THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH & REVIEWS

Safety of a New Subcutaneous Testosterone Enanthate Auto-Injector: Results of a 26-Week Study

Marc Gittelman, MD,[1] Jonathan S. Jaffe, MD,[2] and Jed C. Kaminetsky, MD[3]

ABSTRACT

Introduction: Patients with testosterone deficiency (TD) can be treated with exogenous testosterone (T) to achieve and maintain physiologic T levels and prevent negative clinical symptoms; with many testosterone replacement therapies currently available, this registration safety study was conducted to further characterize the clinical profile of chronically administered, concentration-guided subcutaneous testosterone enanthate (TE) dosing.

Aim: The purpose of this study was to confirm the safety and characterize the pharmacokinetic (PK) profile of the subcutaneous TE auto-injector (SCTE-AI) in adult men with TD.

Methods: In this phase III, 26-week study, 133 men 18−75 years of age with symptomatic TD self-administered SCTE-AI 75 mg once weekly for 6 weeks from July 2015 to June 2016. Dosing was adjusted when indicated to 50 mg or 100 mg to maintain T trough levels between 350 and 650 ng/dL (12.1−22.5 nmol/L). PK data were collected from a subgroup of patients receiving 75 mg SCTE-AI through week 12. Safety, including ambulatory blood pressure monitoring (ABPM), lipid levels, and adverse drug reactions, and PK were assessed.

Main Outcome Measures: The main outcomes were the documentation of the reproducibility of trough concentration-guided exposure to SCTE, 6-month safety profile, and PK data for the 75 mg dose SCTE.

Results: In total, 34 patients (25.6%) experienced adverse drug reactions; the most frequently reported were increased hematocrit (≥52%) in 10 patients (7.5%), injection-site hemorrhage in 6 patients (4.5%), injection-site bruising in 4 patients (3.0%), and increased prostate-specific antigen in 4 patients (3.0%). By week 26, mean systolic and diastolic blood pressure (BP) measured in the clinic increased by 3.4 mmHg (125.6−129.0 mmHg) and 1.8 mmHg (78.2−80.0 mmHg), respectively, from baseline. At week 12, ABPM showed 24-hour mean systolic and diastolic BP increases of 3.7 mmHg and 1.3 mmHg, respectively. All measured lipid fractions were below baseline levels at week 26. T, TE, dihydrotestosterone, and estradiol increased from weeks 1−12. T trough levels ranged from 300−650 ng/dL (10.4−22.5 nmol/L) in 82.4% and 83.2% of patients at weeks 12 and 26, respectively. Of the 965 assessed injections, mild pain was reported by 1 patient.

Clinical Implications: Dosing with SCTE is well-tolerated overall, yet associated with a numerically small mean systolic BP increase.

Strengths & Implications: This study used a standardized ABPM protocol, confirming a numerically small systolic BP increase may be associated with reintroducing therapeutic T exposure in hypogonadal men. It is unknown at this time whether this applies with all routes of T supplementation.

Conclusion: SCTE-AI has a favorable safety profile and is well-tolerated, with a stable PK profile. **Gittelman M, Jaffe JS, Kaminetsky JC. Safety of a New Subcutaneous Testosterone Enanthate Auto-Injector: Results of a 26-Week Study. J Sex Med 2019;XX:XXX−XXX.**
Clinicaltrials.gov Identifier: NCT02504541.

Key Words: Testosterone; Testosterone Deficiency; Hypogonadism; Subcutaneous Injections; Clinical Trial

Received May 2, 2019. Accepted August 19, 2019.

[1]Uromedix, Aventura, FL, USA;
[2]Antares Pharma, Inc., Ewing, NJ, USA;
[3]Manhattan Medical Research, New York, NY, USA

https://doi.org/10.1016/j.jsxm.2019.08.013

INTRODUCTION

Testosterone deficiency (TD), or hypogonadism, is characterized by low circulating androgen levels, specifically ≤300 ng/dL (10.4 nmol/L) of testosterone (T). Symptoms include diminished sexual function, decreased muscle strength, and depressed mood.[1,2] Sexual, psychological, and physical function, quality of life, fertility, and overall health may be affected in patients with TD.[3] In addition, TD has been associated with insulin resistance, dyslipidemia, and hypertension, which are associated with increased cardiovascular (CV) risk.[1,4,5] Development of approximately 1 million cases annually of CV disease may be attributed to TD.[6]

Testosterone replacement therapy (TRT) can provide positive effects on health-related quality of life, sexual function, mood, body composition, and metabolic parameters.[7−10] The current available TRT formulations are often not convenient to use, which can affect compliance and serum T levels, and, thus, efficacy.[11] A subcutaneous testosterone enanthate auto-injector (SCTE-AI) allows patients to self-administer testosterone enanthate (TE) in sesame oil through a thin-walled, one-half inch 27-gauge needle in a single, once-weekly dose. A recent 52-week, phase III study has confirmed that the use of the SCTE-AI, together with total testosterone (TT) trough-guided dosing, is efficacious at correcting TD and is safe and well-tolerated.[12]

Although studies performed thus far indicate that, like other TRTs, SCTE-AI use is well-tolerated, there is concern regarding recent studies relating CV risk to exogenous T exposure.[13,14] Some such studies are of limited generalizability due to narrow patient populations, such as cardiac catheterization patients[13] or those with pre-existing heart disease.[13,14] In addition, studies using controversial statistical methodologies[15] and comparator groups (eg, phosphodiesterase type 5 agents that reduce CV risk)[14,16] undermine the robustness of these reports.

