Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	91297	NCT00185198
Study Phase:	IV Interventional	
Official Study Title:	Multicenter, double blind, randomized, placebo controlled study of Testogel® (testosterone 50 – 100 mg) to evaluate its efficacy and safety in men presenting with typical symptoms of partial androgen deficiency of aging males (PADAM) over a period of 6 months with 12 months open label follow-up	
Therapeutic Area:	Men' s Health	
Test Product		
Name of Test Product:	Testosterone (Testogel, BAY86-5342)	
Name of Active Ingredient:	Testosterone	
Dose and Mode of Administration:	Dose: 50 mg testosterone/5 g gel/day to 75 mg testosterone/7.5 g gel/day for first 6 months, double blind phase, then 50 mg testosterone/5 g gel/day to 100 mg testosterone/10 g gel/day for 12 months, open label follow-up phase. Route of administration: Topical application	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	5 g gel/day to 7.5 g gel/day	
Duration of Treatment:	Test therapy: 18 months (6 months double blind treatment phase with Testogel® or placebo) followed by 12 month open-label Testogel® therapy Reference therapy: 6 months (double-blind treatment period)	
Studied period:	Date of first subjects' first visit:	02 SEP 2004
	Date of last subjects' last visit:	10 OCT 2007
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	There were two amendments to the study protocol: Amendment no. 1 (dated 07 DEC 2004) introduced the following changes: • Change of calculation of bioavailable testosterone: Albumin was	

	added to the values used for the calculation together with total testosterone, and sex hormone binding globulin. The change was implemented to improve accuracy of the calculation. • Inclusion criteria: The bioavailable testosterone value for inclusion was increased from <4.43 nmol/l (<1.28 ng/ml) to <6.68 nmol/l (<1.93 ng/ml) to improve subject recruitment. • Exclusion criteria: Concomitant biphosphonate use was excluded because they affect bone metabolism and thereby may have an effect on Dual-energy X-ray absorptiometry (DEXA) bone measurement. • Procedure change: During the double blind phase of the study the hemoglobin results were not to be notified to the investigator unless hemoglobin values became >19 g/dL. The change was implemented because an increase in hemoglobin could be indicative of testosterone treatment, thus notification could have unblinded the investigator to the subject's treatment. • Procedure change: Two separate blood samples were to be taken 7 to 19 days apart before the baseline visit for central laboratory examination of total testosterone. The average of the two samples was used for inclusion of the subject. The change was implemented because testosterone levels show considerable intra-individual variation; the SmPC (Summary of Product Characterstics) for Testogel® generally accepts to perform two separate measurements for diagnosis. • The statistical protocol section was changed as follows: ➢ Explanation that the Full Analysis Set (FAS) is the primary population of interest. ➢ Removal of references to 12 months DEXA scans. The change was made to provide consistency with other sections of the protocol. ➢ Explanation provided that imputation techniques were to be used if a subject had missing data for the DEXA scan variables at month 6, and that prior to database release other imputation techniques could have been considered once a more precise estimation of the withdrawal rate was available in order to consider the sensitivity of the results. The change was implemented to give a more conservative approach to showing the efficacy of the active treatment. ➢ The general linear model was defined to include the baseline DEXA value as a covariate. This change was implemented to provide clarification on the model to be used for analysing the variable of interest. Amendment no. 2 (dated 18 DEC 2006) introduced the following changes: • 5α-dihydro-testosterone (DHT) and estradiol measurements were introduced for blood samples taken at screening, months 3, 6, 9, 12, and 18. Reason for this change: DHT and estradiol are metabolites of testosterone and are used to help to distinguish between genuine high total testosterone values and high testosterone values caused by contamination of the serum sample by Testogel® on the skin. The analysis of DHT and estradiol did not require any additional blood.

