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A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism

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Abstract

Introduction: Men with hypogonadism exhibit decreased serum testosterone levels and may experience a constellation of clinical symptoms, including decrease in muscle mass, loss of sexual desire, impotence, and infertility. While previous studies have shown that implantation of extended release testosterone pellets can provide therapeutic levels of testosterone over several months, additional data are needed to establish this approach as the standard of care for male hypogonadism.

Aim: To evaluate the safety and efficacy of testosterone pellets over 6 months as a treatment for male hypogonadism in a clinical practice setting.

Methods: A phase IV, single center, open-label study designed to assess the safety and efficacy of subcutaneous insertion of 8 to 12 testosterone 75 mg pellets (450 mg to 900 mg), during a single implantation procedure in hypogonadal men. Subjects who successfully completed the protocol were allowed to enroll in an extension study that included another implantation and 6 months of follow-up.

Main outcome measures: Safety was determined by investigator-reported adverse events, changes in vital signs, physical exam findings, and laboratory tests. Efficacy was based on serum laboratory tests, physical exams, implantation site evaluations, and vital signs. Secondary objectives were to assess patient preference for testosterone pellets and to maintain optimal total testosterone.

Results: Mean testosterone significantly increased and luteinizing hormone (LH) levels significantly decreased from pre-implantation values at weeks 1, 4, and 12, and had returned to pre-implantation levels by week 24. Prostate-specific antigen levels remained unchanged for the duration of the study. Improvements in several symptoms of hypogonadism were determined with multiple questionnaires. Implanted testosterone pellets were generally well tolerated.

Conclusion: Implanted testosterone pellets can normalize testosterone and LH levels and improve symptoms for at least 3 months and up to 6 months in men with hypogonadism, and should be considered as a therapeutic option for hypogonadal men.

Related information

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ORIGINAL RESEARCH—ENDOCRINOLOGY

A Phase IV Prospective Evaluation of the Safety and Efficacy of Extended Release Testosterone Pellets for the Treatment of Male Hypogonadism

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Conclusion. Implanted testosterone pellets can normalize testosterone and LH levels and improve symptoms for at least 3 months and up to 6 months in men with hypogonadism, and should be considered as a therapeutic option for hypogonadal men. **Kaminetsky JC, Moclair B, Hemani M, and Sand M. A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism. J Sex Med 2011;8:1186–1196.**

Key Words. Hypogonadism; Testosterone Replacement Therapy; Testosterone Pellets; Safety and Efficacy of Long-Acting Testosterone Therapy

Introduction

Hypogonadism is defined as inadequate gonadal function, and is marked by deficiencies in the secretion of gonadal hormones and spermatogenesis [1]. Men with hypogonadism exhibit decreased serum testosterone levels and may experience a constellation of clinical symptoms, including decrease in muscle mass, loss of sexual desire, impotence, and infertility [1].

Hypogonadism may also negatively effect qualify of life due to its impact on a variety of factors included in health-related quality-of-life assessments, and may also have economic implications due to health-care resource utilization [2–5].

Exogenous testosterone replacement therapy with injectable or topical formulations is a well-established treatment for hypogonadism [6–8]. Previous studies have shown that testosterone replacement increases fat-free mass, muscle size, strength, and mineral bone density, and decreases cholesterol in hypogonadal men, and also improves mood and sexual function in these patients [7,9–15]. Yet, despite the availability of multiple approaches to therapy, hypogonadism is one of the most clinically underdiagnosed endocrine disorders, with as few as 5% of the 4–5 million affected men in the United States diagnosed and treated [16,17]. The continued evolution of testosterone replacement modalities may help to increase the treatment rate by providing a greater variety of ways in which to match patients with treatment regimens that fit their lifestyles and therapeutic goals.

Injectable testosterone formulations have been used since the 1940s. Testosterone patches were approved in the United States in 1994, and gels were introduced to the U.S. market in 2000. Testosterone pellets were approved in the United States in 1972, but were not widely used. A pellet formulation available outside the United States has been shown to provide an extended-release form of testosterone supplementation that provides therapeutic serum testosterone levels for up to 5 months [18]. An early study of this formulation evaluated the effects of 6,200 mg pellets composed of fused crystalline testosterone implanted in the subdermal fat of the lower abdominal wall of hypogonadal men [18]. Pharmacokinetic analyses were conducted in 14 participants. Peak testosterone concentrations of 49 nmol/L were reached at 0.5 day, followed by a plateau of about 35 nmol/L that was maintained until day 63. Serum testosterone values were below 10 nmol/L after 180 days. The absorption half-time of the implanted testosterone was 74.7 days, and absorption was almost complete by day 189. Serum DHT levels were significantly elevated from day 21 to day 105, and correlated significantly with testosterone levels. The only side effects reported in the 50 men who participated in this study were local infections in 5.4% of the implant sites, which resulted in the extrusion of five pellets in three of the patients. All but one of the 50 patients in this study preferred testosterone pellets compared with the testosterone therapy they had received prior to study entry.