However, a recent meta-analysis of randomized clinical studies, including 3,016 TRT-treated and 2,448 placebo-treated men, for a mean duration of 34 weeks, detected no increased risk of specific or composite CV events and detected CV benefit for patients with metabolic issues.[10] In a study of 83,010 male veterans with TD, a reduction of in CV events and all-cause mortality was associated with normalizing T levels.[17]

Hypertension is both a well-known CV risk factor and frequent comorbidity of hypogonadism.[1,4,5] In addition, high serum T has been associated with increases in blood pressure (BP),[18] and over a span of decades elevation of BP may increase the risk of major adverse cardiovascular events.[19] These observations create concern whether raising serum T with use of exogenous testosterone is associated with increased BP. Careful studies of the effect of TRT on BP using standardized and sensitive techniques are needed to address this concern.

The objective of this phase III study was to assess safety and characterize the PK profile of the SCTE-AI administered once-weekly in adult men with TD, and, in particular, to apply a sensitive standardized ambulatory BP methodology to characterize the BP response to T repletion.

Patients and Methods

This was a single-arm, 26-week, registration safety study with blinded dose adjustments, in adult men with TD. The study (NCT02504541) was conducted from July 2015 to June 2016 in accordance with the Declaration of Helsinki and in compliance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice Guidelines. The protocol was submitted to and approved by the institutional review boards at each study site prior to initiation of the study.

Study Population

The study enrolled 133 men 18−75 years of age with a documented medical history of symptomatic TD. TD was confirmed by 2 morning T measurements <300 ng/dL (10.4 nmol/L) no less than 7 days apart during the screening period. Patients were excluded if they had body mass index ≥40 kg/m^2, hematocrit (HCT) ≥52%, history of breast or prostate cancer, elevated prostate specific antigen (PSA) for age, poorly controlled diabetes, New York Heart Association Class III or IV congestive heart failure, or if their BP could not be controlled lower than 140/90 during the screening period (see Supplemental Appendix for full inclusion/exclusion criteria).

The safety population consisted of all patients who received at least 1 dose of SCTE-AI. The pharmacokinetic (PK) population consisted of all patients who participated in the PK substudy and had at least 1 blood sample drawn postdose for PK analysis. Informed consent was obtained from all patients prior to initiation of the study.

Study Design

Patients were assessed for eligibility during the screening period. Following device use instruction, all patients received 75 mg TE for once-weekly subcutaneous self-administration at home. In the safety population, blinded dose adjustments, if needed, were made at week 7 based upon a TT trough concentration (C_{trough}) drawn a week prior. Dose titration criteria were as follows:

- Decrease dose by 25 mg if TT C_{trough} ≥650 ng/dL (22.5 nmol/L);
- Increase dose by 25 mg if TT C_{trough} <350 ng/dL (12.1 nmol/L); or
- Maintain dose strength if TT C_{trough} ≥350 ng/dL and <650 ng/dL (12.1−22.5 nmol/L).

The maximum dose evaluated in the study was 100 mg weekly with a minimal dose of 50 mg weekly. Dosing for the remainder of the study was at the optimized TE dose, with C_{trough} values assessed at weeks 12 and 18, with subsequent trough-guided blinded dose adjustments as needed.

Table 1. Demographics and Baseline Characteristics

Characteristics	Overall (N = 133)
Mean age (SD), years	54.5 (10.30)
Mean body weight (SD), kg	99.7 (16.22)
Mean BMI (SD), kg/m^2	31.5 (4.43)
Mean baseline TT (SD), ng/dL	214. 9 (102.43)
Mean baseline TT (SD), nmol/L	
Mean baseline SBP (SD), mmHg	125.6 (10.8)
Mean baseline DBP (SD), mmHg	78.2 (8.0)
Ethnicity — n (%)	
Hispanic or Latino	17 (12.8)
Not Hispanic or Latino	116 (87.2)
Race — n (%)	
White	113 (85.0)
Black or African American	18 (13.5)
Asian	1 (0.8)
Other	1 (0.8)
Currently receiving T therapy — n (%)	
No	102 (76.7)
Yes	31 (23.3)
Intramuscular or subcutaneous T injection	23 (17.3)
Topical/transdermal	8 (6.0)

BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; T = testosterone; TT = total testosterone.

Safety assessments were completed at study visits through week 26. In order to define the effect of the SCTE-AI on BP, the sponsor performed ambulatory blood pressure monitoring (ABPM). All patients participated in 24-hour ABPM initially and at weeks 6 and 12, during which BP was assessed every 20 minutes during waking hours and every 60 minutes during sleeping hours.

