalcohol, oleic acid, carbomer 1382, trolamine, butylhydroxytoluene (E321), water, purified and hydrochloric acid (for pH) adjustment
- Supplied by ProStrakan

Arm type	Placebo

Investigational medicinal product name	Placebo gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

3g gel/day applied cutaneously for 2 weeks. At 2 weeks dosage adjusted at random in line with active arm dose titration. Treatment continues for a further 24 weeks.

Number of subjects in period 1	Tostran 2% Gel	Placebo
Started	68	68
Completed	54	56
Not completed	14	12
Consent withdrawn by subject	3	5
Lost to follow-up	11	7

Baseline characteristics

Reporting groups	
Reporting group title	Tostran 2% Gel
Reporting group description:	
- One gram of gel contains 20mg testosterone. One press of the canister piston delivers 0.5g of gel containing 10mg testosterone. - Supplied by ProStrakan	
Reporting group title	Placebo
Reporting group description:	
- Composition: Propylene glycol, ethanol anhydrous, isopropylalcohol, oleic acid, carbomer 1382, trolamine, butylhydroxytoluene (E321), water, purified and hydrochloric acid (for pH) adjustment - Supplied by ProStrakan	

Reporting group values	Tostran 2% Gel	Placebo	Total
Number of subjects	68	68	136
Age categorical			
Patients were stratified by age group (25-37 and 38-50). No patients outside of the age range 25-50 were not eligible for the trial.			
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
25-37 years	29	29	58
38-50 years	39	39	78
Age continuous			
Units: years			
arithmetic mean	38.4	38	
standard deviation	± 6.4	± 6.4	-
Gender categorical			
Patients were only eligible if they were male.			
Units: Subjects			
Female	0	0	0
Male	68	68	136
Body Mass Index			
Units: Subjects			
<25 kg/m^2	12	12	24
25-29.9 kg/m^2	41	41	82
30-35 kg/m^2	15	15	30
Serum testosterone level			
Serum testosterone level measured locally for eligibility and randomisation			
Units: Subjects			
7-9.9 nmol/L	40	41	81

10-12 nmol/L	28	27	55
Type of previous cancer Units: Subjects			
Testicular cancer	60	60	120
Lymphoma	6	7	13
Leukaemia	2	1	3
time between end of curative anti-cancer treatment and study entry Units: Subjects			
12-30 months	27	31	58
31-60 months	17	18	35
61+ months	24	19	43

End points

End points reporting groups

Reporting group title	Tostran 2% Gel
Reporting group description:	
- One gram of gel contains 20mg testosterone. One press of the canister piston delivers 0.5g of gel containing 10mg testosterone. - Supplied by ProStrakan	
Reporting group title	Placebo
Reporting group description:	
- Composition: Propylene glycol, ethanol anhydrous, isopropylalcohol, oleic acid, carbomer 1382, trolamine, butylhydroxytoluene (E321), water, purified and hydrochloric acid (for pH) adjustment - Supplied by ProStrakan	

Primary: Truncal fat mass at 26 weeks

End point title	Truncal fat mass at 26 weeks
End point description:	
Summary statistics reported for absolute change at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo.	
End point type	Primary
End point timeframe:	
collected at baseline and 26 weeks.	

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[1]	68[2]		
Units: kilogram(s)				
arithmetic mean (standard deviation)	-0.864 (± 1.952)	0.028 (± 1.64)		

Notes:

[1] - prior to multiple imputation 8 patients had missing data at 26 weeks

[2] - Prior to multiple 8 patients had missing data at 26 weeks.

Statistical analyses

Statistical analysis title	Truncal fat mass primary endpoint
Comparison groups	Placebo v Tostran 2% Gel
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.3

Secondary: SF36™ physical functioning scale at 26 weeks

End point title	SF36™ physical functioning scale at 26 weeks

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks on a categorical scale.

End point type	Secondary

End point timeframe:

collected at baseline, 13 weeks and 26 weeks

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[3]	68[4]		
Units: unit				
median (inter-quartile range (Q1-Q3))	0 (0 to 5)	0 (0 to 5)		

Notes:

[3] - prior to multiple imputation 3&7 patients were missing abs change at 13&26 weeks respectively.