A review of 13 years of experience using the crystalline testosterone implants available outside the United States for androgen replacement therapy found an overall continuation rate of 92.7%, increasing from 86% after the first implantation to >99% after the 10th implantation [19]. Side effects included extrusion (8.5% of implants), bleeding (2.3%), and infection (0.6%).

This report provides data from a 6-month study of Testopel® Implants (testosterone pellets) in 28 men with hypogonadism (Protocol UUA215). Serum testosterone levels were monitored prospectively in all participants to demonstrate satisfactory correction of hypogonadism. Patient satisfaction during treatment was assessed, as was patient preference regarding treatment modality for hypogonadism. Upon completion of the 6-month study, patients who had successfully received a testosterone pellet implant were allowed to enroll in a 6-month extension study designed to provide additional data on the safety and efficacy of and patient satisfaction with testosterone pellet implants, and to evaluate the maintenance of optimal testosterone levels in hypogonadal men (Protocol UUA216).

Aims

This phase IV, single center, open-label study (UUA215 protocol) was designed to evaluate the safety and efficacy of testosterone pellets over 6 months as a standard of care for male hypogonadism in a clinical practice setting. The primary objective of the study was to assess the safety and efficacy of subcutaneous insertion of 6 to 12 testosterone 75 mg pellets, corresponding to a total dose of 450 mg to 900 mg, during a single implantation procedure in hypogonadal men. The secondary objectives were to maintain optimal total testosterone and patient satisfaction with this approach to testosterone replacement therapy. At the end of the 6-month study period, subjects who had successfully completed the UUA215 protocol were allowed to enroll in an extension study (UUA216) that included a second implantation procedure and an additional 6 months of follow-up.

Methods

Subject Selection

UUA215 Protocol

A total of 30 subjects were initially enrolled in the UUA215 study. Inclusion criteria were: primary or

secondary hypogonadism, historical serum testosterone concentration of ≤315 ng/dL, ≥3 months of testosterone replacement therapy prior to screening, at least 18 years of age, and ability to provide informed consent. Exclusion criteria were: participation in another clinical trial simultaneously or within the 30 days preceding the administration of the study drug; history or suspicion of carcinoma, tumors or induration of the prostate or male mammary gland; prostate-specific antigen (PSA) level >4 ng/mL (for subjects with a PSA between 4 ng/mL and 10 ng/mL, eligibility was determined at the discretion of the investigator); past or present liver tumors, acute or chronic hepatic disease with impairment of liver function, or liver function tests (AST, ALT) exceeding 1.5 times the upper limit of the normal range provided by the laboratory; history of deep vein thrombosis in the past 5 years or any history of cerebrovascular accident; serious psychiatric disease or uncontrolled medical illness, as suspected from history and/or clinical evaluation; use of any sex hormones less than 7 days prior to treatment for topical preparations and less than 4 weeks prior to treatment for injectable preparations, or at any time throughout the study; laboratory values for outside the normal ranges; any chronic use of drugs and/or alcohol abuse; use of steroidal anabolic drugs or supplements by any application 7 days prior to initiation of study drug or at any time during the study; use of antiandrogens, estrogens or p450 enzyme inducers prior to or throughout the course of the study; clinical history suggestive of allergy to testosterone; history of severe or untreated sleep apnea; use of coumadin; naïve to testosterone replacement. Additionally, all participants were required to discontinue plavix, aspirin, and other anti-inflammatory therapy 7 days prior to the implantation procedure, but were allowed to reinitiate these therapies 24 hours following implantation.

UUA216 Protocol

Subjects who were successfully enrolled in the UUA215 protocol and had a total testosterone level ≤315 ng/dL at the end of the study and were able to provide informed consent were eligible to participate in the UUA216 protocol. A total of 24 subjects enrolled in this 6-month extension study. Inclusion and exclusion criteria for the UUA216 protocol were similar to those described here for the UUA215 protocol, with the exception of use of sex hormones within 7 days of implantation, as the last study visit for the UUA215 protocol was also the first visit for the UUA216 protocol.