In the PK substudy, blood samples for PK analysis of TT, TE, dihydrotestosterone (DHT), dihydrotestosterone enanthate (DHTE), and estradiol (E2) were obtained prior to dosing and at specified times up to 168 hours postdose at the first dose, week 6, and week 12. Patients included in this group self-administered 75 mg SCTE-AI through week 12 without dose adjustment.

End Points and Assessments

The primary end point of the study was occurrence of adverse drug reactions (ADRs) after TE was administered subcutaneously once weekly to adult men with TD. Discontinuation criteria can be found in the Supplemental Appendix. The secondary end points of the study were the PK profiles for TT, TE, DHT, DHTE, and E2 in PK substudy patients administered the 75 mg dose. TT, TE, DHT, DHTE, and E2 samples were analyzed via a validated, sensitive, and specific high-performance liquid chromatography—tandem mass spectrometry assay by Medpace Bioanalytical Laboratories (Cincinnati, OH, USA).[20,21] ABPM was analyzed by eResearch Technologies (Philadelphia, PA, USA).

Table 2. ADRs in the Safety Population

Category	Overall (N = 133) n (%)
Patients with ADR*	34 (25.6)
Mild	22 (16.5)
Moderate	12 (9.0)
Severe	0 (0.0)
Patients with any SAE considered related to IP	1 (0.8)
Patients with any ADR leading to discontinuation	4 (3.0)
Patients with any AE leading to death	0 (0.0)
Specific ADRs	
HCT increased	10 (7.5)
Injection-site hemorrhage	6 (4.5)
Injection-site bruising	4 (3.0)
PSA increased	4 (3.0)

ADR = adverse drug reaction; AE = adverse event; HCT = hematocrit; IP = investigational product; PSA = prostatic-specific antigen; SAE = serious adverse event.
*Any treatment-emergent adverse event assessed by investigator as related to IP.

Statistical Analyses

Patient demographics and baseline characteristics were summarized descriptively. Summary statistics (n, mean, SD, median, minimum, and maximum) are presented for continuous variables. Counts and percentages are presented for categorical data. PK for TT, TE, DHT, DHTE, and E2 were summarized descriptively (n, mean, SD, coefficient of variation %, median, minimum, and maximum) by dose and overall.

For the safety population, a linear regression analysis was performed using the TT C_{trough} data from the current study and the TT average concentration ($C_{avg0-168h}$) data from a recent 52-week, phase III SCTE-AI study (NCT02159469,[12]) to extrapolate TT $C_{avg0-168h}$ and peak plasma concentration based on TT C_{trough} values.

RESULTS

Patient Disposition

In total, 133 patients were treated at 19 U.S. study sites. Of these, 113 (85%) completed the study (Supplemental Table 1). 21 of the 133 enrolled patients participated in the PK substudy. The mean age of study participants was 54.5 years, mean baseline body mass index was 31.5 kg/m^2, and mean predose baseline TT was 214.9 ng/dL (4.0 nmol/L; Table 1). Common comorbid conditions in addition to TD were hypertension, erectile dysfunction, and gastroesophageal reflux disease.

Overall compliance was 99.2% for the safety population; patients were exposed for an average of 167.44 days and received an average of 23.56 injections. By week 7, 61% of patients