[4] - Prior to multiple imputation 7&8 patients were missing abs change data at 13 &26 weeks respectively.

Statistical analyses

Statistical analysis title	SF36 Physical Functioning

Statistical analysis description:

Repeated measures Logistic regression was used to model the binary endpoint of perfect physical functioning (score=100) vs non perfect physical functioning (score<100) because the data were strongly negatively skewed. Baseline measurement, stratification factors, treatment, time and treatment-time interaction were adjusted for as fixed effects. All missing Physical Functioning scores were assumed to be <100. point estimates are presented for the 26 week timepoint.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6105 [5]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.788
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.313
upper limit	1.985

Notes:

[5] - p-value for timepoint=0.8108
p-value for treatment-time interaction=0.9890

Secondary: BMI (at 13 and 26 weeks)

End point title	BMI (at 13 and 26 weeks)

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

measured at baseline, 13 weeks and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[6]	68[7]		
Units: kilogram(s)/square meter				
arithmetic mean (standard deviation)	-0.053 (± 1.258)	0.221 (± 1.052)		

Notes:

[6] - Prior to multiple imputation 6&5 patients were missing data at 13&26 weeks respectively.

[7] - Prior to multiple imputation 4&8 patients were missing data at 13&26 weeks respectively.

Statistical analyses

Statistical analysis title	BMI

Statistical analysis description:

Repeated measures linear regression adjusting for baseline measurement, stratification factors, treatment, time and treatment-time interaction.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.22

Secondary: Fasting insulin: glucose ratio (at 26 weeks)

End point title	Fasting insulin: glucose ratio (at 26 weeks)

End point description:

Summary statistics reported for untransformed values on the continuous scale at 26 weeks. Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

collected at baseline and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[8]	68[9]		
Units: pmol/L over mmol/L				
median (inter-quartile range (Q1-Q3))	11.37 (5.8 to 16.25)	11.96 (8.04 to 17.2)		

Notes:

[8] - Prior to multiple imputation 9 and 17 patients missing data at baseline and 26 weeks respectively.

[9] - prior to multiple imputation 7 and 14 patients missing data at baseline and 26 weeks.

Statistical analyses

Statistical analysis title	ln(insulin:glucose ratio)

Statistical analysis description:

linear regression of log transformed insulin:glucose ratio adjusting for log(baseline measurement), stratification factors and treatment.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.19

Secondary: Total cholesterol

End point title	Total cholesterol

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

baseline and 26 weeks

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[10]	68[11]		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.2 (± 0.7)	-0.1 (± 0.7)		

Notes:

[10] - prior to multiple imputation 13 patients were missing abs change at 26 weeks

[11] - prior to multiple imputation 7 were missing abs change at 26 weeks

Statistical analyses

Statistical analysis title	total cholesterol
Statistical analysis description: linear regression adjusting for baseline, stratification factors and treatment	
Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.21

Secondary: LH levels (at 26 weeks)

End point title	LH levels (at 26 weeks)
End point description: Summary statistics reported for absolute change in LH levels on the continuous scale at 26 weeks (from baseline). The subgroup analysis has been conducted using pre-defined normal and high levels of LH.	
End point type	Secondary
End point timeframe: collected at baseline at 26 weeks	

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	56		
Units: IU/L				
arithmetic mean (standard deviation)	-5.7 (± 4.9)	0.1 (± 2.2)		

Statistical analyses

Statistical analysis title	likelihood ratio test

Statistical analysis description:

Likelihood ratio test to assess the statistical significance of baseline-LH and treatment interaction on truncal fat mass at 26 weeks.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7665 [12]
Method	LRT

Notes:

[12] - corresponds to likelihood ratio test

Secondary: Bone density (at 26 weeks)

End point title	Bone density (at 26 weeks)

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

measured at baseline and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[13]	68[14]		
Units: g/squared cm				
arithmetic mean (standard deviation)	0.005 (± 0.025)	0 (± 0.026)		

Notes:

[13] - prior to multiple imputation 8 patients were missing their 26 week measurement.