Dosing and Administration

UUA215 Protocol

Participants were screened (Visit 1) 1 to 4 weeks prior to the treatment visit. At this visit, subjects provided written informed consent and underwent a complete physical examination that included a medical history. Blood and urine samples were taken for hematology, chemistry, and lipid laboratory panels, PSA measurement and urinalysis, and blood pressure, heart rate, weight, and height measurements (body mass index [BMI]) were recorded. Previous treatment for hypogonadism (drug and nondrug) was recorded, as was concomitant treatment with drug or nondrug therapies. Questionnaires were reviewed and subjects were given instructions for proper completion of the forms. Subjects completed the International Index of Erectile Function (IIEF)-erectile function domain, the International Prostate Symptom Score (IPSS), the Male Patient Global Assessment, and treatment preference questionnaires.

Testosterone pellets were administered at visit 2 (week 0/day 1) after the results of laboratory tests, physical examination, and other evaluations were reviewed, and continued eligibility was determined. Concomitant drug/nondrug treatment was recorded, blood pressure, heart rate, and BMI were measured, and blood samples were taken for laboratory analyses. The number of pellets implanted was determined based on subjects' testosterone level and BMI, as shown in Table 1. The use of patients' BMI in determining the number of pellets is due to the inverse correlation that has been observed between BMI and testosterone levels, as well as the potential for increased aromatization of testosterone to estradiol in the peripheral fat tissue of obese men [20]. Both of these findings suggest that increased BMI may lead to lower testosterone levels through multiple mechanisms.

Pellets were implanted subcutaneously by trocar in the posterior gluteal region. Prior to the procedure, the implantation area was thoroughly

Table 1 Testosterone pellet dosing criteria—UUA215 protocol

Baseline testosterone level	Body mass index (BMI)	Pellets implanted
226–315 ng/dL	Underweight: <18.5	6
226–315 ng/dL	Normal: 18.5 to 24.9	8
226–315 ng/dL	Overweight: 25–29.9	10
226–315 ng/dL	Obesity: >30	12
<225 ng/dL	Normal: 18.5 to 24.9	10
<225 ng/dL	Overweight/obese: >25	12

cleaned with antiseptic solution and surrounded by a sterile drape. Local anesthetic (1% lidocaine with epinephrine) was injected into the implantation area. The trocar was introduced and manipulated back and forth to create a fan-shaped subcutaneous pocket into which the testosterone pellets were placed. Pellets were inserted in groups of four or five, and the trocar was then removed. Benzoin was applied to the incision area and the implantation incision was closed with adhesive sterile strips and covered with a sterile dressing. Subjects were instructed to avoid undue exercise or submerging the implantation site in water (bathing and swimming) for 2 days following the implantation procedure.

Subjects returned 1 week after implantation (visit 3), at which time, the implantation site was evaluated, adverse events were reported, and eligibility was reconfirmed. Pulse, blood pressure, height, weight, and BMI were assessed and patients were asked about the use of concomitant medications. Subjects completed the IIEF, IPSS, Male Patient Global Assessment, and treatment preference questionnaires.

Subsequent study visits were scheduled for weeks 2, 4, 8, 12, 16, 20, and 24 following the first study visit (corresponding to visits 4–10), during which eligibility was confirmed, vital signs were checked, and blood was drawn prior to noon for total testosterone assessment. The implantation site was checked, and adverse events and concomitant medications were recorded. Subjects also completed the IIEF, IPSS, Male Patient Global Assessment, and treatment preference questionnaires. At week 24 or early termination due to testosterone <315 ng/dL ("Study End"), a medical history and physical exam were also conducted, and samples were taken for chemistry and hematology panels, and PSA, and luteinizing hormone (LH) measurements.

UUA216 Protocol

The first study visit of the UUA216 protocol corresponded with visit 10 (week 24) of the UUA215 protocol or an earlier visit if the patient terminated the study early due to testosterone levels <315 ng/dL ("Study End"). At the first UUA216 visit (Day 1), subjects had their eligibility confirmed and provided informed consent to participate in the protocol. A medical history and physical exam (including pulse, blood pressure, height, weight, and BMI) were conducted and samples were taken for hematology, chemistry, and lipid laboratory panels, PSA measurement, and urinalysis. Blood was drawn prior to noon for both total and free testosterone measurements; LH also was measured. Subjects completed the IIEF, IPSS, Male Patient Global Assessment, and treatment preference questionnaires.

The number of pellets implanted was determined for each subject based on his peak total testosterone level in the UUA215 protocol, as follows: if peak total testosterone was between 500 ng/dL and 1,000 ng/dL, subjects received the same number of pellets as in the UUA215 protocol; if >1,000 ng/dL, two fewer pellets; if <500 ng/dL, two additional pellets. For most men in the UUA215 protocol, peak testosterone levels were achieved by week 1 or week 4; one subject reached peak testosterone at week 12.