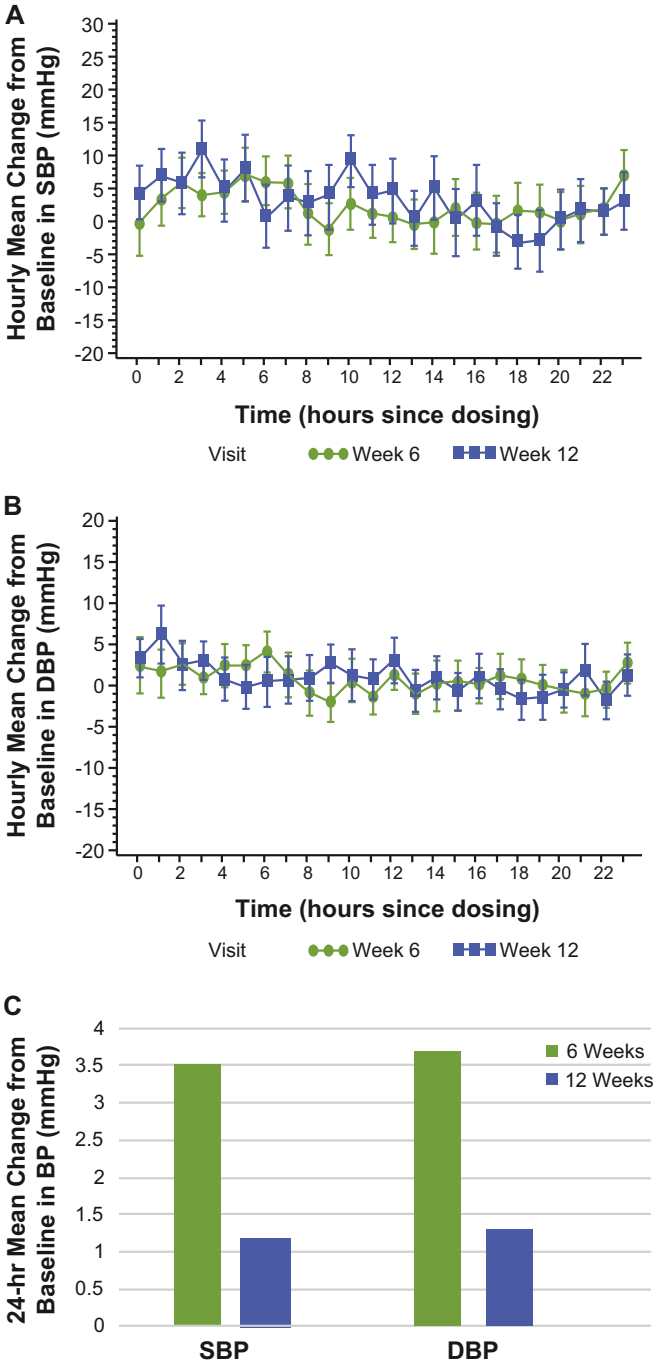

Figure 1. Hourly mean changes from baseline in panel A SBP and panel B DBP in the safety population and panel C is the 24-hour mean change in SBP and DBP from baseline at 6 and 12 weeks. Treatment with SCTE-AI resulted in nonsignificant changes in both SBP and DBP. DBP = diastolic blood pressure; SBP = systolic blood pressure; SCTE-AI = subcutaneous testosterone enanthate auto-injector.

remained at the 75 mg dose, with 30% titrated upward to 100 mg and 9% downtitrated to 50 mg weekly. By the final titration visit at week 19, 51% of patients were maintained on 75 mg. Of these patients, 90.6% had been on 75 mg at week 7 and 9.4% had been on 100 mg and then reduced back to 75 mg. At week 19, 34% of patients were receiving 100 mg weekly and 15% of patients were receiving 50 mg weekly. Patients reviewed device instructions at study visits and performed all other essential tasks related to self-administration with ≥99.3% compliance.

Safety

In total, 87 patients (65.4%) experienced a treatment-emergent adverse event (TEAE) during the study. The majority of TEAEs was considered mild or moderate; 5 patients (3.8%) had TEAEs that were considered severe. TEAEs that occurred at a frequency of ≥2% are included in Supplemental Table 2. Overall, 34 patients (25.6%) experienced ADRs (TEAE considered by the investigator to be related to the investigational product; Table 2). All of the ADRs were considered mild or moderate. No patient had an ADR that led to death during the study period. Two serious ADRs resulted in discontinuation, but only one was determined to be related to the study drug: a patient developed deep vein thrombosis following a transatlantic flight after 96 days of treatment (which resolved but was assessed by the investigator as related). Another patient had a history of unstable angina that predated the study. This should have excluded his participation; however, the information was not volunteered by the patient, and only discovered following the start of the study incidental to the review of a hospital discharge summary following a knee injury. As the illness preceded the first dose of study medication, it was deemed unrelated to the study drug. 3 additional patients had increased HCT or polycythemia related to the study medication and were discontinued from the study (although they remained in follow-up observation until their hematocrit decreased). All cases were discovered at the week 13 visit and the individual hematocrit values at presentation were 54%, 56%, and 57%.

The most frequently reported ADRs were increased HCT in 10 patients (7.5%), injection-site hemorrhage in 6 patients (4.5%), injection-site bruising in 4 patients (3.0%), and increased PSA in 4 patients (3.0%). Pain was assessed during 965 self-injections in-clinic; only 1 patient reported pain and rated it a score of 3 on a 10-point scale.

By week 26, in-clinic systolic BP (SBP) and diastolic BP (DBP) increased from a mean (SD) of 125.6 (10.8) mmHg and 78.2 (8.0) mmHg at baseline to 129.0 (11.0) mmHg and 80.0 (8.3) mmHg at week 26, respectively. The change from baseline to week 26/early termination (ET) was 3.4 (10.0) mmHg for SBP and 1.9 mmHg (11.9) for DBP. There was no correlation between serum T and BP changes. Similarly, during ABPM, the mean (SD) 24-hour SBP increased by 3.5 (9.7) to 3.7 (11.0) mmHg and mean 24-hour DBP increased by 1.2 (4.6) to 1.3 (6.0) mmHg (Figure 1C) at weeks 6 and 12, respectively.