	• DEXA scan was to be performed as part of the end of study visit for subjects withdrawing early from the study in order to collect as much information as possible about body composition changes for subjects who discontinued the study prematurely.
Study Centre(s):	The study was conducted in 30 centers in 8 countries: Austria 5 centers, Finland 3 centers, Germany 5 centers, Ireland 1 center, Italy 4 centers, Spain 3 centers, Sweden 3 centers, and the UK 6 centers.
Methodology:	The study consisted of two periods: During the first six months, subjects were randomized to either Testogel® or placebo in a double-blind manner. During the second study period, all subjects received 12 month open label active Testogel® treatment. As a result of this study design, subjects either received 12 or 18 months of active Testogel® treatment depending on their initial six months treatment group. The initial dose of Testogel® was 50 mg testosterone/5 g gel per day. If clinically indicated, the dose could be increased in steps of 25 mg testosterone/2.5 g Testogel® to a maximum of 75 mg testosterone/7.5 g Testogel® or the equivalent dose of placebo by the end of the six-months double blind period and to a maximum of 100 mg testosterone/10 g Testogel® during the open label study phase. These doses are identical to those used in the marketed product. Data were analyzed for the overall population and within two subgroups defined by age (<65 years, ≥65 years) and 3 subgroups defined by baseline testosterone values (<10 nmol/l; 10 to <12 nmol/l; >12 nmol).
Indication/ Main Inclusion Criteria:	Indication: Partial Androgen Deficiency of Aging Male (PADAM) Main Inclusion Criteria: Symptomatic hypogonadism confirmed by clinical features and biochemical tests; willingness to avoid significant change in the pattern of physical exercise and lifestyle for the duration of the study; age 50 - 80 years.
Study Objectives:	Overall: To assess the efficacy and safety of Testogel® in men with symptomatic late onset hypogonadism (LOH).
Evaluation Criteria:	Efficacy (Primary): Change in lean body mass after 6 months as measured by DEXA. Efficacy (Secondary): • Changes in lean body mass (month 18). • Changes in total body mass, fat mass, and bone density (month 6 and month 18). • Evaluation of symptoms by the aging males' symptoms (AMS) rating scale (month 6 and month 18) for total scale and the three AMS subscales (sexual function, psychological function, somato-vegetative function) • Changes in testosterone serum values.

	Subgroup analyses were performed based on the variables age (<65 or ≥65 years) and total testosterone values at study entry. Safety: • Prostate safety (digital rectal examination, international prostate symptom score) • Standard laboratory tests for androgen treatment: prostate specific antigen (PSA); hemoglobin; hematocrit • Laboratory tests for lipids and liver function • Adverse events • Vital signs
Statistical Methods:	Efficacy (Primary): Lean body mass and its absolute change from baseline was displayed by descriptive statistics. The primary evaluation was performed on the FAS population, using different ANCOVA (Analysis of Covariance) models with a random subject intercept, baseline value as continuous explanatory variable and treatment and center as factor variables. The conservative estimate for the treatment difference was derived from an ANCOVA model which also contained random effects for center and center-by-treatment interaction. Efficacy (Secondary): All secondary variables, except AMS subscale scores were summarized using descriptive statistics and analyzed in a similar manner as the primary efficacy variable. AMS subscale scores were summarized using frequency tables. Additionally, shift in AMS subscale score classification categories from screening was displayed as frequency table. The AMS subscale scores were examined using a Mantel-Haenszel Test and using center as a stratification variable. Safety: • Prostate safety: The results of the digital rectal examination and the international prostate symptom score were summarized by visit. • Standard laboratory tests for androgen treatment: PSA, hemoglobin, and hematocrit were summarized by visit and by change from baseline (screening). If any of the laboratory parameters was repeated then the last value reported was used as the baseline value, but once on treatment the first value reported was used in the summaries. • Lipids and liver function tests: The results of the lipids and liver function laboratory tests were summarized by visit and by change from screening. • Adverse events: Treatment-emergent adverse events were summarized by system organ class and preferred term. Events were coded using the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary and summary tables were produced.

	• Vital signs: Vital signs including systolic and diastolic blood pressure, heart rate, and weight were summarized by visit and by change from baseline.
Number of Subjects:	Planned: 360 (180 Placebo/180 Testogel® during the double blind study period). Analyzed: 362 (179 placebo/183 Testogel® during the double blind study period).

Study Results

Results Summary — Subject Disposition and Baseline

A total of 1316 men from 30 study centers in 8 European countries were screened. After exclusion of 951 screening failures, 365 subjects were randomized to receive placebo (n = 180) or Testogel® (n = 185). The Full Analysis set included 362 subjects (179 placebo/183 Testogel®).