Subsequent study visits were scheduled for week 4, week 16, and week 24 (corresponding to 1 month, 4 months, and 6 months) following the first study visit, during which eligibility was confirmed, vital signs were checked, and blood was drawn prior to noon for total testosterone assessment. The implantation site was checked, and adverse events and concomitant medications were recorded. Subjects also completed the IIEF, IPSS, Male Patient Global Assessment, and treatment preference questionnaires. At Study End, a medical history and physical exam also were conducted, and samples were taken for chemistry and hematology panels, and PSA, and LH measurements.

Subjects who experienced a decline in testosterone level below 315 ng/dL were allowed to leave the study and begin standard of care treatment. Terminal values for these subjects were taken at their last visit and are reported as Study End data.

Main Outcome Measurements

The safety of subcutaneous implantation of 6 to 12 testosterone 75 mg pellets was determined based on investigator-reported adverse events. Additional safety end points were determined based on changes from baseline to study end in vital signs, physical exam findings, and laboratory tests. Efficacy was determined based on results of serum laboratory tests, complete physical exams, implantation site evaluations, and vital signs.

Results

Biologic Responses

Thirty subjects were initially enrolled in the UUA215 protocol, all of who had been previously

Table 2 Response summary—UUA215 Protocol (N = 28)

	Week 0	Week 1	Week 4	Week 12	Study End
Testosterone (ng/dL)	216 (23–638)	845 (333–1,264) ($P < 0.0001$)	838 (393–1,210) ($P < 0.0001$)	524 (180–1,070) ($P < 0.0001$)	232 (63–480) ($P = 0.58$)
LH (ng/dL)	5.1	1.3 ($P < 0.0001$)	0.2 ($P < 0.0001$)	0.6 ($P < 0.0001$)	5.2 ($P = 0.87$)
PSA (ng/dL)	1.6	1.7 ($P = 0.8$)		1.9 ($P = 0.56$)	1.6 ($P = 0.97$)
Hct	43.9	43.2 ($P = 0.6$)		46.1 ($P = 0.06$)	44.2 ($P = 0.3$)
BMI	30.0	30.4 ($P < 0.0001$)	30.4 ($P < 0.0001$)	30.1 ($P = 0.54$)	29.5 ($P = 0.053$)

P values reflect comparison to the preimplant value
LH = luteinizing hormone; PSA = prostate-specific antigen; Hct = hematocrit; BMI = basal metabolic index.

treated with some form of testosterone replacement therapy. Two subjects had previously used testosterone undecanoate, an injectable depot formulation of testosterone, but had received their last dose 4 or 10 months prior to entering the UUA215 protocol. Of the 30 subjects who entered the study, one moved out of state and was lost to follow-up and one was found to be supplementing his testosterone pellet regimen with a topical testosterone preparation, which was inconsistent with the study protocol. Results from both of these subjects have been excluded from the analysis.

Responses for the 28 subjects who completed the study are summarized in Table 2. The mean number of pellets implanted was 10.57 and the median number was 10. The preimplantation mean testosterone level was 216 ng/dL. Mean testosterone levels were significantly higher at the week 1, week 4, and week 12 visits (845 ng/dL, 838 ng/dL, 524 ng/dL, respectively) compared with the preimplantation level ($P < 0.0001$ at all time points). All subjects had increased testosterone levels compared with baseline at week 1 and week 4. All but one subject had achieved peak testosterone levels by week 1 or week 4; the other subject achieved peak testosterone at week 12. Mean testosterone at Study End (week 24, or earlier for subjects who opted for a second implant when testosterone levels were <315 ng/dL) had returned to preimplantation levels (232 ng/dL, $P = 0.58$).

At week 1 and week 4, 100% of the 28 subjects had testosterone levels >315 ng/dL. At week 12 and week 16, 24 of 28 subjects (86%) had testosterone levels >315 ng/dL. At week 20, 21 of the 28 subjects (75%) had testosterone levels >315. This had dropped to 4 of 28 subjects (14%) with testosterone >315 ng/dL by week 24 (Figure 1).

