SUPPLEMENTARY DATA

List of investigators

K. S. Channer (Royal Hallamshire Hospital, Sheffield, UK); T. H. Jones (University of Sheffield, Sheffield and Barnsley Hospital, Barnsley, UK); P. D. Kell (The Hospital of St. John and St. Elizabeth, London, UK); R. Steeds (University Hospital Birmingham, Birmingham, UK); C. McKinnon (Castlemilk Health Center, Glasgow, UK); T. Wright (Hathaway Surgery, Chippenham, UK); K. Young (St. Mary's Surgery, Ely, UK); J. Buvat (Center ETPARP, Lille, France); M. H. Colson (Center Medical du Palais, Marseille, France); O. Cambau (68 Cours Gambetta, Lyon, France); D. Chevallier (University Hospital Pasteur, Nice, France); P. Desvaux (11 rue Magellan, Paris, France); A. Corman (7 rue Romiguières, Toulouse, France); H. M. Behre (Martin-Luther University Halle-Wittenberg, Halle, Germany); B. Boehm (Medizinische Universitätsklinik Ulm, Ulm, Germany); J. Hensen (Klinikum Hannover Nordstadt, Hannover, Germany); K. Badenhoop (Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt / Main, Germany); R. Bretzel (Universitätsklinikum Giessen und Marburg, Giessen, Germany); C. Auernhammer (Ludwig-Maximilians-Universität, München, Germany); C. Kasperk (Medizinische Universitätsklinik Heidelberg, Heidelberg); J. J. Legros (CHR Citadelle, Service d'endocrinologie, Liège, Belgium); E. Meuleman (VU University Medical Center, Amsterdam, Netherlands); K. P. Bouter

(Eekbrouwersweg 10, 5233 VG`s Hertogenbosch, Netherlands); G. Spera (Università La Sapienza, Rome, Italy); V. Toscano (Università La Sapienza, Rome, Italy); G. Delitala (University of Sassari, Sassari, Italy) G. Frajese (Tor Vergata University, Rome, Italy); M. Vetri (Azienda Ospedaliera 'Garibaldi-Nesima', Catania, Italy); M. Volterranni (IRCCS San Raffaele Pisana, Rome, Italy); I. Moncada (Hospital Sanitas-La Zarzuela, Madrid, Spain); A. M. Morales (Carlos Haya University Hospital, Malaga, Spain); N. Cruz (Hospital Virgen del Rocío, Seville, Spain); G. T. Cortada (Policlinic Lleida, Alcalde Sol 4, Lleida, Spain) A. Puigvert (Institut Medic Tecnologic, Barcelona, Spain); L. Bassas (Hospital Fundació Puigvert, Barcelona, Spain); S. Arver (Karolinska University Hospital and the Karolinska Institute, Stockholm, Sweden); A. Giwercman (Malmö Universitetssjukhus [UMAS], Malmö, Sweden); T. Rosen (Sahlgrenska Universitetssjukhuset, Göteborg, Sweden).

Criteria for type 2 diabetes and metabolic syndrome

Type 2 diabetes diagnosis was defined as FPG level 7.0 mmol/L on two occasions, or, random glucose level 11.1 mmol/L and symptoms of type 2 diabetes (polyuria, polydipsia, polyphagia, with or without weight loss) or previously diagnosed type 2 diabetes (1). MetS was defined as central obesity (waist circumference 94 cm for Europid men [with ethnicity-specific values for other groups]) and any two of the following: triglyceride (TG) level 1.7 mmol/L or specific treatment for this lipid abnormality; HDL-cholesterol <1.03 mmol/L, or specific treatment for this lipid abnormality; hypertension (systolic blood pressure [BP] 130 mmHg or diastolic BP 85 mmHg or treatment of previously diagnosed hypertension); FPG 5.6 mmol/L, or previously diagnosed type 2 diabetes (2).