During the first six months, subjects received placebo or Testogel® in a double blind manner. During the following 12 month, open label active Testogel® treatment was provided. Throughout the 18 month study period, 338 subjects underwent Testogel® treatment.

Altogether, 244 subjects completed the 18 months study course. Premature study discontinuation occurred in 39 subjects during the double blind phase (24 placebo/15 Testogel®) and in 79 subjects during the open label phase.

The FAS included 362 men. Approximately 98.3% of the subjects were Caucasian. In addition, one Black, 4 Asian, and one subject originating from a mixed ethnic group were included in the FAS.

The mean age of subjects was 62.0 years (range: 48.0 - 80.0 years), and mean BMI was 28.57 kg/m^2 (range: 20.40 - 35.00 kg/m^2).

Results Summary — Efficacy

Primary efficacy variable: Change in lean body mass after 6 months

Lean body mass changed by a mean value of +1.28 (Standard Deviation [SD] 2.02) kg following six months treatment with Testogel® versus +0.015 (SD 1.38) kg following placebo. This was a statistically significant change in favor of Testogel®.

In addition to the primary efficacy analysis, the primary efficacy variable was tested with a similar model in subgroups for age and testosterone baseline levels: Statistically significant increases in lean body mass were observed regardless of age (<65 or ≥65 years) or baseline testosterone group (<10 nmol/l; 10 to <12 nmol/l; and ≥12 nmol/l).

Secondary efficacy variable: Change from baseline in lean body mass after 18 months

At month 18, subjects from the initial placebo group had received 12 months of Testogel® treatment; subjects from the initial Testogel® group had received 18 months of Testogel® treatment. At this time-point, a clear increase in lean body mass also in the placebo/Testogel group was measured. Month 18 mean change in lean body mass was 1.00 kg (SD 2.26) in the placebo/Testogel® group and 1.25 kg (SD 2.18) in the Testogel/Testogel group.

Secondary efficacy variable: Change in lean body mass [g] in three subgroups with different baseline total testosterone levels (<10 nmol/l; 10 to <12 nmol/l; 12 to <15 nmol/l)

Until month 6, a significant change from baseline in lean body mass was observed for subjects treated with Testogel® in all subgroups: +1.13 kg (SD 2.04 kg), +1.36 kg (SD 1.78 kg) and +1.40 kg (SD 2.25 kg), respectively. For the subjects treated with placebo, the respective changes were +0.23 kg (SD 1.52 kg), +0.19 kg (SD 1.30 kg), -0.26 kg (SD 1.26 kg).

Secondary efficacy variable: Change from baseline in body fat mass (months 6 and 18)

After 6 months, DEXA demonstrated a significant change in body fat mass following testosterone therapy of -1.16 (SD 2.13) kg versus -0.14 (SD 1.66) kg in the placebo group.

At month 18 (i.e., after 12 – 18 month of active Testogel® treatment), a marked decrease of body fat mass compared to baseline was observed in all subjects. The mean change compared to baseline after 18 month was -1.37 kg (SD 3.09) in the placebo/Testogel group and -1.87 (SD 2.99) kg in the Testogel/Testogel group. The effects on body fat mass were most pronounced in the population ≥65 years of age.

Secondary efficacy variable: Change from baseline in total body mass (months 6 and 18)

The change of body composition (increase of lean body mass and reduction of body fat mass) under active treatment did not significantly change total body mass.

Secondary efficacy variable: Change from baseline in bone mineral density (months 6 and 18)

An increase of bone mineral density was observed over time for both treatment groups, however, treatment effects were not significant.

Secondary efficacy variable: AMS rating scale

Mean AMS total scores at baseline were 46.9 (SD 8.53) in the placebo/Testogel group and 47.5 (SD 8.9) in the Testogel/Testogel group. An improvement was observed in both treatment groups. At the end of the double-blind treatment at month 6, the change in AMS score was significantly superior in the Testogel group compared to the placebo group (AMS mean score change –6.9 (SD 10.5) in the placebo group and -10.7 (SD 10.0) in the Testogel® group).

Evaluation of AMS subscales (psychological/somatic/sexual) at month 6 revealed significant differences between treatment groups for the subscore "sexual" with an improvement of -3.4 points in the Testogel® treated population versus –1.8 in the placebo group. No significant differences were detected for the subscores "somatic" and "psychological".

Further improvement was observed under open label Testogel® therapy: At month 18, the mean AMS score for all subjects was 33.4 (SD 9.82). The mean change to baseline for both treatment groups at month 18 was –13.9 (SD 10.85) [-13.6 (SD 11.24) in the placebo/Testogel group and -14.2 (SD 10.45) in the Testogel/Testogel group]. Improvement for the subscales was as follows: A mean decrease of 5.5 points for the subscore "somatic" (SD 4.7), -3.6 (SD 3.8) for the subscore "psychological", and -4.8 for the "sexual" subscore.

Secondary efficacy variable: Changes in testosterone values

Testogel® treatment resulted in significant increases of serum testosterone and bioavailable testosterone (calculated from total testosterone, sex hormone binding globulin, and albumin).

Results Summary — Safety

Adverse events (AEs):

During the 6 month double blind period, 171 AEs occurred in 79 (44.1%) subjects from the placebo group and 199 AEs were recorded in 88 (48.1%) subjects from the Testogel® group. A total of 34 (19.9%) AEs in 23 subjects from the placebo group and 61 (30.7%) AEs in 36 subjects from the Testogel® group were considered study medication related. Most AEs were of mild or moderate in intensity. Thirteen (13) (7.6%) AEs in the placebo group and 9 (4.5%) AEs in the Testogel® group were assessed as being severe.

Of the 338 subjects who received testosterone, 253 (74.9%) experienced 792 AEs. Of these, 249 (31.4%) AEs occurring in 147 (43.5%) subjects were related to the study drug. Most AEs were of mild or moderate intensity; a proportion of 29 (6.4%) was assessed as severe.

During the 6 month double blind treatment period, 12 placebo- and 10 Testogel® subjects prematurely discontinued study participation due to AEs.

During the following open-label Testogel® treatment period, AE-related premature discontinuations occurred in 51 subjects.

Deaths:

One death due to coronary artery disease was reported in a subject from the Testogel® group. The event was not assessed to be study- or study-drug related.

Serious adverse events (SAEs):

Seventeen (17) adverse events during the double blind period fulfilled the seriousness criteria (9 events in 6 subjects in the placebo group, and 8 events in 7 subjects in the Testogel® group).

Of 792 adverse events recorded for the 338 subjects who received Testogel®, 41 events (5.2%) were SAEs, occurring in 28 subjects. Five (5) SAEs were considered to be possibly or probably related to the study medication: Tendon rupture (assessment possible), prostate cancer (assessment possible), prostatic intraepithelial neoplasia (assessment possible), prostatism (assessment probable), and deep vein thrombosis (assessment possible).

Clinical laboratory evaluations:

- Hepatic enzymes: Individual values did not raise any specific concerns.

- Hemoglobin: Mean hemoglobin values at screening were 14.69 g/dl (SD 0.88) in the placebo group and 14.77 g/dl (SD 0.83) in the Testogel® group. At month 6, mean values in the placebo group were 14.55 g/dl (SD 0.84) and 15.43 g/dl (SD 1.1) in Testogel® treated subjects.

  At month 18, the mean change from baseline for all subjects receiving Testogel® was +0.85 g/dl (SD 0.97).

- Hematocrit: Hematocrtit mean values were 44.99% (SD 2.74) vs 45.32% (SD 2.55) (placebo vs Testogel® group) at screening, and 45.01% (SD 2.93) vs 48.11% (SD 3.87) after 6 months of treatment. Mean change from baseline for all subjects receiving Testogel® was +3.32% (SD 4.16) at month 18. Twenty-one (21) subjects prematurely discontinued study participation due to hematocrit elevation.

- Lipids: A reduction of cholesterol and triglyceride levels was observed with Testogel® therapy. Reductions were also recorded for the placebo group.

  The mean decrease of total cholesterol was -12.82 mg/dl (SD 26.98) in the placebo group and -14.06 mg/dl (SD 26.47) in the Testogel® group at month 6. At month 18, the mean decrease in all Testogel® treated subjects was -21.77 (SD 29.33).

  For serum triglycerides, a change at month 6 was observed as follows: -8.99 mg/dl (SD 99.63) in the placebo group and -3.964 (SD 107.73) in the Testogel® group. At month 18, the mean decrease for all Testogel® treated subjects was -10.88 (SD 101.98).

- PSA: Baseline mean values for PSA were recorded as follows: 1.31 ng/ml (SD 0.86) and 1.25 ng/ml (SD 0.79) (placebo vs Testogel® group). At month 6, a mean value of 1.23 ng/ml (SD 0.82) was recorded in the placebo group, and Testogel® treated subjects showed mean values of 1.44 ng/ml (SD 0.94).

  Mean change from baseline to month 18 for all subjects receiving Testogel® was +0.29 ng/ml (SD 0.68). Fifteen (15) subjects prematurely discontinued study participation due to PSA increases.

Prostate safety:

- Digital rectal examination: During the study the percentage of abnormal findings did not increase (placebo group: 13.6% abnormal findings at baseline and 8.5% abnormal findings after 6 months treatment. Testogel® group: 14.4% abnormal findings at baseline and 9.8% abnormal findings after 6 months treatment. The percentage of abnormal findings in all subjects who received Testogel® throughout the study was 11.7 at baseline and 11.3 after month 18).

- International Prostate Symptom Score: The IPSS showed mean values of 8.1 (SD 5.78) vs 7.1 (SD 5.14) (placebo vs Testogel® group) at screening, and 8.7 (SD 7.2) vs 6.4 (SD 5.62) after 6 months of treatment. Subsequent Testogel® treatment until month 18 resulted in mean values of 6.1 (SD 4.97).

Vital signs:

Assessment of vital signs did not raise any specific safety concerns:

- Weight: Mean change from baseline was +0.48 kg (SD 2.8) vs -0.02 kg (SD 2.5) at month 6 (placebo vs Testogel® group) and -1.07 kg (SD 3.7) at month 18 in the overall Testogel® group.

- Heart rate: Mean change (in beats/min) from baseline was +2.0 (SD 11.68) and +0.4 (SD 10.62) at month 6 (placebo vs Testogel® group) and +1.0 (SD 12.02) in the overall Testogel® group after month 18.

- Systolic blood pressure: Mean change from baseline (in mmHg) was +1.5 (SD 15.82) vs -0.5 (SD 14.91) at month 6 (placebo vs Testogel® group) and +2.3 (SD 18.20) in the overall Testogel® group after month 18.

- Diastolic blood pressure: Mean change from baseline (in mmHg) was -0.1 (SD 8.94) vs +0.6 (SD 9.32) at month 6 (placebo vs Testogel® group) and +0.3 SD 9.64 in the overall Testogel® group after month 18.

Conclusion(s)

In this study, there was a statistically significant increase in the lean body mass at month 6 with Testogel® as compared to placebo for the overall treatment group as well as all subgroups evaluated (age <65 or ≥65 years and baseline testosterone levels <10, 10 - <12, and 12-<15 nmol/L). Lean body mass increase was associated with a significant reduction of body fat mass under Testogel® treatment.

No statistically significant differences were observed for the other DEXA assessments: Total body composition and mineral bone density.

Mean total AMS score improved in both, the placebo and the Testogel® treatment groups during the first six months with significant improvement in the Testogel® group. Further improvement was observed during the open label active Testogel® treatment period. The evaluation of AMS subscales (psychological/somatic/sexual) at month 6 revealed significant differences between treatment groups for the subscore "sexual" with an improvement of -3.4 points in the Testogel® treated population versus –1.8 in the placebo group. No significant differences between treatment groups were detected for the subscores "somatic" and "psychological". A marked improvement of the three subscores compared to baseline was also observed after month 18 in the overall study population.

Levels of serum testosterone and bioavailable testosterone significantly increased under treatment.

The safety evaluation did not highlight any specific concern.

Publication(s):	None		
Date Created or Date Last Updated:	18 MAY 2012	Date of Clinical Study Report:	31 MAR 2009