In the UUA215 protocol, mean peak testosterone levels increased with increasing pellet number. Subjects receiving 8 ($n = 3$), 10 ($n = 14$), or 12 ($n = 11$) pellets achieved mean peak testosterone levels of 746 ng/dL, 866 ng/dL, and 913 ng/dL, respectively. Mean testosterone levels remained above 300 ng/dL at week 12 regardless of pellet number. The mean testosterone increase per pellet

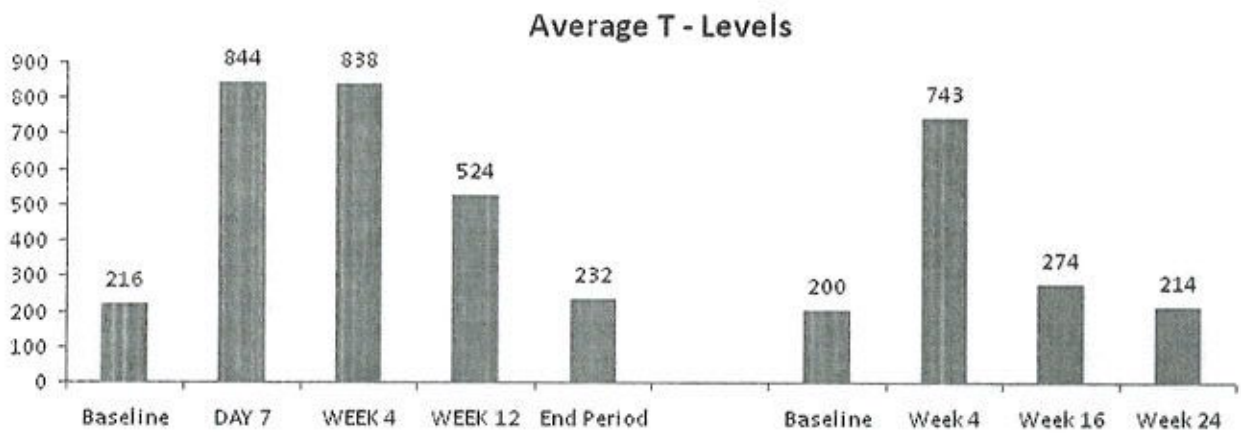

Figure 1 Percentage of subjects with testosterone >315 ng/dL between weeks 12 and 24.

was 56 ng/dL, 60 ng/dL, and 60 ng/dL for subjects receiving 8, 10, or 12 pellets, respectively. Based on the peak mean testosterone levels achieved at week 4, the mean testosterone increase per pellet for the three groups combined was 59 ng/dL.

Mean LH was reduced from a preimplantation level of 5.1 ng/dL to 1.3 ng/dL, 0.2 ng/dL, and 0.6 ng/dL at week 1, week 4, and week 12, respectively ($P < 0.0001$ at all time points). Similar to the testosterone results, mean LH had returned to pre-implantation level by Study End (5.2 ng/dL, $P = 0.87$). Mean PSA levels did not change significantly over the course of the study. Mean hematocrit (Hct) levels remained below 50 throughout the study, and were similar to pre-implantation values at weeks 1, week 12, and week 24. Mean BMI was significantly increased from baseline (30.0) at week 1 and week 4 (30.4 at both time points, $P < 0.0001$), but had returned to the pre-implantation level at week 12 and week 24.

Of the 28 subjects who completed the UUA215 protocol, 24 continued on the UUA216 extension protocol. The mean number of pellets implanted was 9.92 and the median number was 10. The number of subjects receiving 8, 10, or 12 pellets was 5, 15, and 4, respectively. Biological response data for the UUA216 protocol were similar to results in the UUA215 study, and are summarized in Table 3. Note that 22 and 23 subjects were available for analysis at the week 16 and Study End visits, respectively. Two subjects, whose testosterone levels had dropped below 315 ng/dL, underwent a second implantation prior, as permitted by study protocol, to the week 16 visit and are not included in the week 16 analysis. Data from their early termination visit are included in the Study End analysis. Another subject was lost to follow-up subsequent to the week 16 visit, and Study End data for this subject were not available for analysis. Mean testosterone levels increased from 201 ng/dL at the time of implant to 743 ng/dL at week 4 ($P < 0.0001$), and all subjects had increased testosterone levels at this time point compared with baseline. Although mean testosterone levels had fallen below 315 ng/dL in the 22 subjects for whom week 16 data are available, they were still significantly higher at this time point compared with the time of implant (200 ng/dL vs. 275 ng/dL, $P = 0.003$). Mean testosterone levels at Study End were similar to those at the time of implant (200 ng/dL vs. 214 ng/dL, $P = 0.53$). All subjects had testosterone levels >315 ng/dL at week 4, and nearly a third (31.8%) were still above 315 ng/dL at week 16.

Functional Responses

In the UUA215 protocol, mean scores on the IIEF were significantly higher compared with baseline (15.9) at week 4 (20.1, $P = 0.003$) and week 12 (20.9, $P = 0.001$). Results at week 1 (16.5) and Study End (18.5) were not significantly different compared with baseline. The greatest improvement was noted at week 12, at which time, 21 of the participants (70%) reported improvements in erectile function. The severity of voiding symptoms, as assessed by IPSS, decreased at all time points compared with pre-implantation scores, but did not reach statistical significance. With respect to quality-of-life assessments related to urinary

Table 3 Response summary—UUA216 Protocol

	Week 0 (N = 24)	Week 4 (N = 24)	Week 16 (N = 22)	Week 24 (N = 23)
Testosterone (ng/dL)	201 (114–328)	201 vs. 743 (376–1,119) ($P < 0.0001$)	200 vs. 275 (160–677) ($P = 0.003$)	214 (133–553) ($P = 0.44$)
LH (ng/dL)	5.5			3.6 ($P = 0.004$)
PSA (ng/dL)	1.5			1.7 ($P = 0.20$)
Hct	43.7			44.4 ($P = 0.13$)
BMI	30.2		30.6 vs. 30.5 ($P = 0.37$)	29.8 ($P = 0.02$)
IIEF	19.0	19.0 vs. 20.8 ($P = 0.06$)	18.7 vs. 20.0 ($P = 0.22$)	18.7 vs. 18.0 ($P = 0.56$)
IPSS	6.8	6.8 vs. 6.6 ($P = 0.76$)	7.0 vs. 7.1 ($P = 0.92$)	7.0 vs. 7.4 ($P = 0.68$)

P values reflect comparison to the value on the day of implant for the subjects available at the indicated time point.
LH = luteinizing hormone; PSA = prostate-specific antigen; Hct = hematocrit; BMI = basal metabolic index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score.

Table 4 UUA215 patient satisfaction response summary

Questions			
1. Overall, how satisfied are you with your prior Testosterone replacement therapy versus the current Testopel Implant?			
2. Would you prefer to resume your prior testosterone replacement therapy or continue using the Testopel Implant?			
3. Overall, how satisfied are you with your current Testosterone replacement treatment?			
		Week 12 (N = 29)	Week 24 (N = 29)
Question 1	Number (%) of patients Somewhat to Very Satisfied with prior therapy versus testosterone pellets	16 (62.1)	9 (36.0) (N = 25)
Question 2	Number (%) of patients preferring testosterone pellets to prior therapy	25 (89.3)	23 (92.0) (N = 25)
Question 3	Number (%) of patients Somewhat to Very Satisfied with current therapy (testosterone pellets)	22 (75.9)	20 (76.9) (N = 26)

symptoms, patients most often reported that they were delighted or pleased with their urinary status. More than 75% of patients indicated some degree of satisfaction with their urinary status at all visits. Similar results were observed in the UAA216 protocol (Table 3).

Patient Satisfaction Survey

With respect to patient satisfaction (Table 4), 25 of 28 subjects (89.3%) at week 12 and 23 of 25 subjects (92.0%) at Study End of the UUA215 protocol for whom responses are available indicated that they would prefer to continue using testosterone pellets rather than returning to their prior testosterone replacement therapy. Similarly, 82.1% and 76.9% of subjects reported that they were somewhat-to-very satisfied with the testosterone pellets at these same time points, respectively. Quality-of-life assessments revealed that a majority of subjects reported improvements in confidence or self-esteem, satisfaction with sexual performance, general moods and behavior, and overall feeling of well-being (Table 5).

Adverse Events

Testosterone pellets were generally well tolerated. Most investigator-reported adverse events were mild and transient, and included pain, tenderness, erythema/redness, swelling, and ecchymosis. In both the UUA215 and UUA216 protocols, these symptoms were most commonly observed on the day of implantation and at week 1 visit. One patient experienced an extrusion of two pellets, but his testosterone remained in the therapeutic range and there was no evidence of infection, abscess, or seroma. At the week 1 visit of the UUA215 protocol, one patient had moderate erythema/redness and moderate ecchymosis, one patient had moderate pain, and one patient had moderate ecchymosis. At the week 2 visit, two patients had moderate pain. At the week 1 visit of the UUA216 protocol, two patients had moderate erythema/redness and moderate ecchymosis. Other investigator-reported adverse events were mild in nature and transient in duration. None of the patients in either the UUA215 or UUA216 protocols required removal of pellets, antibiotics, or prescription pain medication related to study treatment. Investigator-reported adverse event results are summarized in Table 6. Additionally, only three subjects reported adverse events. One subject reported moderate implantation site pain at week 0 and week 1, another reported mild ecchymosis at week 0, and the third reported mild erythema, redness, and itching at week 0.