Laboratory methods

Lipoprotein a (LpA) was measured by immunoturbidometric assay. Total cholesterol, LDL-cholesterol and HDL-cholesterol were measured using homogenous enzymatic colorimetric assay. Triglycerides were measured using the colorimetric glycerol-3-phosphate oxidase-peroxidase anti-peroxidase assay. HbA1c was measured using high-performance liquid chromatography. Fasting serum insulin was measured using chemiluminescence. Fasting plasma glucose was measured using enzymatic hexokinase assays. Free testosterone concentrations were calculated from serum total testosterone, albumin and sex hormone binding globulin concentrations (all measured using chemiluminescence), using Vermeulen's equation (3). All laboratory assessments were performed centrally by Pivotal Laboratories Limited, York, UK.

1. World Health Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications.* Geneva, Switzerland. World Health Organization, 1999 (WHO/NCD/NCS/99.2).
2. International Diabetes Federation. (2006) The IDF consensus worldwide definition of the metabolic syndrome. Brussels: International Diabetes Federation. Available from http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf. Accessed 25 March 2010

3. Vermeulen A, Kaufman JM. Diagnosis of hypogonadism in the aging male. *Aging Male* 2002;**5:**170–6

SUPPLEMENTARY DATA

Supplementary Table 1. Summary of PSA concentrations (Safety Population)

	All patients	
Variable	**Testosterone**	**Placebo**
Mean ± SD (µg/L)		
Baseline (n)	1.50 ± 1.80 (108)	1.19 ± 1.18 (112)
Phase 1: Month 6 (n)	1.37 ± 1.14 (73)	1.38 ± 2.24 (76)
Phase 2: Month 12 (n)	1.41 ± 1.29 (49)	1.18 ± 1.17 (59)
Age-adjusted categorization*, n (%)		
Baseline		
n	108	112
Normal	105 (97)	109 (97)
High	3 (3)	3 (3)
Phase 1: Month 6		
n	73	76
Normal	73 (100)	74 (97)
High	0 (0)	2 (3)
Phase 2: Month 12		
n	49	59
Normal	46 (94)	58 (98)
High	3 (6)	1 (2)
Mean ± SD change from baseline (ng/mL)		
Phase 1: Month 6 (n)	0.19 ± 0.66 (73)	0.22 ± 1.99 (76)
Phase 2: Month 12 (n)	0.13 ± 0.86 (49)	-0.02 ± 0.69 (59)
Change from baseline by category, n (%)		
Phase 1: Month 6		
n	73	76
Change 0.75 ng/mL	65 (89)	70 (92)
Change > 0.75 ng/mL	8 (11)	6 (8)
Phase 2: Month 12		
n	49	59
Change 0.75 ng/mL	42 (86)	56 (95)
Change > 0.75 ng/mL	7 (14)	3 (5)

PSA: Prostate Specific Antigen; SD: standard deviation.

*Age-specific PSA reference ranges

	Reference Range		
Age Range	**Asians**	**African-Americans**	**Caucasians**
40-49 years	0-2.0 ng/mL	0-2.0 ng/mL	0-2.5 ng/mL
50-59 years	0-3.0 ng/mL	0-4.0 ng/mL	0-3.5 ng/mL
60-69 years	0-4.0 ng/mL	0-4.5 ng/mL	0-4.5 ng/mL
70-79 years	0-5.0 ng/mL	0-5.5 ng/mL	0-6.5 ng/mL

Supplementary Table 2. Mean ± SD change from baseline in HOMA-IR (ITT population, LOCF) in patients without type 2 diabetes only

	Testosterone	Placebo
Phase 1: Month 6 (n)	-0.40 ± 1.90 (35)	0.12 ± 1.64 (40)
Phase 2: Month 12 (n)	-0.10 ± 2.21 (35)	0.09 ± 1.89 (40)

SUPPLEMENTARY DATA

*P<0.05; **P<0.01 between groups.
HOMA-IR: homeostatic model assessment of insulin resistance; ITT: intention-to-treat; LOCF: last observation carried forward; SD: standard deviation.
HOMA-IR calculated excluding insulin values >=249 pmol/L (greater than 3 standard deviations above published mean fasted insulin value in Type 2 diabetics)