[14] - Prior to multiple imputation 8 patients were missing their 26 week measurement.

Statistical analyses

Statistical analysis title	Bone density

Statistical analysis description:

Linear regression adjusting for baseline measurement, stratification factors and treatment as fixed effects.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.01

Secondary: Physical Component summary from the SF36™

End point title	Physical Component summary from the SF36™

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

Collected at baseline, 13 weeks and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[15]	68[16]		
Units: units				
arithmetic mean (standard deviation)	0.61 (± 5.70)	1.04 (± 5.25)		

Notes:

[15] - prior to multiple imputation 3&9 patients were missing their abs change at 13&26 weeks respectively.
[16] - Prior to multiple imputation 7&8 patients were missing abs change at 13&26 weeks respectively.

Statistical analyses

Statistical analysis title	Physical component summary

Statistical analysis description:

Repeated measures analysis adjusting for baseline measurement, stratification factors, treatment, time and treatment-time interaction.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	0.9

Secondary: Waist circumference (at 13 and 26 weeks)

End point title	Waist circumference (at 13 and 26 weeks)

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

measured at baseline, 13 weeks and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[17]	68[18]		
Units: cm				
arithmetic mean (standard deviation)	-0.52 (± 7.76)	-0.89 (± 3.85)		

Notes:

[17] - prior to multiple imputation 6&8 patients were missing abs change at 13&26 weeks respectively.

[18] - prior to multiple imputation 6&11 patients were missing abs change at 13&26 weeks respectively.

Statistical analyses

Statistical analysis title	waist circumference

Statistical analysis description:

Repeated measures linear regression adjusting for baseline measurement, stratification factors, treatment, time, treatment-time interaction.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	2.13

Secondary: whole body fat mass

End point title	whole body fat mass

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

Measured at baseline and 26 weeks

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[19]	68[20]		
Units: kilogram(s)				
arithmetic mean (standard deviation)	-1.63 (± 3.05)	0.1 (± 2.72)		

Notes:

[19] - prior to multiple imputation 8 patients were missing their 26 week measurement

[20] - prior to multiple imputation 8 patients were missing their 26 week measurement.

Statistical analyses

Statistical analysis title	Whole body fat mass
Statistical analysis description: linear regression adjusting for baseline measurement, stratification factors and treatment.	
Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-0.7

Secondary: Lean body mass

End point title	Lean body mass
End point description: Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.	
End point type	Secondary
End point timeframe: measured at baseline and 26 weeks	

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[21]	68[22]		
Units: kilogram(s)				
arithmetic mean (standard deviation)	1.8 (± 1.6)	0.2 (± 1.44)		

Notes:

[21] - prior to multiple imputation 8 were missing values at 26 weeks

[22] - prior to multiple imputation 8 were missing values at 26 weeks

Statistical analyses

Statistical analysis title	Lean body mass
Statistical analysis description: linear regression adjusting for baseline measurement, stratification factors and treatment.	
Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.1

Secondary: mental component summary from the SF36

End point title	mental component summary from the SF36
End point description: Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.	
End point type	Secondary
End point timeframe: collected at baseline, 13 weeks and 26 weeks.	

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[23]	68[24]		
Units: units				
arithmetic mean (standard deviation)	5.54 (± 14.22)	5.03 (± 9.45)		

Notes:

[23] - prior to multiple imputation 3&9 patients were missing abs change at 13&26 weeks respectively.

[24] - prior to multiple imputation 7&8 patients were missing abs change data at 13&26 weeks.

Statistical analyses

Statistical analysis title	Mental component summary
Statistical analysis description: Repeated measures linear regression adjusting for baseline measurement, stratification factors, treatment, time, treatment-time interaction.	
Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.49
upper limit	3.82

Secondary: Rosenberg Self-Esteem Scale

End point title	Rosenberg Self-Esteem Scale

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

collected at baseline, 13 weeks and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[25]	68[26]		
Units: Units				
arithmetic mean (standard deviation)	1.67 (± 4.79)	1.84 (± 4.49)		

Notes:

[25] - prior to multiple imputation 6&11 patients missing abs change at 13&26 weeks

[26] - prior to multiple imputation 9&13 patients missing abs change at 13&26 weeks.