Mean (SD) PSA levels for patients in the safety population were 1.07 μg/L (0.64 μg/L) at screening and increased to 1.24 μg/L (0.76 μg/L) and 1.29 μg/L (0.81 μg/L) at weeks 13 and 26/ET, respectively (Figure 2A). 4 patients (3%) had increased PSA levels reported as TEAEs, but none led to study

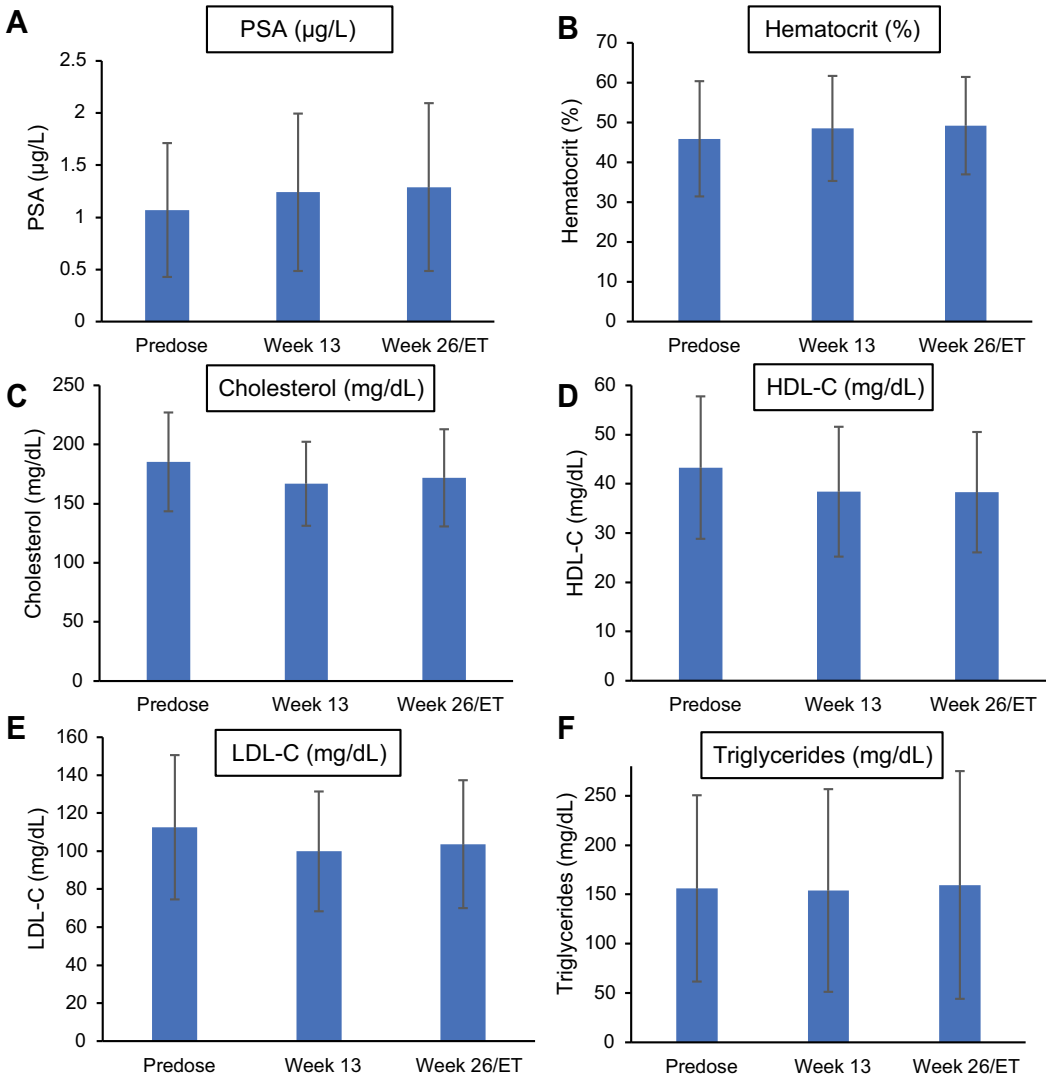

Figure 2. Clinical laboratory values for the safety population: panel A shows the PSA (μg/L); panel B shows the hematocrit (%); panel C shows the total cholesterol (mg/dL); panel D shows the HDL-C (mg/dL); panel E shows the LDL-C (mg/dL); and panel F shows the triglycerides (mg/dL). Values are expressed as mean (SD). HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PSA = prostate-specific antigen.

discontinuation or biopsy as the associated PSA increases did not equal or exceed the stopping criteria of 1.4 ng/ml. Significant ($P < .001$) increases in HCT from baseline were also observed from screening to weeks 13 and 26/ET, by 2.6% and 3.2, respectively (Figure 2B); overall, 11 patients (8.3%) had increases in HCT, but only 3 met stopping criteria. All measured cholesterol fractions were reduced during the study (Figure 2C–E). Conversely, there was a slight increase in nonfasting triglycerides by week 26/ET (Figure 2F) from the fasting baseline. Few isolated abnormalities were seen in clinical chemistry, hematology, coagulation, and other lipid parameters but were not considered clinically meaningful.

Safety Population PKs

Efficacy (based on C_{avg}) was not an end point in this study; however, a summary of TT C_{trough} for the safety population can be found in Supplemental Table 3. TT C_{trough} increased from week 1 and continued through all time points assessed. The mean (SD) TT C_{trough} at week 1 was 214.9 ng/dL (102.4 ng/dL; 4.0 nmol/L; 3.5 nmol/L) and increased to 450.0 ng/dL (150.5 ng/dL; 15.6 nmol/L; 5.2 nmol/L) at week 6. For weeks 12, 18, and 26/ET, the mean (SD) TT C_{trough} values were 471.8 ng/dL (129.8 ng/dL; 16.4 nmol/L (4.5 nmol/L; 495.9 ng/dL (168.2 ng/dL; 17.2 nmol/L; 5.8 nmol/L), and 514.3 ng/dL (145.0 ng/dL; 17.8 nmol/L; 5 nmol/L), respectively. The percentage of patients with TT C_{trough} values >300 ng/dL (10.4 nmol/L) and ≤650 ng/dL (22.5 nmol/L) was 17.3% at week 1, 82.4% at week 12, 79.6% at week 18, and 83.2% at week 26/ET (Supplemental Figure 1).

Overall, 128 patients (96.2%) and 125 patients (94%) had imputed TT $C_{avg0-168h}$ 300–1,100 ng/dL (10.4 to 38.1 nmol/L) at week 1 and week 12, respectively. The mean (SD)

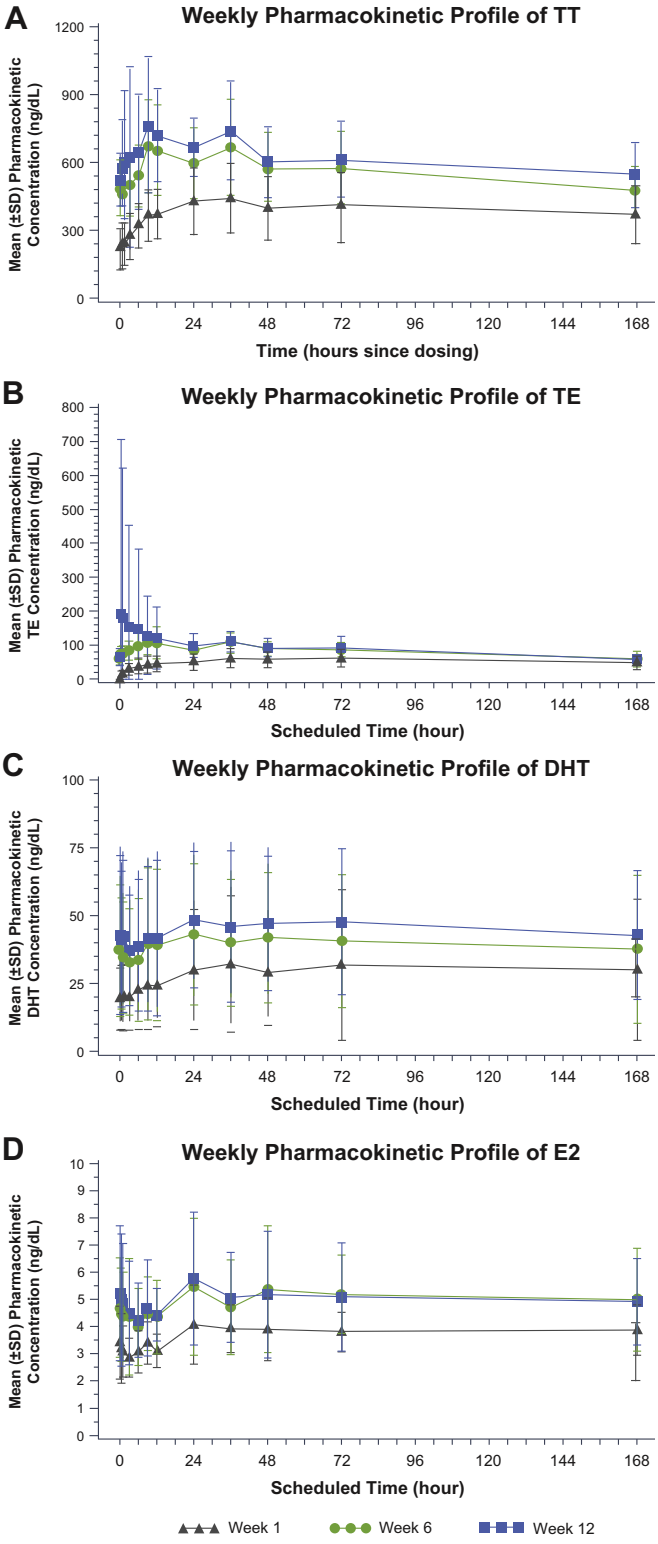

Figure 3. Panel A is the weekly pharmacokinetic profile of TT concentrations at weeks 1, 6, and 12 for patients in the PK substudy. Panel B is the weekly pharmacokinetic profile of TE concentrations at weeks 1, 6, and 12 for patients in the PK substudy. Panel C is the weekly PK profile of DHT concentrations at weeks 1, 6, and 12 for patients in the PK substudy. Panel D is the weekly PK profile of E2 concentrations at weeks 1, 6, and 12 for patients in the PK substudy. All groups represent the PK substudy population. Error bars represent SD. PK blood samples were obtained predose, 0.5, 1, 3, 6, 9, 12, 24, 26, 48, 72, and 168 hours postdose. DHT = dihydrotestosterone; E2 = estradiol; PK = pharmacokinetic; TE = testosterone enanthate; TT = total testosterone.

estimated TT $C_{avg0-168h}$ was 387.5 ng/dL (61.8 ng/dL; 13.5 nmol/L; 2.1 nmol/L) at week 1 and 552.5 ng/dL (94.6 ng/dL; 19.2 nmol/L; 3.3 nmol/L) at week 12.

Nearly all patients had estimated or measured TT C_{max} <1,500 ng/dL (40 nmol/L) at weeks 1 and 12; 133 patients (100%) at week 1 and 124 patients (99.2%) at week 12. The mean (SD) TT C_{max} for the safety population was 526.3 (62.76) ng/dL at week 1 and 797.5 (196.08) ng/dL at week 12.

PK Population Substudy PKs

In the PK substudy population (patients who received 75 mg SCTE-AI through week 12), TT concentrations increased from predose week 1 to week 12 (Figure 3A). Mean TT C_{trough} increased from 223.7 ng/dL (7.8 nmol/L) at predose week 1, to 373.7 ng/dL (13.0 nmol/L), 478.9 ng/dL (16.6 nmol/L), and 541.2 ng/dL (18.8 nmol/L) at weeks 1, 6, and 12, respectively.

The majority of the 21 PK substudy patients had TT $C_{avg0-168h}$ 300−1,100 ng/dL (10.4−38.1 nmol/L): 18 patients (86%), 20 patients (95%), and 21 patients (100%) at weeks 1, 6, and 12, respectively. TE, DHT, and E2 concentrations also increased as anticipated from week 1 to week 12, and from predose to postdose at scheduled time points within each of weeks 1, 6, and 12 (Figure 3B−D). DHTE was undetectable at most time points in most patients. Endocrine parameters of follicle-stimulating hormone, luteinizing hormone, and sex hormone-binding globulin decreased from baseline to weeks 13 and 26/ET (Supplemental Table 4).

DISCUSSION

This phase III study was conducted to assess the safety of SCTE-AI in adult men with TD. Use of the SCTE-AI resulted in normalization of T levels, and the treatment was well-tolerated. On average, SBP increased by a few mmHg during dosing, but no ADRs for hypertension were reported. No correlation was observed between changes in BP and T. As with other dosage forms of T, cholesterol fractions decreased. The statistically significant increases in HCT and PSA values were consistent with those seen with other currently available TRTs.[15]

Only 4 ADRs led to study discontinuation. Injection-site assessments were unremarkable and consistent with needle trauma as opposed to drug effect, with only 1 patient reporting mild pain upon injection.

The strength of the study was the inclusion of ABPM to investigate whether concentration-guided SCTE dosing impacts BP. The overall finding was a small numerical increase in SBP. Physician and patient blinding to the T concentrations and dose

prevented any potential influence of patient or physician preferences on dosing. A limitation of this study was lack of a control group to comparatively assess the safety parameters in the absence of T administration or in subjects using an alternate route of T administration. However, it is notable that ABPM BP studies are not sensitive to placebo effect, so the results of this ABPM study should be considered reliable.[22] Trough concentration control reduced T exposure variation and may have affected the ability to explore the relationship between T exposure and BP. Further, although clinical trials (excepting antihypertensive trials) typically exclude uncontrolled hypertension for safety reasons, use of this common exclusion means that the BP findings of this study may not be generalizable to patients with uncontrolled hypertension. It is for this reason that the prescribing information emphasizes BP control before and during use of this product.[23] An additional limitation is the short duration of this study, which was designed to meet regulatory requirements of product development.

Dosing with SCTE-AI and a simple titration scheme led to the majority of patients achieving serum T levels within the physiologic range. Weekly dosing and at-home convenience of the regimen may translate into improved compliance among patients, especially relative to topical T treatment.[24]

CONCLUSIONS

Overall, when considering clinical laboratory assessments, vital signs, clinical findings, and ADRs, this study demonstrates that once-weekly use of SCTE-AI in patients with TD is well-tolerated and has a safety profile similar to other T products. Patients in the study were highly compliant and successfully self-administered weekly injections with few remarkable injection-site reactions and reports of pain.

ACKNOWLEDGMENTS

The authors acknowledge editorial assistance in development and submission of this manuscript from Ashleigh Pulkoski-Gross, PhD, and Cindy Schultz, PhD, of AXON Communications, funded by Antares Pharma, Inc. Additional editorial assistance was provided by MedVal Scientific Information Services, LLC (Princeton, NJ), and funded by Antares Pharma, Inc.

Corresponding Author: Jonathan S. Jaffe, MD, Antares Pharma, Inc., 100 Princeton South Corporate Center, Suite 300, Ewing, NJ 08628, USA. Tel: +1-609-359-3020 x324; Fax: +1-609-359-3015; E-mail: jjaffe@antarespharma.com

Conflict of Interest: Marc Gittelman received clinical research grant from Antares Pharma, Inc. Jonathan S. Jaffe is an employee of Antares Pharma, Inc. Jed C. Kaminetsky received clinical research grants from Antares Pharma, Inc., Valencia Technologies, Taris Biomedical, and Allergan.

Funding: Antares Pharma, in collaboration with the authors, had a role in the study design; collection, analysis, and interpretation of data; writing of the report, and decision to submit the article for publication.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Jonathan S. Jaffe; Jed C. Kaminetsky; Marc Gittelman

(b) Acquisition of Data
Marc Gittelman; Jed C. Kaminetsky; Jonathan S. Jaffe

(c) Analysis and Interpretation of Data
Jonathan S. Jaffe; Jed C. Kaminetsky; Marc Gittelman

Category 2

(a) Drafting the Article
Jonathan S. Jaffe; Jed C. Kaminetsky; Marc Gittelman

(b) Revising It for Intellectual Content
Jonathan S. Jaffe; Marc Gittelman; Jed C. Kaminetsky

Category 3

(a) Final Approval of the Completed Article
Jonathan S. Jaffe; Jed C. Kaminetsky; Marc Gittelman

REFERENCES

1. Morgentaler A, Zitzmann M, Traish AM, et al. Fundamental concepts regarding testosterone deficiency and treatment: International Expert Consensus Resolutions. **Mayo Clin Proc 2016;91:881-896.**
2. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. **J Clin Endocrinol Metab 2018;103:1715-1744.**
3. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. **N Engl J Med 2010;363:123-135.**
4. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. **Diabetes Care 2004;27:1036-1041.**
5. Antonio L, Wu FC, O'Neill TW, et al. Associations between sex steroids and the development of metabolic syndrome: A longitudinal study in European men. **J Clin Endocrinol Metab 2015;100:1396-1404.**
6. Moskovic DJ, Araujo AB, Lipshultz LI, et al. The 20-year public health impact and direct cost of testosterone deficiency in U.S. men. **J Sex Med 2013;10:562-569.**
7. Behre HM, Tammela TL, Arver S, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. **Aging Male 2012;15:198-207.**

8. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. **N Engl J Med 2016; 374:611-624.**
9. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: Results from a meta-analysis of observational studies. **J Endocrinol Invest 2016;39:967-981.**
10. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: A meta-analysis study. **J Sex Med 2014;11:1577-1592.**
11. Kaminetsky J, Jaffe JS, Swerdloff RS. Pharmacokinetic profile of subcutaneous testosterone enanthate delivered via a novel, prefilled single-use autoinjector: A phase II study. **Sex Med 2015;3:269-279.**
12. Kaminetsky JC, McCullough A, Hwang K, et al. A 52-week study of dose adjusted subcutaneous testosterone enanthate in oil self-administered via disposable auto-injector. **J Urol 2019;201:587-594.**
13. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. **JAMA 2013; 310:1829-1836.**
14. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. **PLoS One 2014;9:e85805.**
15. Monath JR, McCullough DL, Hart LJ, et al. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. **Urology 1995; 46:58-61.**
16. Andersson DP, Trolle Lagerros Y, Grotta A, et al. Association between treatment for erectile dysfunction and death or cardiovascular outcomes after myocardial infarction. **Heart 2017; 103:1264-1270.**
17. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. **Eur Heart J 2015; 36:2706-2715.**
18. Zhou G, Huang R, Roenker N, et al. Quantification of testosterone and dihydrotestosterone in human plasma using qtrap 6500 systems [abstract]; 2013; AAPS Annual Meeting and Exposition, November 10-14, 2013, San Antonio, TX.
19. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. **Circulation 2008;117:743-753.**
20. Zhu A, Lu T-S, Snider E, et al. A sensitive and rapid UPLC-MS/MS quantification of estradiol in human plasma [abstract]; 2013; AAPS Annual Meeting and Exposition, November 10-14, 2013, San Antonio, TX.
21. Fernandez-Balsells MM, Murad MH, Lane M, et al. Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. **J Clin Endocrinol Metab 2010; 95:2560-2575.**
22. Mancia G, Omboni S, Parati G, et al. Lack of placebo effect on ambulatory blood pressure. **Am J Hypertens 1995;8:311-315.**
23. XYOSTED prescribing information 2018. Available at: https://www.xyosted.com/index.php/hcp?utm_source=bing&utm_medium=cpc&utm_campaign=Xyosted_HCP_Patient_Support_Brand_BMM&utm_term=%2Bprescribing%20%2Binformation%20%2BXyosted&utm_content=Prescribing&gclid=COmlhOfZsuQCFYPkswodeNAHXA&gclsrc=ds.
24. Schoenfeld MJ, Shortridge E, Cui Z, et al. Medication adherence and treatment patterns for hypogonadal patients treated with topical testosterone therapy: A retrospective medical claims analysis. **J Sex Med 2013;10:1401-1409.**

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jsxm.2019.08.013.