SUPPLEMENTARY DATA

Supplementary Table 3. Mean ± SD change from baseline in lipid parameters, abdominal obesity and body composition (mPP, study completers)

	All patients		MetS patients		Type 2 diabetes patients	
Variable	**Testosterone**	**Placebo**	**Testosterone**	**Placebo**	**Testosterone**	**Placebo**
Insulin resistance						
HOMA-IR						
Phase 1: Month 6 (n)	-0.68 ± 2.81 (59)	-0.07 ± 2.59 (54)	-0.74 ± 2.93 (52)	-0.18 ± 2.74 (41)	-0.85 ± 2.99 (40)	-0.20 ± 2.95 (31)
Phase 2: Month 12 (n)	-0.92 ± 2.87 (34)	0.42 ± 3.15 (46)	-0.97 ± 3.01 (30)	0.27 ± 3.47 36)	-1.49 ± 2.95 (23)	0.66 ± 3.60 (27)
Glycemic control						
HbA1c (%)						
Phase 1: Month 6 (n)	0.20 ± 0.58 (63)	0.32 ± 0.57 (58)	0.23 ± 0.48 (55)	0.37 ± 0.60 (45)	0.21 ± 0.68 (42)	0.36 ± 0.68 (32)
Phase 2: Month 9 (n)	0.03 ± 0.72 (55)*	0.33 ± 0.69 (52)	0.07 ± 0.62 (47)	0.37 ± 0.75 (40)	-0.05 ± 0.81 (39)†	0.47 ± 0.78 (30)
Phase 2: Month 12 (n)	-0.04 ± 1.02 (42)	0.17 ± 0.67 (49)	-0.01 ± 0.93 (36)	0.23 ± 0.72 (39)	-0.13 ± 1.21 (28)	0.30 ± 0.69 (28)
Lipid parameters						
Lpa (µmol/L)						
Phase 1: Month 6 (n)	-0.21 ± 0.45 (64)‡	0.29 ± 1.65 (57)	-0.25 ± 0.46 (56) §	0.14 ± 1.03 (44)	-0.29 ± 0.44 (42)**	0.50 ± 2.18 (32)
Phase 2: Month 12 (n)	-0.21 ± 0.34 (41)	0.36 ± 2.01 (49)	-0.18 ± 0.35(35)††	0.11 ± 0.54 (39)	-0.25 ± 0.35 (27)	0.64 ± 2.63 (28)
Total cholesterol (mmol/L)						
Phase 1: Month 6 (n)	-0.23 ± 0.63 (64)‡‡	0.02 ± 0.67 (57)	-0.26 ± 0.64 (56) §§	0.03 ± 0.74 (44)	-0.19 ± 0.64 (42)	0.05 ± 0.67 (32)
Phase 2: Month 12 (n)	-0.29 ± 0.82 (41)	-0.22 ± 0.90 (49)	-0.39 ± 0.81 (35)	-0.28 ± 0.94 (39)	-0.34 ± 0.78 (27)	-0.15 ± 0.74 (28)
LDL-cholesterol (mmol/L)						
Phase 1: Month 6 (n)	-0.20 ± 0.53 (64)***	-0.01 ± 0.42 (57)	-0.22 ± 0.55† (56)	0 ± 0.47 (44)	-0.09 ± 0.53 (42)	-0.01 ± 0.44 (32)
Phase 2: Month 12 (n)	-0.32 ± 0.60 (41)	-0.15 ± 0.63 (49)	-0.38 ± 0.62 (35)	-0.20 ± 0.67 (39)	-0.30 ± 0.55 (27)	-0.08 ± 0.50 (28)
HDL-cholesterol (mmol/L)						
Phase 1: Month 6 (n)	-0.08 ± 0.20 (64)	-0.04 ± 0.14 (57)	-0.08 ± 0.19 (56)	-0.02 ± 0.12 (44)	-0.07 ± 0.22 (42)	-0.02 ± 0.15 (32)
Phase 2: Month 12 (n)	-0.08 ± 0.28 (41)	-0.05 ± 0.18 (49)	-0.11 ± 0.24 (35)	-0.04 ± 0.15 (39)	-0.09 ± 0.30 (27)	-0.04 ± 0.21 (28)
Triglycerides (mmol/L)						
Phase 1: Month 6 (n)	-0.01 ± 0.77 (64)	0 ± 0.75 (57)	0 ± 0.81 (56)	-0.09 ± 0.74 (44)	-0.09 ± 0.58 (42)	0.1 ± 0.73 (32)
Phase 2: Month 12 (n)	0.02 ± 0.86 (41)	0.07 ± 1.06 (49)	0.06 ± 0.92 (35)	-0.09 ± 1.04 (39)	0 ± 0.80 (27)	0.13 ± 1.13 (28)
Abdominal obesity and body composition						

SUPPLEMENTARY DATA

Body fat, mean ± SD (%)						
Phase 1: Month 6 (n)	-1.28 ± 2.11 (66)[††]	0.80 ± 5.31 (59)	-1.47 ± 1.76 (58)[††]	0.80 ± 5.82 (46)	-0.98 ± 2.21(44)[†††]	1.10 ± 5.63 (33)
Phase 2: Month 12 (n)	-0.91 ± 3.15 (46)[‡‡‡]	1.43 ± 6.10 (49)	-1.02 ± 2. 92 (40)	1.22 ± 6.68 (39)	-0.81± 3.30 (29)[§§§]	1.85 ± 5.75 (29)
BMI, mean ± SD (kg/m^2)						
Phase 1: Month 6 (n)	-0.22 ± 0.95 (68)	0.09 ± 1.03 (60)	-0.25 ± 0.93 (60)	-0.04 ± 1.00 (47)	-0.08 ± 0.91 (44)	0.28 ± 0.95 (33)
Phase 2: Month 12 (n)	-0.19 ± 1.51 (46)	0.14 ± 1.55 (49)	-0.25 ± 1.41 (40)	-0.24 ± 1.12 (39)	-0.16 ± 1.72 (29)	0.47 ± 1.63 (29)
Waist circumference, mean ± SD (cm)						
Phase 1:Month 6 (n)	-1.31 ± 3.86 (68)	-0.42 ± 3.17 (60)	-1.36 ± 3.97 (60)	-1.03 ± 2.82 (47)	-0.40 ± 3.48 (44)	0.23 ± 3.14 (33)
Phase 2: Month 12 (n)	-1.78 ± 4.85 (46)	0.09 ± 4.94 (49)	-1.70 ± 4.66 (40)	-0.57 ± 4.64 (39)	-1.59 ± 5.34 (29)[‡‡‡]	1.62 ± 4.89 (29)

*P=0.018, [†]P=0.005, [‡]P=0.034, [§]P=0.016, **P=0.039, [††]P=0.004, [‡‡]P=0.037, [§§]P=0.03, ***P=0.019, [†††]P=0.041, [‡‡‡]P=0.026, [§§§]P=0.046 between groups; Lpa: Lipoprotein a; mPP: modified per-protocol.

SUPPLEMENTARY DATA

Supplementary Table 4. Mean ± SD change from baseline in secondary outcomes (PP)

	All patients		MetS patients		Type 2 diabetes patients	
Variable	**Testosterone**	**Placebo**	**Testosterone**	**Placebo**	**Testosterone**	**Placebo**
Glycemic control						
HbA1c, %						
Phase 1: Month 6 (n)	0.28 ± 0.56 (45)	0.24 ± 0.60 (48)	0.28 ± 0.47 (39)	0.25 ± 0.65 (40)	0.35 ± 0.64 (30)	0.23 ± 0.74 (24)
Phase 2: Month 9 (n)	0.22 ± 0.92 (37)	0.18 ± 0.57 (43)	0.26 ± 0.89 (31)	0.22 ± 0.62 (35)	0.22 ± 1.07 (27)	0.22 ± 0.63 (22)
Phase 2: Month 12 (n)	0.04 ± 1.12 (29)	0.10 ± 0.63 (41)	0.05 ± 1.04 (25)	0.13 ± 0.68 (34)	-0.04 ± 1.35 (19)	0.22 ± 0.63 (21)
Fasting blood glucose, mmol/L						
Phase 1: Month 6 (n)	0.17 ± 2.23 (47)	-0.01 ± 1.56 (48)	0.13 ± 2.34 (41)	-0.12 ± 1.64 (40)	0.19 ± 2.70 (31)	-0.10 ± 2.04 (24)
Phase 2: Month 12 (n)	0.56 ± 2.12 (29)	0.11 ± 2.29 (41)	0.30 ± 1.99 (25)	-0.01 ± 2.45 (34)	0.73 ± 2.61 (19)	0.26 ± 3.0 (21)
Fasting serum insulin, pmol/L						
Phase 1: Month 6 (n)	-55.62 ± 183.07 (46)	-33.75 ± 132.65 (48)	-61.25 ± 193.14 (41)	-39.73 ± 144.18 (40)	-51.46 ± 211.0 (30)	-23.47 ± 43.10 (24)
Phase 2: Month 12 (n)	-33.61 ± 239.74 (28)	-28.27 ± 142.16 (41)	-60.70 ± 235.02 (24)	-38.13 ± 153.35 (34)	-29.31 ± 284.75 (19)	-16.81 ± 65.56 (21)
Lipid parameters						
Lpa (µmol/L)						
Phase 1: Month 6 (n)	-0.21± 0.45 (39)*	0.16 ± 1.07 (40)				
Phase 2: Month 9 (n)	-0.10 ± 0.33 (33)*	0.14 ± 0.55 (34)				
Phase 2: Month 12 (n)	-0.16 ± 0.38 (23)**	0.18 ± 0.47 (32)				
Total cholesterol (mmol/L)						
Phase 1: Month 6 (n)	-0.15 ± 0.59 (47)*	0.09 ± 0.66 (48)				
Phase 2: Month 9 (n)	-0.17 ± 0.65 (37)	-0.01 ± 0.72 (43)				
Phase 2: Month 12 (n)	-0.24 ± 0.84 (29)	-0.17 ± 0.93 (41)				
LDL-cholesterol (mmol/L)						
Phase 1: Month 6 (n)	-0.17 ± 0.52 (47)**	0.06 ± 0.40 (48)				
Phase 2: Month 9 (n)	-0.15 ± 0.48 (37)	0.01 ± 0.53 (43)				
Phase 2: Month 12 (n)	-0.28 ± 0.64 (29)	-0.11 ± 0.65 (41)				
HDL-cholesterol (mmol/L)						
Phase 1: Month 6 (n)	-0.09 ± 0.19 (47)*	-0.03 ± 0.11 (48)				
Phase 2: Month 9 (n)	-0.10 ± 0.18 (37)	-0.05 ± 0.13 (43)				
Phase 2: Month 12 (n)	-0.12 ± 0.20 (29)	-0.05 ± 0.17 (41)				
Triglycerides (mmol/L)						
Phase 1: Month 6 (n)	0.13 ± 0.61 (47)	0.04 ± 0.74 (48)				
Phase 2: Month 9 (n)	0.13 ± 0.64 (37)	0.13 ± 1.45 (43)				
Phase 2: Month 12 (n)	0.21 ± 0.75 (29)	0.22 ± 0.99 (41)				

SUPPLEMENTARY DATA

Abdominal obesity and body composition						
Body fat, %						
Phase 1: Month 6 (n)	-1.03 ± 2.02 (45)	0.26 ± 5.11 (47)				
Phase 2: Month 12 (n)	-0.49 ± 3.4 (29)	0.41 ± 5.25 (39)				
BMI (kg/m^2)						
Phase 1: Month 6 (n)	-0.16 ± 0.95 (47)	-0.03 ± 1.29 (48)				
Phase 2: Month 12 (n)	-0.07 ± 1.70 (29)	-0.04 ± 1.26 (39)				
Waist circumference (cm)						
Phase 1: Month 6 (n)	-1.50 ± 3.86 (47)	-0.40 ± 3.76 (48)				
Phase 2: Month 12 (n)	-2.40 ± 5.32 (29)*	0.50 ± 5.17 (39)				
Sexual dysfunction						
Total IIEF score						
Phase 1: Month 6 (n)	5.60 ± 17.10 (41)	4.60 ± 13.05 (40)	-	-	-	-
Phase 2: Month 12 (n)	7.70 ± 14.46 (24)	4.20 ± 19.54 (34)	-	-	-	-
Erectile function						
Phase 1: Month 6 (n)	1.90 ± 7.22 (44)	2.30 ± 7.23 (42)	-	-	-	-
Phase 2: Month 12 (n)	2.20 ± 5.78 (26)	1.60 ± 9.70 (37)	-	-	-	-
Orgasmic function						
Phase 1: Month 6 (n)	0.90 ± 3.79 (45)	0.70 ± 2.92 (44)	-	-	-	-
Phase 2: Month 12 (n)	0.70 ± 2.40 (27)	0.90 ± 2.80 (37)	-	-	-	-
Sexual desire						
Phase 1: Month 6 (n)	0.90 ± 2.12 (46)	0.30 ± 2.08 (45)	-	-	-	-
Phase 2: Month 12 (n)	1.50 ± 2.04 (26)*	0.10 ± 2.431 (39)	-	-	-	-
Intercourse satisfaction						
Phase 1: Month 6 (n)	0.80 ± 3.64 (46)	1.40 ± 3.76 (45)	-	-	-	-
Phase 2: Month 12 (n)	1.50 ± 3.68 (27)	0.80 ± 4.11 (37)	-	-	-	--
Overall sexual satisfaction						
Phase 1: Month 6 (n)	0.60 ± 2.09 (44)	0.70 ± 2.68 (43)	-	-	-	-
Phase 2: Month 12 (n)	1.40 ± 2.87 (25)	0.80 ± 2.91 (36)	-	-	-	-
AMS score						
Phase 1: Month 6 (n)	-3.20 ± 8.53 (42)	-4.60 ± 9.42 (41)	-	-	-	-
Phase 2: Month 12 (n)	-6.50 ± 9.48 (26)	-3.90 ± 12.63 (33)	-	-	-	-

*P<0.05; **P<0.01 between groups.

SUPPLEMENTARY DATA

AMS: Aging Males Symptoms; IIEF: International Index of Erectile Function; Lpa: Lipoprotein a.

SUPPLEMENTARY DATA

Supplementary Table 5. Incidence of the most common adverse events (2% in any treatment group; Safety Population)

Incidence of AEs, n (%)	Testosterone (n=108)	Placebo (n=112)
Patients experiencing 1 AE	71 (65.7)	66 (58.9)
Erythema	11 (4.0)	11 (4.8)
Pruritis	11 (4.0)	10 (4.3)
Nasopharyngitis	8 (2.9)	8 (3.5)
Arthralgia	8 (2.9)	6 (2.6)
Dizziness	8 (2.9)	4 (1.7)
Lower respiratory tract infection	5 (1.8)	7 (3.0)
Paresthesia	4 (1.5)	7 (3.0)
Back pain	2 (0.7)	8 (3.5)
PSA concentration increased	6 (2.2)	3 (1.3)
Anxiety	6 (2.2)	0
Pain in extremity	1 (0.4)	5 (2.2)
Xerosis	1 (0.4)	5 (2.2)

AE: adverse events; PSA: Prostate-specific antigen.

Supplementary Figure 1. Patient disposition