Statistical analyses

Statistical analysis title	Rosenberg Self-Esteem Scale

Statistical analysis description:

Repeated measures linear regression adjusting for baseline measurement, stratification factors, treatment, time and treatment-time interaction.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	1.2

Secondary: FACIT Fatigue

End point title	FACIT Fatigue

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

collected at baseline, 13 weeks and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[27]	68[28]		
Units: units				
arithmetic mean (standard deviation)	4.32 (± 10.65)	5.14 (± 7.12)		

Notes:

[27] - Prior to multiple imputation, 3&8 patients were missing abs change at 13&26 weeks.

[28] - prior to multiple imputation, 7&9 patients were missing data at 13&26 weeks.

Statistical analyses

Statistical analysis title	FACIT Fatigue

Statistical analysis description:

Repeated measures linear regression adjusted for baseline score, stratification factors, treatment, time, treatment-time interaction.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	2.13

Secondary: DISF-SR (II) M

End point title	DISF-SR (II) M

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline).

Note that a formal analysis has not been conducted on this endpoint because of large amounts of missing data. We were unable to ascertain reasons for missing data as they could be because the questions are not relevant (if they do not have a partner) or because they did not want to complete them (e.g. due to the sensitivity of the questions).

End point type	Secondary

End point timeframe:

collected at baseline, 13 weeks and 26 weeks.

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[29]	40[30]		
Units: units				
median (inter-quartile range (Q1-Q3))	7.5 (-6.5 to 20.5)	12 (-2 to 25.5)		

Notes:

[29] - 24 patients missing data at 26 weeks

[30] - 28 patients missing data at 26 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: high-density lipoprotein

End point title	high-density lipoprotein

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

baseline and 26 weeks

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[31]	68[32]		
Units: mmol/L				
arithmetic mean (standard deviation)	0.019 (± 0.508)	-0.098 (± 0.607)		

Notes:

[31] - prior to multiple imputation 16 were missing abs change at 26 weeks

[32] - prior to multiple imputation 10 were missing abs change at 26 weeks,

Statistical analyses

Statistical analysis title	high-density lipoprotein
Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.18

Secondary: low-density lipoprotein

End point title	low-density lipoprotein
End point description:	
Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.	
End point type	Secondary
End point timeframe:	
baseline and 26 weeks	

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[33]	68[34]		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.116 (± 0.618)	-0.069 (± 0.569)		

Notes:

[33] - prior to multiple imputation 24 were missing abs change at 26 weeks

[34] - prior to multiple imputation 18 were missing abs change at 26 weeks

Statistical analyses

Statistical analysis title	low-density lipoprotein
Statistical analysis description:	
linear regression adjusting for baseline, stratification factors and treatment.	
Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.17

Secondary: triglycerides

End point title	triglycerides

End point description:

Summary statistics reported for absolute change on the continuous scale at 26 weeks (from baseline). Treatment effect estimates are reported for Active Tostran vs placebo at 26 weeks.

End point type	Secondary

End point timeframe:

baseline and 26 weeks

End point values	Tostran 2% Gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[35]	68[36]		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.15 (± 1.47)	0.03 (± 1.09)		

Notes:

[35] - prior to multiple imputation 13 patients were missing abs change at 26 weeks

[36] - prior to multiple imputation 9 patients were missing absolute change at 26 weeks

Statistical analyses

Statistical analysis title	ln(Triglycerides)

Statistical analysis description:

linear regression of log transformed data adjusting for ln(baseline measurement), stratification factors and treatment.

Comparison groups	Tostran 2% Gel v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.15

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reports at 6, 13, 19 and 26 weeks after randomisation. A further follow-up phone call was made to the participant 30 days after finishing trial treatment.