Table 5 UUA215 quality of life response summary

When thinking about the following, how much has this symptom changed in comparison before you started the study drug treatment?	% of respondents stating improvement	
	Week 12 (N = 29)	Week 24 (N = 29)
Level of confidence/self-esteem	75	63
Satisfaction with sexual performance	75	79
General moods and behavior	54	50
Overall feeling of well being	79	75

Discussion

Both the UUA215 and UUA216 protocols demonstrate that testosterone pellets result in reliable and clinically significant increases in mean testosterone to therapeutic levels. Testosterone levels were maintained above 315 ng/dL for at least 12 weeks following implantation, and were significantly higher than baseline for up to 16 weeks following implantation, even though mean testosterone levels had fallen below 315 ng/dL by week 16 in the UUA216 protocol. Mean testosterone levels reached 845 ng/dL, 838 ng/dL, and 524 ng/dL in the UUA215 study at weeks 1, 4, and 12, respectively, and 743 ng/dL and 275 ng/dL at

Table 6 Summary of investigator-reported adverse events (%)

	UUA215										UUA216									
	Week 0		Week 1		Week 4		Week 12		Study End		Week 0		Week 1		Week 4		Week 16		Study End	
	M	MO	M	MO	M	MO	M	MO	M	MO	M	MO	M	MO	M	MO	M	MO	M	MO
Pain			29	4					4				28							
Tenderness			32								17		20							
Erythema/redness	32		50	4	7		7				4		48	8	16					
Swelling			18								17		16							
Ecchymosis			32	7									36	8						

M = mild; MO = moderate.

weeks 4 and 16 in the UUA216 study (Tables 2 and 3). The durability of the testosterone response was also demonstrated by consistent suppression of LH levels at the same time points in the UUA215 protocol (1.3 ng/dL, 0.2 ng/dL, and 0.6 ng/dL, $P < 0.0001$ at each time point compared with 5.1 ng/dL at the preimplantation visit).

It should be noted that there was a noticeable difference in testosterone levels achieved in the UUA215 and UUA216 protocols. Peak testosterone levels reached 845 ng/dL and 743 ng/dL at week 1, respectively. This may have resulted from differences in the number of pellets implanted in each study due to the differing criteria for dosage selection. Nine subjects received two fewer pellets in the UUA216 protocol than in the UUA215 protocol. This was because the UUA216 protocol required the implantation of two fewer pellets in subjects who had a peak testosterone level >1,000 ng/dL in the UUA215 study. Additionally, fewer subjects completed the UUA216 protocol compared with the UUA215 protocol (24 vs. 28). The smaller sample size resulted in fewer data points, which could skew the results by making biologic variation appear more significant.

Results show that mean testosterone levels increased with increasing pellet number in the UUA215 protocol. The mean testosterone increase per pellet was 56 ng/dL, 60 ng/dL, and 60 ng/dL for subjects receiving 8, 10, or 12 pellets, respectively. Based on the peak mean testosterone levels achieved at week 4 of the UUA215 protocol, the mean change in testosterone per pellet implanted was 59 ng/dL. This value can be used to guide decision making with respect to the initial number of pellets to implant based on an individual patient's baseline and target testosterone levels. The smaller sample size in UUA216, as well as the protocol requirement to use two fewer pellets in those subjects who had achieved peak testosterone levels >1,000 ng/dL in the UUA215 protocol make it difficult to draw similar conclusions from the second study.

Testosterone implants were generally well tolerated. Irritation at the site of implantation was usually mild and occasionally moderate, and there was a low rate of pellet extrusion (one patient). These results may be due to the meticulous surgical technique designated in the protocols and use of the sterile implantation kit provided by the manufacturer. Unlike the recently reported results from a study of testosterone gel in men aged 65 years or older, with limitations in mobility and total testosterone of 100 ng/dL to 350 ng/dL, no cardiovascular events were observed in subjects treated with testosterone pellets [21]. It should be noted that the patient population in that study differed substantially from the subjects in the UUA215 and 216 protocols with respect to age and overall health status, and was intended to increase muscle mass and strength in older men with limitations in mobility rather than to treat for hypogonadism. Nevertheless, results reported here were based on the experiences of 24–28 subjects, and it is possible that cardiovascular effects might be observed in a larger patient population. Consequently, further study of the effects of testosterone pellets on cardiovascular health in men with hypogonadism should be considered.

No significant increases in PSA or Hct were observed (Table 2). Two patients entered the UUA215 study with Hct >50 (51.8 and 51.2). One of these subjects had a peak Hct of 53.5 at week 12 and dropped to 49.5 at Study End. The other subject had a decrease in Hct below 50 at week 1 and week 2 and had returned to 51.2 at Study End. At week 12, four additional subjects had Hct >50 (range: 50.8–52.2), three of whom had dropped below 50 by Study End. These increases were deemed to be clinically insignificant by the investigator. Taken as a whole, the adverse events and changes in PSA and Hct suggest that the side effect profile of testosterone pellets is similar to that of other testosterone supplementation approaches.

Results from the UUA215 protocol shows a significant improvement in IIEF for the period

during which mean testosterone levels remained in the therapeutic range (week 1 through week 12 for UUA215). These results correlate with other studies describing the effects of testosterone supplementation on erectile function [22,23]. Implantation of testosterone pellets had no clinically significant impact on IPSS responses, suggesting that this method of testosterone supplementation does not contribute significantly to prostatic hyperplasia and the corresponding worsening of lower urinary tract symptoms. There were no statistically significant changes in the UUA216 protocol, which may result from the smaller sample size of this study and from the higher baseline score in UUA216 compared with UUA215 (19 vs. 15.9).

Repeated collection of patient satisfaction survey data over the course of both the UUA215 and UUA216 protocols showed that a majority of patients preferred testosterone pellet supplementation compared with their prior testosterone replacement therapy. At week 12 and week 24 of the UUA215 protocol, 89.3% and 92.0% of subjects for whom responses are available preferred testosterone pellets to their prior therapy, and 82.1% and 76.9%% reported some degree of satisfaction with testosterone pellet therapy. Consistent with these results, 24 of the 28 subjects who completed the UUA215 protocol opted to continue in the extension protocol (UUA216) rather than return to their pre-study testosterone replacement regimens. This reflects subjects' satisfaction with testosterone pellets.

Testosterone pellets offer several advantages compared with other testosterone replacement therapies. Gels and patches are short acting and require daily application for continuous therapeutic results. This daily regimen may provide for a diurnal variation in testosterone levels that mimics the normal physiologic testosterone profile, in which testosterone levels rise early in the morning, reach a midday trough, and then rise steadily until early morning [24]. However, the need for daily application may lead to patient compliance issues. Although patient compliance has been high in clinical trials, in which medication is provided at no cost and follow-up is rigorous, it is likely that compliance is lower in actual clinical practice. The depot nature of testosterone pellets obviates concerns related to patient compliance with daily regimens.

While injectable depot formulations of testosterone provide another option for long-lasting testosterone replacement therapy, no such products are currently approved in the United States. A randomized crossover clinical trial that compared injectable testosterone with an implantable depot testosterone formulation distinct from the one used in the UUA215 and UUA216 protocols demonstrated that the products are clinically interchangeable despite having distinct pharmacokinetic profiles [25]. While the majority of patients in that study preferred the injectable formulation over testosterone implants, results reported here for the UUA215 and UUA216 protocols show a high level of satisfaction with testosterone pellets compared with other testosterone replacement regimens available in the U.S. market.

Moreover, a retrospective safety analysis found that Testopel, the formulation used in the UUA215 and UUA216 protocols, had a lower rate of infection (0.3%) and a substantially lower rate of extrusion (0.3%) compared with historical data for the implantable depot testosterone formulation available outside the United States, which was used in the crossover study (1.4–6.8% and 8.5–12%, respectively) [26]. These data suggest that the manufacturing process and packaging of Testopel may result in an improved safety profile compared with other implantable depot testosterone formulations, and are consistent with the safety data reported for the UUA215 and UUA216 studies. It is not clear how the historically higher rate of extrusions and infections reported with other implantable testosterone pellets may have impacted the patient preference for injectable testosterone reported in the crossover study.

The depot formulation also offers patients a treatment regimen that does not carry a risk of transferring testosterone from patients' skin to children or partners, which may occur with testosterone gel therapy. A recent review of published and unpublished reports of hyperandrogenism in spouses and children of men using testosterone gels concluded that the risk of such transfer is probably limited [27]. Nevertheless, some patients may choose to avoid this risk entirely by using alternative therapeutic approaches, including testosterone pellets.

Testosterone pellets may also offer economic benefit compared with other testosterone replacement data. Industry data estimate the average wholesale price (AWP) for a year of testosterone pellet therapy at $2,250, compared with AWPs of $5,475, $5,612, and $3,659 for testosterone gels (Androgel and Testim®) or a testosterone patch (Androderm), respectively [28].

Conclusions

The results of these studies demonstrate that implanted testosterone pellets provide a reliable and reproducible improvement in serum testosterone in subjects with hypogonadism, and also demonstrate the feasibility of testosterone pellet implantation in a clinical practice setting. Based on the safety, efficacy, and ease of administration observed with testosterone pellets, this approach should be considered for the treatment of hypogonadism. Further study of implanted testosterone pellets will help to define the long-term benefits and risks of this approach to testosterone replacement therapy and identify those patients most likely to benefit from this regimen.

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