Adverse event reporting additional description:

Adverse events of specific interest (urinary symptoms or skin rash/irritation) and/or severity (CTCAE grade 3 and above) were recorded with relevant information recorded as volunteered by the participant, discovered by investigator questioning or detected through physical examination, lab test, or other investigation,.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Active

Reporting group description:

Participants allocated to receive Tostran 2% gel (active treatment).

Reporting group title	Placebo

Reporting group description:

Patients allocated to receive placebo gel

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 68 (0.00%)	0 / 68 (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	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 68 (39.71%)	26 / 68 (38.24%)	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Fatigue			

subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	0 / 68 (0.00%) 0	
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	 1 / 68 (1.47%) 1	 1 / 68 (1.47%) 1	
Skin and subcutaneous tissue disorders non-specific rash subjects affected / exposed occurrences (all)	 25 / 68 (36.76%) 41	 21 / 68 (30.88%) 34	
Renal and urinary disorders Urinary symptoms subjects affected / exposed occurrences (all)	 1 / 68 (1.47%) 2	 5 / 68 (7.35%) 5	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	 1 / 68 (1.47%) 1 1 / 68 (1.47%) 1	 0 / 68 (0.00%) 0 0 / 68 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2011	Schedule of Events table in protocol updated to document SAE collection at baseline and during eligibility assessment. Additional withdrawal criterion added to include withdrawal of patients who suffer AE grade 3 or higher.
15 May 2013	Protocol updated to include statement that eligibility waivers are not permitted; addition of inclusion criteria to allow patients who are more than 12 months from end of glucocorticoid treatment following allogeneic bone marrow transplant; clarification that both oral & IV corticosteroid treatment are exclusions; addition of historical allergic reaction to Tostran as an exclusion; addition of active chronic graft vs host disease as an exclusion; addition of disease or current medication known to have effects on body fat mass added as an exclusion; addition of severe obstructive sleep apnoea as an exclusion; addition of active liver disease as an exclusion; addition of uncontrolled hypertension as an exclusion; exclusion criterion renal failure changed to renal impairment; deep vein thrombosis deleted as an exclusion criterion; clarification that patients may not be randomised more than once; additional information provided on how patients should be approached about participating in the trial; clarification that canister code lists will only be password protected when treatment allocation info is included on the list; addition of advice stating that IMP should be applied in the morning; various amendments to information given about the titration sample; amendment to state that for serum testosterone levels between 35nmol/l & 40nmol/l testosterone dose will be reduced by 20mg and if testosterone level is greater than 40nmol/l the independent endocrinologist will determine an appropriate dose between 20-40mg; deletion of significant changes to other hormone replacement therapy as a withdrawal criterion; deletion of treatment with oral corticosteroids for longer than a week as a withdrawal criterion; changes to timing of blood samples; inclusion of additional oestradiol measurement; changes to definition of end of trial, SAEs, SUSARs; amendment to state that the significance levels for the two primary endpoints have been adjusted to avoid an inflated type I error.
25 November 2013	Protocol amended to exclude participation of patients who are intending to conceive in the next 12 months (6 months of trial treatment + 6 months for sperm count to return to pre-trial levels).
02 April 2014	Protocol and patient information amended to allow addition of optional preliminary consent process to allow eligibility assessments to be performed prior to main consent; clarification regarding timing of testosterone samples clarification regarding the storage of serum samples; clarification that the measurement of fasting lipids is not time dependent.
16 October 2014	Major amendment to the protocol to change the trial design and sample size. For the primary endpoint the two baseline testosterone subgroups (7.0-9.9nmol/L: 10-12nmol/L) were combined and a minimum sample size of 112 participants introduced, with the treatment effect for each of the subgroups to be estimated in an exploratory manner. Protocol also amended to clarify that only deaths occurring after randomisation and within the trial period should be reported and that pregnancies in trial participants partners will be followed up until the outcome is know.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Please note that there was 1 patient in the placebo group who experienced an SAE but this was not related to treatment. Details have not been included in the database due to potential risk of identifiability.

Notes: