Author's Accepted Manuscript

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PII: S0022-5347(18)43964-X
DOI: 10.1016/j.juro.2018.09.057
Reference: JURO 15843

To appear in: *The Journal of Urology*
Accepted Date: 22 September 2018

Please cite this article as: Kaminetsky JC, McCullough A, Hwang K, Jaffe JS, Wang C, Swerdloff RS, A 52-Week Study of Dose-Adjusted Subcutaneous Testosterone Enanthate in Oil Self-Administered via Disposable Auto-injector, *The Journal of Urology*® (2018), doi: https://doi.org/10.1016/j.juro.2018.09.057.

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Suggested Journal Target: *Journal of Urology*

Word Count: 2,443 [max: 2,500 words for original clinical articles]

Abstract Word Count: 235 [max: 250 words]

Tables/Figures: 9 [max: 10 illustrations]

References: 27 [max: 30, including references from the last 3 years]

Brief descriptive running head: Evaluation of a SC Testosterone Enanthate Auto-injector [49 characters; max: 50 characters]

Clinical Trial Registration: NCT02159469

Keywords: testosterone enanthate, testosterone deficiency, male hypogonadism, subcutaneous injections, clinical trial [MeSH terms, max 5]

Abstract

Purpose: This open-label, single-arm, dose-blinded, 52-week, registration-phase study evaluated the efficacy and safety of subcutaneous testosterone enanthate auto-injector (SCTE-AI) administered weekly to men with hypogonadism.

Methods: Patients (N=150) were initiated on 75 mg SCTE-AI self-administered weekly. Dose adjustments were made at week 7 to 50, 75, or 100 mg testosterone enanthate (TE) based on week 6 total testosterone (TT) trough concentration. If required, dose adjustments continued through the extended treatment phase. Pharmacokinetic (PK) and clinical laboratory parameters, treatment-emergent adverse events (TEAEs), and injection site reactions were captured.

Results: The primary endpoint was met: 92.7% of patients achieved an average TT concentration of 300–1100 ng/dL (553.3 ± 127.29 ng/dL, mean ± SD) at week 12. A C_{max} of <1500 ng/dL was achieved by 91.3% of patients, and no patients had levels >1800 ng/dL at week 12. Mean TT C_{trough} was 487.2 ± 153.33 ng/dL at week 52. Most patients (>95%) reported no injection-related pain. The most frequently-reported TEAEs were increased hematocrit, hypertension, and increased prostate-specific antigen, which led to discontinuation in 30 men. There were no study drug-related serious AEs.

Discussion: Dose-adjusted SCTE-AI demonstrated a steady serum TT PK profile, with small peak and trough fluctuations. SCTE-AI was safe, well tolerated, and virtually painless, indicating that SCTE-AI offers a testosterone delivery system that is a convenient weekly option for treatment of testosterone deficiency.

INTRODUCTION

Testosterone deficiency (TD) in men is diagnosed when signs and symptoms of hypogonadism (HG) are present, and circulating total testosterone (TT) levels persist below the lower limit of normal (300 ng/dL).[1] In the US, TD is estimated to affect ~6% of men, with higher rates seen with obesity and increased age.[2,3] TD negatively affects male sexual and physical function, quality-of-life (QoL), overall health, and, potentially, fertility.[1,4,5] TD has also been linked to osteoporosis, metabolic syndrome, insulin resistance, dyslipidemia, erectile dysfunction, and hypertension (HTN).[1,6-8] T replacement (TR) has been shown to improve health-related QoL in men with TD.[5] Treatment improves sexual function and mood,[9,10] and has been shown to reduce fat mass and increase bone and muscle mass.[1,11]

The subcutaneous testosterone enanthate auto-injector (SCTE-AI) is a novel disposable drug-device combination that allows patients to self-administer a single, premeasured TE dose once-weekly through a ⅝-inch, 27-gauge needle.[12] Previously, treatment with SCTE-AI was found to provide T levels within reference range (300–1100 ng/dL) over a one-week dosing interval, with steady-state T levels approached by weeks 5–6.[12] In this study, we assess the long-term efficacy and safety of dose-adjusted SCTE-AI in patients with HG to maintain TT within the reference range.

METHODS

This was an open-label, single-arm, dose-blinded, 52-week, registration-phase study following a Phase 2 dosing study, with all patients receiving active dosing, to evaluate the efficacy and safety of SCTE-AI administered weekly to adult males with HG. This study was supported by Antares Pharma, Inc. Patients and investigators were blinded after week 6 to dosage strength and T level. The trial was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines and is registered at ClinicalTrials.gov (NCT02159469). The protocol was approved by each study center's institutional review board. Informed consent was obtained from all patients prior to study initiation.

Study Participants

Men ≥18 years of age were eligible for inclusion if past patient medical records documented a diagnosis of HG based on T levels and classical signs and symptoms. T levels during screening were used to qualify patients. See Supplementary Appendix for details on HG diagnostic criteria, inclusion and exclusion criteria, and stopping criteria.

Study Design

Eligibility was established during the screening period (Supplementary Figure 1). During the titration phase, patients self-administered 75 mg SCTE-AI once weekly for 6 weeks. Blinded dose adjustments, at 25 mg increments, were allowed at weeks 7, 13, 19, 27, and 39 based on the preceding week pre-dose TT trough concentration (C_{trough}) by an interactive web response system, to maintain the C_{trough} level in a controlled range (350–650 ng/dL). Patients remained on their concentration-optimized SCTE-AI dose

(50-, 75-, or 100-mg dose) for up to 52 weeks (Supplementary Figure 1). Follow-up was completed 7–14 days after final assessments.

Endpoints and Assessments

Serum TT, TE, dihydrotestosterone (DHT), and estradiol (E2) concentrations were analyzed with validated high-performance liquid chromatography–tandem mass spectrometry assays by Medpace Bioanalytical Laboratories (Cincinnati, OH, USA) as previously described.[13,14] Pharmacokinetic (PK) parameters (maximum [C_{max}], minimum [C_{min}], and average concentration over the 7-day dosing interval [0–168 h; $C_{avg0–168h}$]) were derived from serum TT.

The primary endpoint was the percentage of patients with TT $C_{avg0–168h}$ within the defined range of 300–1100 ng/dL. Blood samples for determining $C_{avg0–168h}$ were collected at the following week-12 time points: pre-dose and 6, 9, 12, 24, 36, 48, 72, and 168 hours post-dose. This endpoint was met if ≥75% of patients had TT $C_{avg0–168h}$ within range at week 12, with a lower bound of the 95% confidence interval (CI) ≥65%. Key secondary endpoints were the percentage of patients with TT C_{max} <1500 ng/dL, within 1800–2500 ng/dL, and >2500 ng/dL at week 12. These endpoints were considered met if ≥85% of patients had C_{max} <1500 ng/dL, <5% within 1800–2500 ng/dL, and no patients >2500 ng/dL.

Safety data included treatment-emergent adverse events (TEAEs; defined as an AE that started or worsened on or after the first dose), vital signs (including systolic and diastolic blood pressure [SBP/DBP]), physical examinations, and injection site assessments (ISAs). ISAs were completed prior to dose administration, then 30 minutes, 1 hour, and 24 hours post-dose at week 6, 7, 13, 18, 19, 26, 27, 38, 39, and 52. ISAs considered clinically significant by the Investigator were considered injection site reaction TEAEs. Clinical safety laboratory assessments were performed at screening, weeks 13, 26, 38, and 52, and follow-up.

Patients also completed the Self-Injection Assessment Questionnaire (SIAQ) and Psychosexual Daily Questionnaire (PDQ).[15,16]

Statistical Analyses

The primary study population was the safety population (all patients who received at least one dose of SCTE-AI). The per-protocol (all patients who followed the study protocol and did not have any significant protocol deviations) and PK (all patients in the safety population who had at least one blood sample drawn post-dose for the PK analysis) populations were used for sensitivity analyses.

PK parameters for TT, DHT, TE, and E2 were summarized descriptively by dose. Patient demographics and baseline characteristics were summarized descriptively. For continuous data, summary statistics were provided. For categorical data, counts and percentages were presented. Safety data were summarized overall and by dose when applicable.

RESULTS

Trial Participants

One hundred fifty patients received one or more doses of SCTE-AI, 137 (91.3%) patients completed the study through week 12, and 97 (64.7%) completed all study visits (Figure 1). Demographics and baseline characteristics are shown in Table 1.

Pharmacokinetics

The primary endpoint was met as 92.7% (139/150) of patients overall and 100% (25/25), 90.4% (94/104), and 95.2% (20/21) of those titrated to 50, 75, and 100 mg, respectively, achieved mean TT $C_{avg0–168h}$ within range at week 12. Secondary endpoints were also met as 91.3% (137/150) of patients achieved C_{max} <1500 ng/dL and no patients had a measured C_{max} exceeding 1500 ng/dL. Of the 150 patients, 13 (8.7%) had missing C_{max} values (11 from the 75-mg and 2 from the 100-mg group). Baseline C_{trough} (SD) was 231.6 (94.77) ng/dL and remained steady and above 300 ng/dL though one year; 501.9 (172.70) ng/dL by week 6 and 487.2 (153.33) ng/dL at week 52 (Figure 2A).

SCTE-AI demonstrated a week-12 mean TT $C_{avg0–168h}$ (SD) of 553.3 (127.29) ng/dL, a median TT $C_{avg0–168h}$ (Q1, Q3) of 534.6 ng/dL (471.2, 626.6), a range of 276-1036 ng/dL, a mean TT C_{max} and C_{min} within the prespecified range for $C_{avg0–168h}$, and a peak-to-trough ratio of 1.813 (Table 2). For patients titrated to 50, 75, and 100 mg, mean TT $C_{avg0–168h}$ (SD) was 598.2 (177.73) ng/dL, 537.6 (108.09) ng/dL, and 571.1 (127.23) ng/dL, respectively. The time course of mean TT and TE concentrations pre- and post-dose during the dosing interval at week 12 is shown in Figures 2B and 2C.

Mean TT exposures across all dose groups as measured by C_{max}, C_{min}, and $C_{avg0–168h}$ at week 12 (Table 2), as well as TT concentration curves for all three doses (Supplementary Figure 2A) were similar, further validating C_{trough}–guided dose adjustment.

The T metabolites DHT and E2 demonstrated little fluctuation during the dosing interval through week 12 (Figures 2D and 2E). Mean and median DHT and E2 levels and DHT/TT and E2/TT ratios at week 12 are shown in Supplementary Table 1, and DHT and E2 concentration curves for all three TE doses are shown in Supplementary Figures 2B and 2C. Overall, the mean (SD) decrease in sex hormone–binding globulin (SHBG) was 1.9 (5.56) nmol/L, from baseline (26.4±17.44 nmol/L) to week 52 (21.4± 8.9 nmol/L) (Supplementary Figure 3).

Most patients remained on their week 7 dose at any subsequent visit (Supplementary Figure 4).

TEAEs and ADRs

In total, 125 (83.3%) patients experienced a TEAE during the study; most were mild or moderate (Table 3). Thirty patients discontinued due to TEAEs. The most frequently reported TEAEs were increased hematocrit in 21 [14.0%] patients, of which 7 discontinued, HTN in 19 [12.7%] patients, of which 1 discontinued, and increased prostate-specific antigen (PSA) in 18 [12.0%] patients, of which 13 discontinued (an increase in serum PSA concentration of ≥1.4 ng/mL was used as a stopping criteria[1]). Sixty-six (44.0%) patients experienced an ADR (Table 3); of these, only one (0.7%) was considered severe (polycythemia and increased hematocrit).

Overall, three (2.0%) patients experienced treatment-emergent serious AEs (SAEs), none of which was related to SCTE-AI as assessed by the Investigators. However, one patient died during the study as a

result of suicide, and this was considered possibly related to investigational product (IP) because the suicide could have been secondary to depression, which has been reported with other T products.[17]

Clinical and Laboratory Evaluations

Mean hematocrit (SD) levels (Supplementary Figure 5A) increased from 44.5% (3.41%) at baseline to 50.1% (3.73%) at week 52 (change from baseline [SD]: 5.4% [3.42%]). Mean PSA (SD) levels (Supplementary Figure 5B) were 1.08 (0.853) µg/L at baseline and increased to 1.39 (1.030) µg/L by week 13, remaining steady through week 52 (1.33 [0.818] µg/L; change from baseline [SD]: 0.36 µg/L [0.485]).

Overall, mean SBP and DBP (SD) increased from 126.7 (11.58) mmHg and 79.8 (8.26) mmHg at baseline to 130.6 (10.64) mmHg and 81.2 (9.17) mmHg at week 52 (Supplementary Figure 5C and 5D). Sixty (40.0%) patients had a high post-dose SBP value (>180 mmHg or increase ≥20 mmHg) during the study; 36 of them had normal SBP at baseline. Thirty (20.0%) patients had a high post-dose DBP value (>105 mmHg or increase ≥15 mmHg) during the study; 19 of them had normal DBP at baseline.

Injection Site Assessments

Injection site observations experienced by >8% of patients included erythema, pinprick/needle mark, and pressure mark from the needle guard (Table 3); all of these observations were resolved by study completion. ISR (observations >25 mm in diameter) of erythema, induration, hematoma, or ecchymosis occurred in one (0.7%) patient for each. Of the 1519 self-injections observed in clinic, only nine injections among 3 patients were accompanied by pain. When pain was reported, it was reported as mild in intensity (1 or 2 out of 10). No patients discontinued as a result of ISR.

Treatment Adherence and Questionnaire Results

During the 12-week treatment titration phase, patients received a mean of 11.7 injections, with a mean exposure of 81.3 days. During the extended treatment phase, patients received an average of 33.2 injections, with a mean exposure of 235.3 days. Overall, mean compliance (calculated as 100 × number of injections/weeks of treatment) was 98.5%. Patients indicated satisfaction with self-injection (Supplementary Figure 6), and the PDQ demonstrated significant improvements in several areas, at both week 12 and week 26 (Supplementary Figure 7).

DISCUSSION

SC delivery of TE through an auto-injector resulted in a steady PK profile at week 12, without the higher peaks and troughs commonly associated with intramuscular T injection-. The peak-to-trough ratio in this study was 1.813. Most patients (92.7%) stayed within physiologic T range for the entire dosing interval; no patients had a measured T levels >1500 ng/dL. C_{trough} also remained constant during the 52-week

study. As fluctuations in T levels affect tolerability of T treatment used to alleviate symptoms of TD and have been associated with more side effects such as acne and mood disturbance, the steady PK profile of SCTE-AI may lead to better control of symptoms.[16] Although symptom resolution was not a primary endpoint in this study, improvements in the PDQ were observed. As expected, DHT and E2 increased from baseline to week 12; DHT remained within normal range, and E2 remained close to the upper limit of normal.

HTN, a common comorbid condition found in TD,[18] was part of the medical history in 49.3% of patients at enrollment; therefore, it was not surprising that HTN TEAEs were common. Most patients (16/19) with an HTN TEAE had one or more elevated readings (SBP ≥140 mmHg or DBP ≥90 mmHg) during the screening period before SCTE-AI was administered. Only one patient discontinued because of HTN, and this was not considered related to the treatment. This suggests that the HTN TEAEs in this study likely reflected issues with BP control present before the dosing study medication that continued during the study.

A small increase in mean SBP and DBP was noted. Though the significance of BP changes of this magnitude is unclear, as differences in BP larger than this in a population of intermediate cardiac risk has no detectable effect on cardiovascular (CV) events.[19] There are no long-term data regarding the impact of small BP changes on CV outcomes in treated TD men.

Reports on the impact of T therapy on CV outcomes in men with TD have been inconsistent.[20-25] Several studies and meta-analyses have not found a correlation between T therapy and increased CV events or adverse CV outcomes.[22-24] Similar to other registration studies for TR, patients in this study did not have cardiac or cerebrovascular ischemic AEs.

An increase in serum PSA is an expected AE, as the prostate is an androgen-sensitive organ. As such, a change in PSA in the setting of TR lacks specificity for prostate cancer. The 12% incidence of increased PSA observed in this one-year study is substantial and reflects both frequent laboratory monitoring as well as strict application of the Endocrine Society Guideline.[1,26] Even so, this incidence is comparable to that shown in the most recent label for testosterone gel 1.62%, which shows an AE rate of 11.1% for increased PSA during the 182 days of treatment.[27] Whereas increases in PSA were considered of questionable clinical significance, factors predicting greater PSA increases included age ≥60 years and baseline T ≤250 ng/dL.[28]

Use of any marketed TR requires monitoring for PSA elevation, and this expected AE should be amenable to management including monitoring, discontinuation (as was employed in this trial), or dose reduction, and cancer workup for extreme or progressive elevations. The question as to whether TR increases the risk for prostate cancer will be directly addressed as an endpoint in the ongoing placebo-controlled, 60-month, 6000 patient TRAVERSE study (ClinicalTrials.gov identifier: NCT03518034).

Patients may face barriers to adherence to TR, including inconvenience and discomfort. In this study, patients were highly adherent to the dosing regimen, indicated a virtually pain-free experience, and demonstrated a high degree of satisfaction with SCTE-AI, as measured by the SIAQ.

SCTE-AI conveys several advantages over other modes of T administration. There is no risk of secondary exposure as with gels and theoretically less risk of pulmonary oil embolism, as has been

reported with higher volume intramuscular testosterone in oil injection.[17] The Investigator and patient blinding to dose titration and dosing was a strength of this study, as was its 52-week duration, permitting examination of long-term efficacy and safety. However, because there was no blinded comparator, it is difficult to assess SCTE-AI in relation to other therapies.

Conclusions

Overall, this study demonstrates the steady PK profile and safety of SCTE-AI. SCTE-AI dosing guided by TT C_{trough} reduces peak and trough fluctuations, making SCTE-AI a convenient additional option for treatment of TD.

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Table 1. Demographics and baseline characteristics*

Demographics	**Overall (N=150)**
Age, years, mean (SD)	53.4 (12.04)
Age, years, median (Q1, Q3)	54.0 (45.00, 63.00)
Body weight, kg, mean (SD)	99.9 (18.40)
Body weight, kg, median (Q1, Q3)	98.35 (88.90, 111.50)
BMI, kg/m^2, mean (SD)	31.2 (4.66)
BMI, kg/m^2, median x (Q1, Q3)	31.05 (28.10, 34.90)
Baseline TT, ng/dL, mean (SD)	230.4 (94.01)
Baseline TT, ng/dL, median x (Q1, Q3)	229.0 (173.00, 290.00)
Ethnicity	
Hispanic or Latino	8 (5.3)
Not Hispanic or Latino	142 (94.7)
Race	
Caucasian	133 (88.7)
Black or African American	11 (7.3)
Asian	4 (2.7)
Multiple	1 (0.7)
Other	1 (0.7)
Baseline Characteristics	
Medical history at enrollment	
Hypertension	74 (49.3)
Erectile dysfunction	51 (34.0)
Gastroesophageal reflux disease	40 (26.7)
Diagnosis of hypogonadism	
Hypogonadism	149 (99.3)
Secondary hypogonadism	1 (0.7)
Currently receiving T therapy	
No	129 (86.0)
Yes	21 (14.0)
IM or SC T injection	8 (5.3)
Topical/transdermal	12 (8.0)
Pellets	1 (0.7)
Concomitant medications by class	
HMG-CoA reductase inhibitors	49 (32.7)
Platelet aggregation inhibitors, excluding heparin	42 (28.0)
Other lipid-modifying agents	32 (21.3)
ACE inhibitors, plain	30 (20.0)

ACE, angiotensin-converting enzyme; BMI, body mass index; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IM, intramuscular; SC, subcutaneous; SD, standard deviation; T, testosterone; TT, total testosterone.

*Values for baseline characteristics are n values (percentage), unless stated otherwise.

Table 2. Summary of week 12 TT PK parameters

	$C_{avg0–168h}$, ng/dL	C_{max}, ng/dL*	C_{min}, ng/dL*	T_{max}, h
Overall (N = 137)				
Mean (SD)	553.3 (127.29)	789.8 (215.43)	435.6 (109.22)	22.8 (24.44)
Median (Q1, Q3)	534.6 (471.2, 626.6)	767.0 (630.0, 893.0)	422.0 (365.0, 507.0)	11.9 (8.98, 35.15)
Range	276–1036	389–1410	166–788	5.8–168.7
50 mg (n = 25)				
Mean (SD)	598.2 (177.73)	849.6 (274.82)	458.2 (139.88)	25.3 (20.32)
Median (Q1, Q3)	532.5 (483.3, 659.1)	810.0 (698.0, 983.0)	421.0 (372.0, 506.0)	12.00 (8.90, 35.55)
Range	379–1036	510–1410	265–788	5.8–72.6
75 mg (n = 93)				
Mean (SD)	537.6 (108.09)	758.2 (185.94)	431.2 (97.46)	20.34 (22.27)
Median (Q1, Q3)	534.6 (471.2, 622.3)	730.0 (627.0, 881.0)	423.0 (367.0, 502.0)	11.9 (8.98, 35.03)
Range	276–826	389–1240	236–747	5.9–168.2
100 mg (n = 19)				
Mean (SD)	571.1 (127.23)	866.3 (238.64)	427.7 (120.92)	31.6 (36.17)
Median (Q1, Q3)	558.8 (467.8, 667.3)	876.0 (632.0, 1070.0)	422.0 (326.0, 548.0)	24.1 (8.97, 35.95)
Range	373–833	506–1260	166–619	5.8–168.7

$C_{avg0–168h}$, average concentration over the 7-day dosing interval (0–168 hours); C_{max}, maximum (peak) blood concentration; C_{min}, minimum blood concentration; PK, pharmacokinetic; T_{max}, time to reach maximum blood concentration; TT, total testosterone.

*The fluctuation (peak-to-trough) ratios were 1.813 for the overall study population and 1.854, 1.758, and 2.025 for the 50-, 75-, and 100-mg dose groups, respectively.

Table 3. TEAEs and ADRs in the safety population (N=150)*

ADRs	**n (%)**
Mild	45 (30.0)
Moderate	20 (13.3)
Severe	1 (0.7)
Patients with any SAE	3 (2.0)
Related to IP	0 (0)
Patients with any TEAE leading to discontinuation	30 (20.0)
Related to IP	24 (16.0)
Patients with any AE leading to death**	1 (0.7)
ADRs according to system class[†]	
Investigations	37 (24.7)
Hematocrit increased	18 (12.0)
Prostatic-specific antigen increased	15 (10.0)
Blood testosterone increased[‡]	4 (2.7)
Mean cell volume increased	2 (1.3)
General disorders and administration site conditions	19 (12.7)
Injection site bruising	10 (6.7)
Injection site hemorrhage	5 (3.3)
Injection site erythema	4 (2.7)
Injection site induration	2 (1.3)
Injection site pruritus	2 (1.3)
Skin and subcutaneous tissue disorders	9 (6.0)
Acne	3 (2.0)
Reproductive system and breast disorders	5 (3.3)
Prostatomegaly	2 (1.3)
Blood and lymphatic system disorders	3 (2.0)
Polycythemia	3 (2.0)
ISAs[§]	
Erythema	31 (20.7)
>25 mm	1 (0.7)
Induration	11 (7.3)
>25 mm	1 (0.7)
Bleeding	10 (6.7)
Hematoma	11 (7.3)
>25 mm	1 (0.7)
Ecchymosis	9 (6.0)
>25 mm	1 (0.7)

Pinprick/needle mark	87 (58.0)
Pressure mark	29 (19.3)
>25 mm	0 (0.0)
Itching	9 (6.0)
Pain	7 (4.7)
Any reported reaction (≥25 mm or smaller if accompanied by itching)	6 (4.0)
Reported TEAEs Leading to Study Discontinuation	**n**
Increased PSA	13
Increased HCT	7
Increased blood testosterone	4
Polycythemia	2
Prostate neoplasm	1
Hypersexuality	1
Fatigue	1
Hyperhidrosis	1
Dyspnea	1
Heart rate increased	1
Vision blurred	1
Bundle branch block	1
Prostatitis	1
Depression	1
Hypertension	1

ADR, adverse drug reaction (a TEAE that was assessed by the investigator as related to SCTE-AI); AE, adverse event; IP, investigational product; ISA, injection-site assessment; PK, pharmacokinetic; SAE, serious AE; SD, standard deviation; TEAE, treatment-emergent adverse event;; TT, total testosterone.

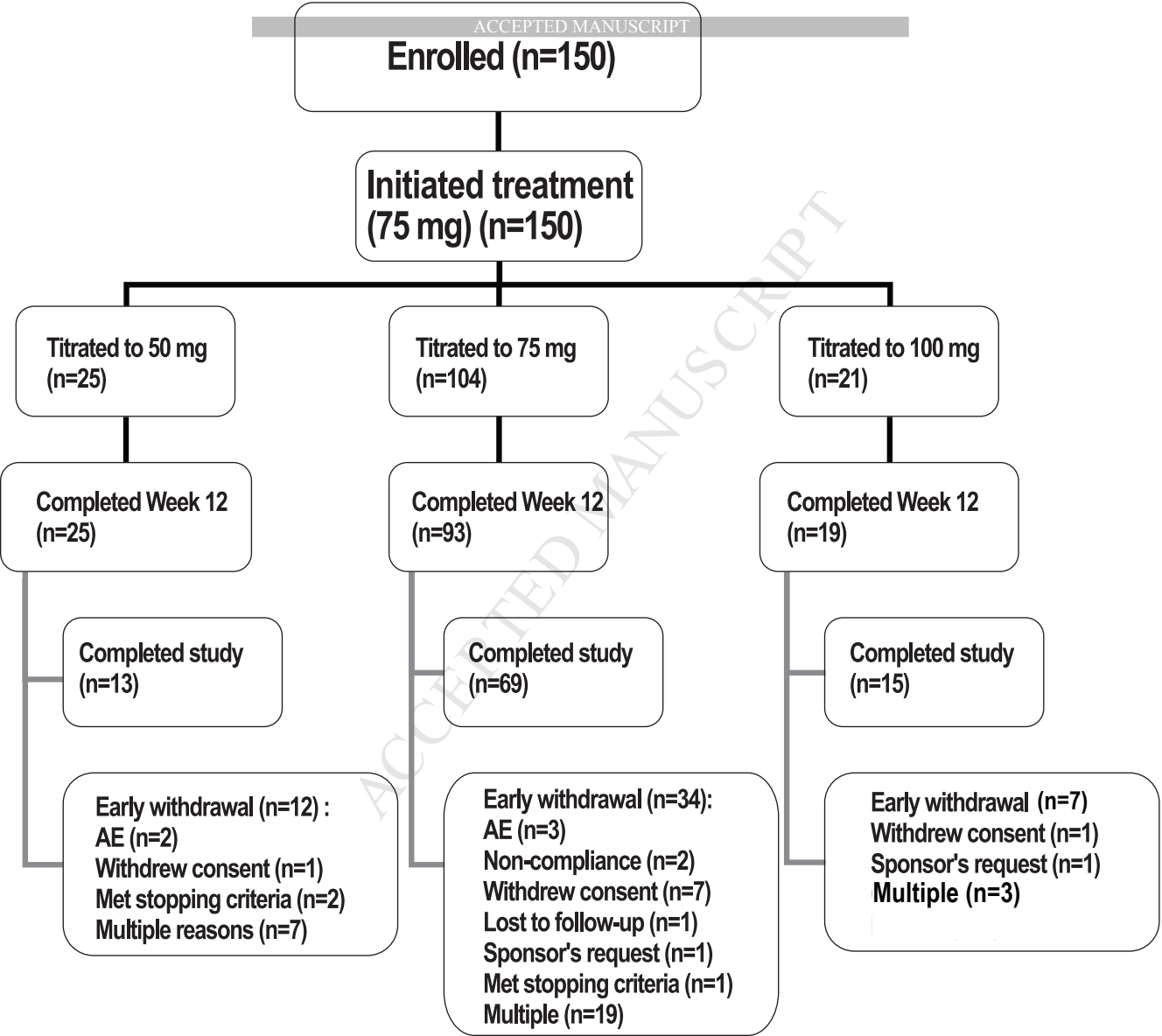
*AEs were coded using MedDRA version 16.0; patients may report more than one TEAE as reason for discontinuation; one patient was reported to have small palpable prostate nodules considered by the investigator to be mild in intensity and unrelated to study medication; this event was documented as a "prostate neoplasm" based on the MedDRA SOC preferred term for a nodule palpable upon digital rectal exam.

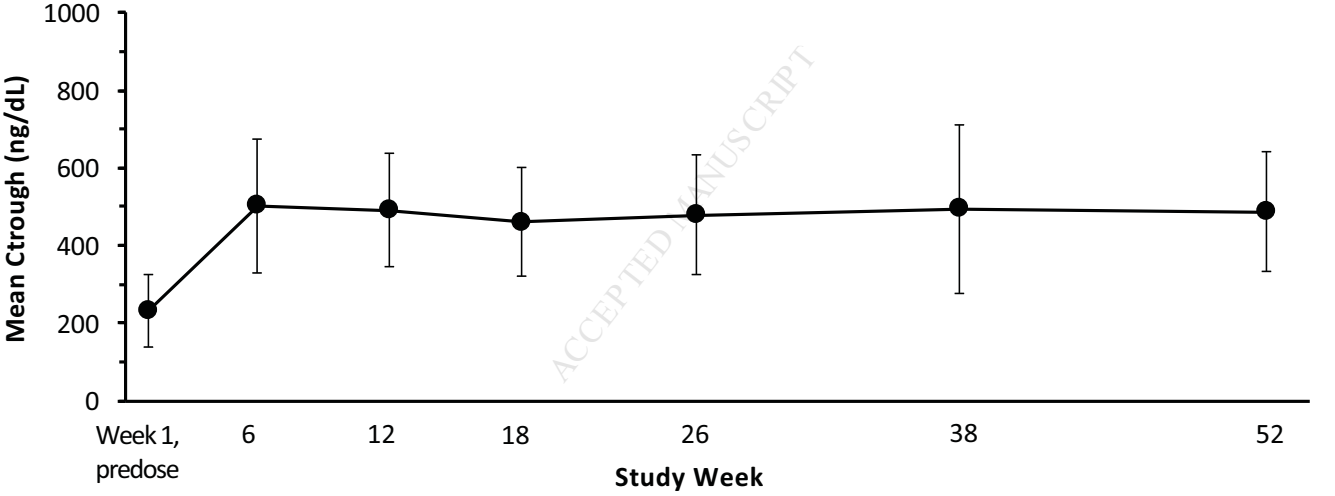
**One patient died during the study as a result of suicide that was assessed by the Investigator as not related to IP, but was considered by the Sponsor as possibly due to worsening depression. Because depression is an adverse event labelled for other testosterone products, it is possible that there is a relationship to IP.

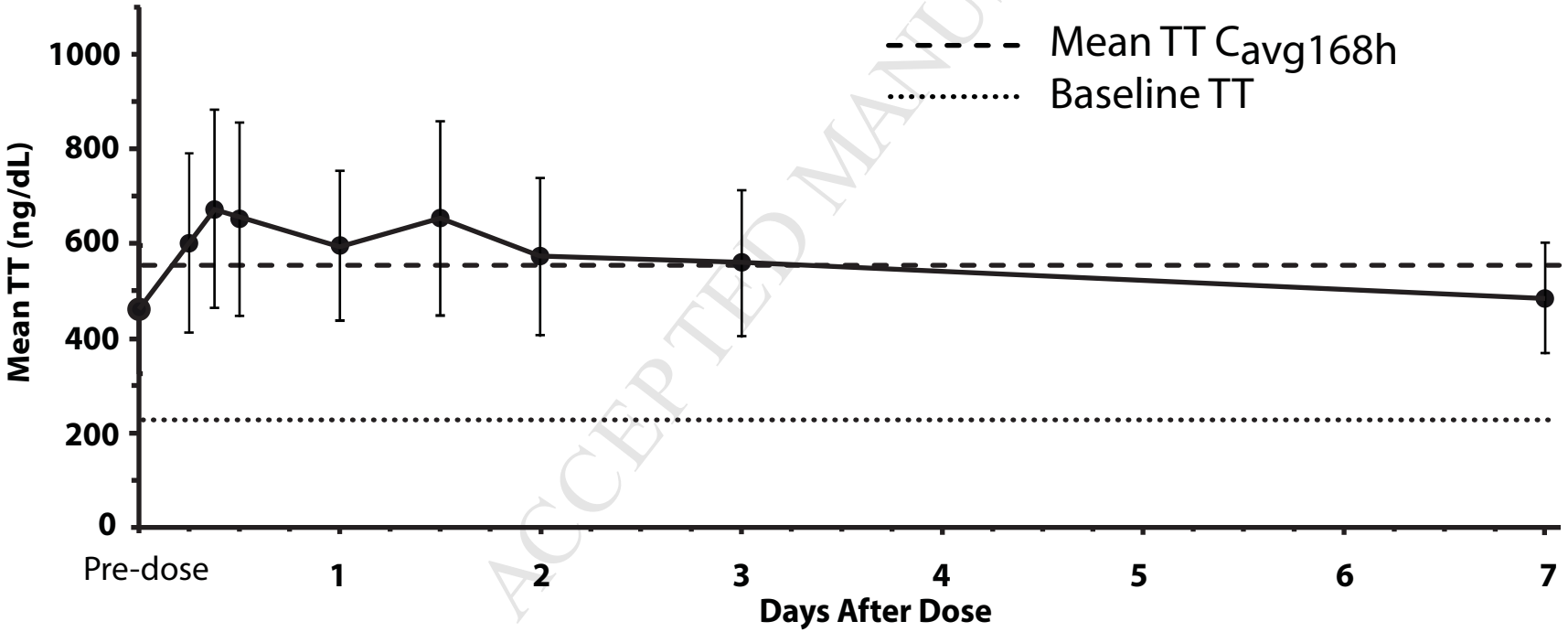
[†]Only TEAEs by system organ class experienced by ≥1% of patients are listed

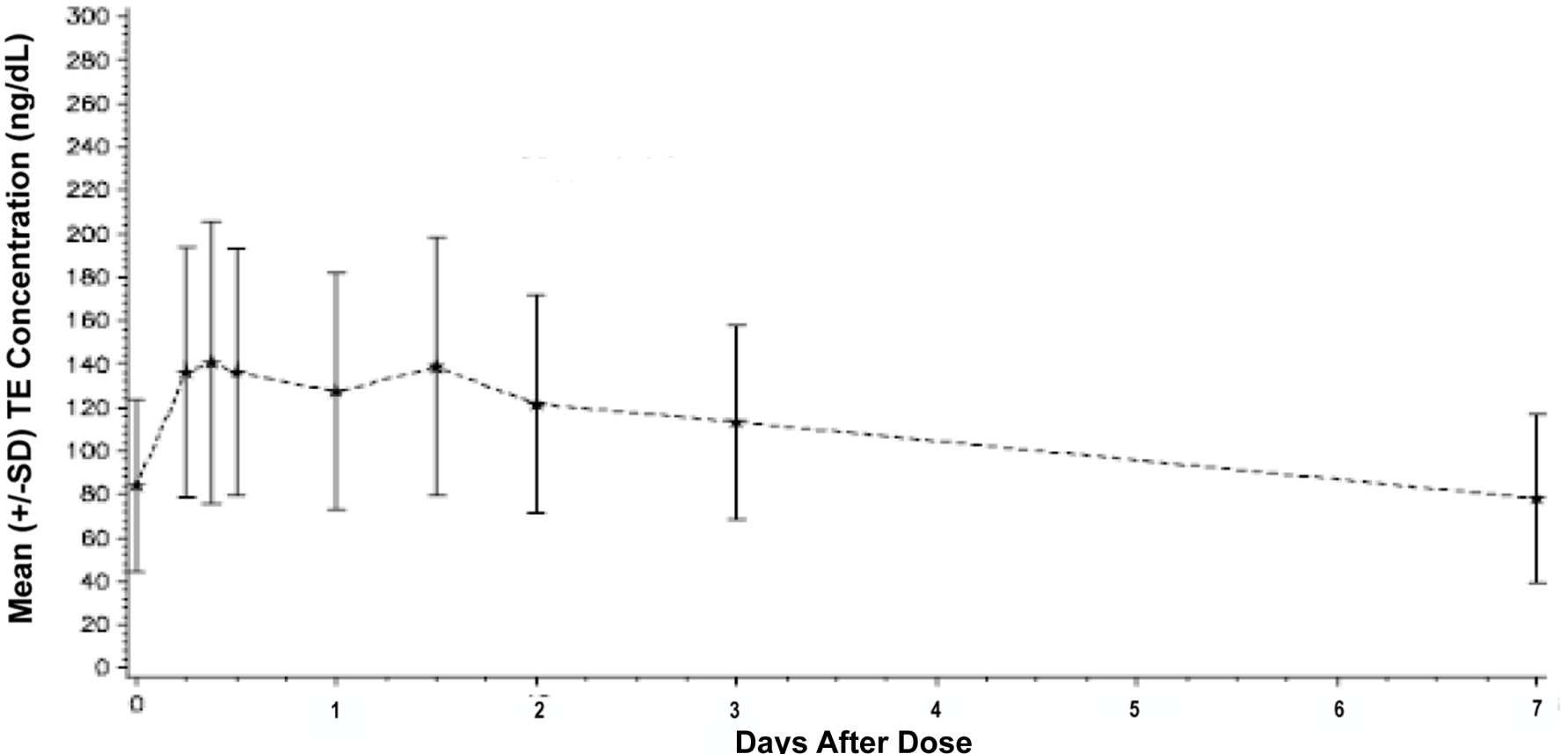
[‡]Predefined protocol stopping criteria for discontinuation from study; specifically, patients receiving the lowest available dose, QST 50 mg, who required a further dose reduction and who had a C_{trough} ≥650 ng/dL, as part of the concentration-monitored dosing regimen

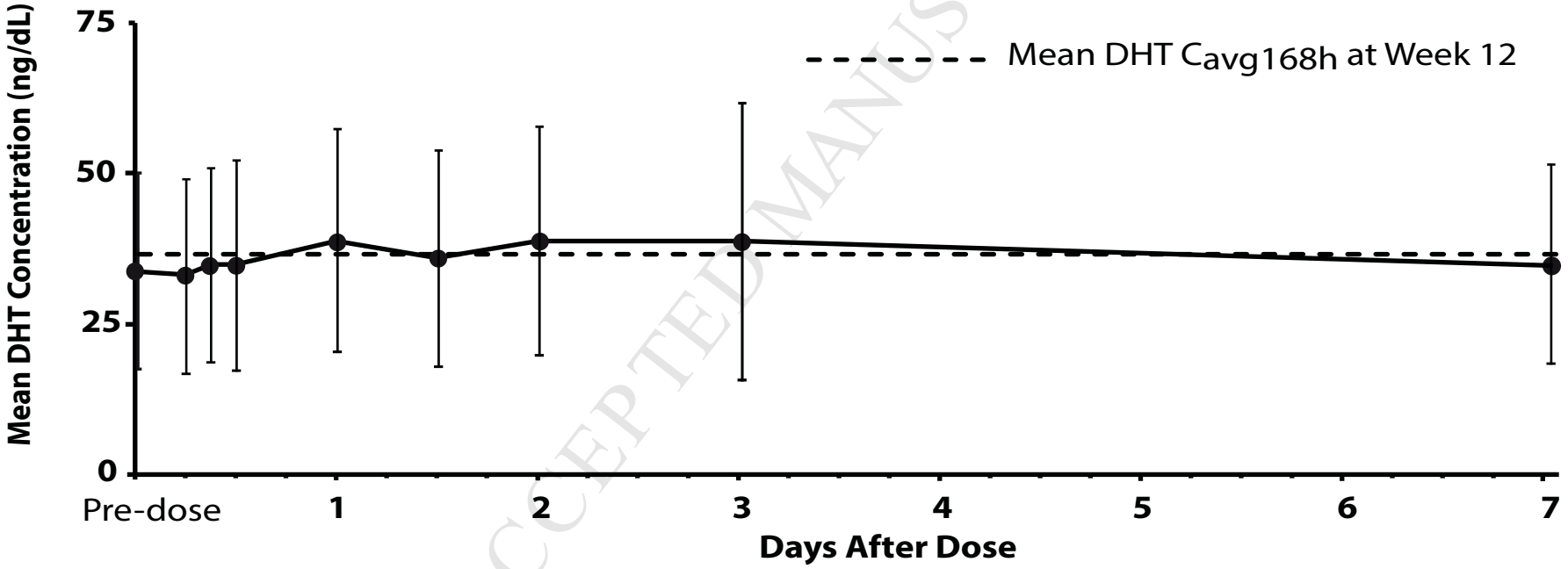
[§]ISAs are tabulated as the worst post-baseline assessment throughout the course of the study. An injection site reaction was defined as an injection site observation >25 mm in diameter.

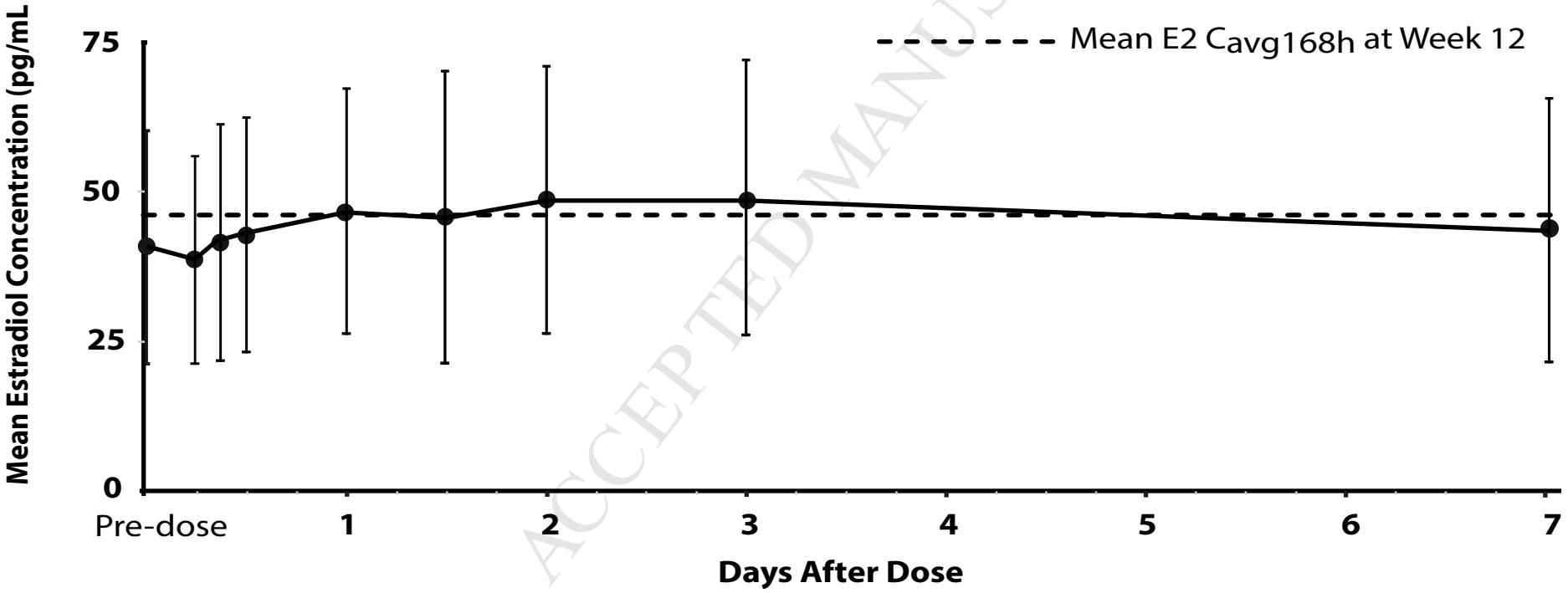







Mean (+/-SD) TE Concentration (ng/dL)
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Days After Dose





Key of Definitions for Abbreviations:

SCTE-AI, subcutaneous testosterone enanthate auto-injector

TT, total testosterone

TE, testosterone enanthate

TEAE, treatment-emergent adverse event

PK, pharmacokinetic

PSA, prostate-specific antigen

TD, testosterone deficiency

TR, testosterone replacement

DHT, dihydrotestosterone

E2, estradiol

SBP, systolic blood pressure

DBP, diastolic blood pressure

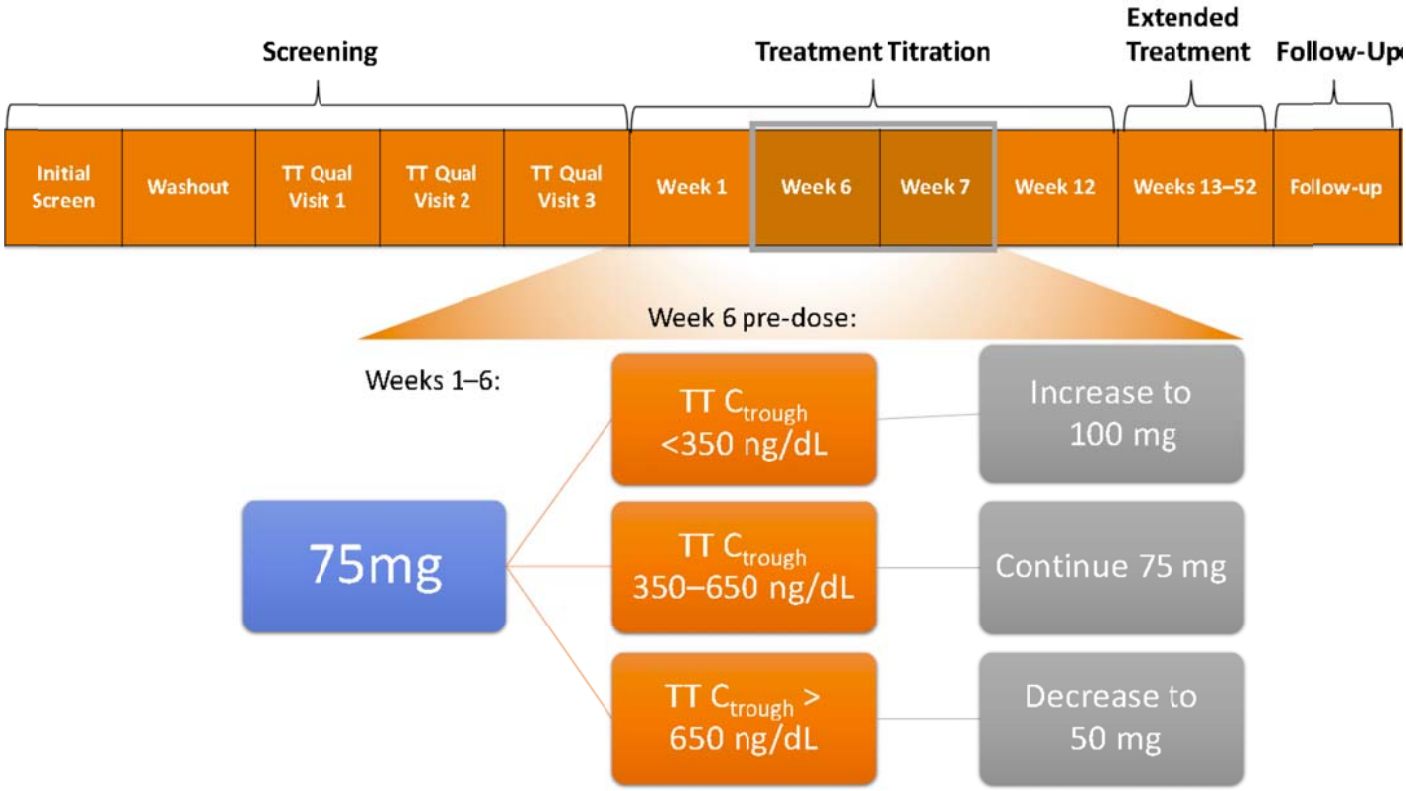
CV, cardiovascular

Supplementary Tables and Figures

Supplementary Table 1. Mean T metabolite levels and ratios at week 12 in the PK population

	$C_{avg0–168h}$	C_{max}	C_{min}
DHT, ng/dL, mean (SD)	36.6 (17.72)	45.2 (23.66)	28.0 (13.58)
DHT, ng/dL, median (Q1, Q3)	32.2 (24.7, 43.9)	40.3 (30.6, 51.8)	24.9 (18.6, 32.8)
E2, pg/mL, mean (SD)	46.3 (18.43)	64.2 (27.60)	29.9 (12.40)
E2, pg/mL, median (Q1, Q3)	43.0 (35.8, 55.9)	40.3 (30.6, 51.8)	24.9 (18.6, 32.8)
	% (SD)		
DHT/TT ratio	7.36 (2.676)		
E2/TT ratio	0.93 (0.416)		

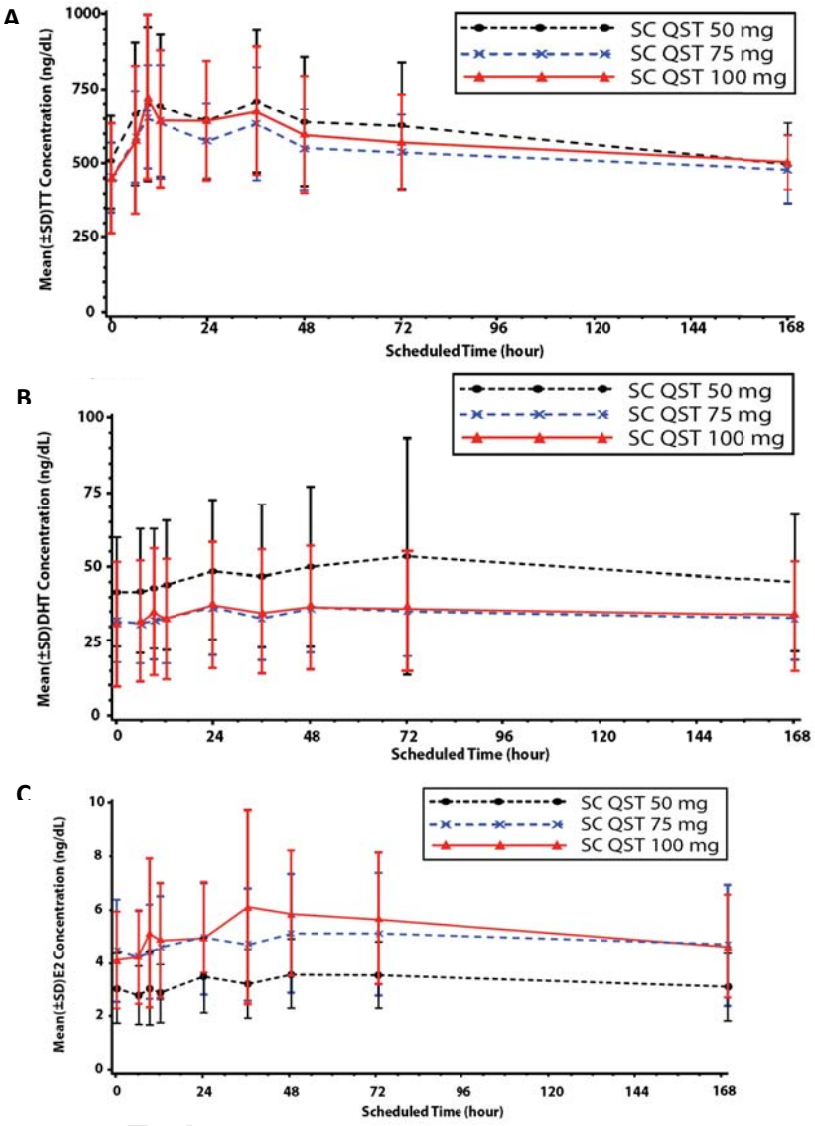
DHT, dihydrotestosterone; E2, estradiol; PK, pharmacokinetic; SD, standard deviation; TT, total testosterone.



Supplementary Figure 1. Study design

Qual, qualification visit; TT, total testosterone.

Screening phase was 2–7 weeks' duration depending on the T therapy washout status of the patient. During the treatment titration phase, dose was decreased by 25 mg if TT C_{trough} ≥650 ng/dL, increased by 25 mg if TT C_{trough} was <350 ng/dL, or maintained at 75 mg if TT C_{trough} was ≥350 ng/dL and <650 ng/dL. Study visits occurred at weeks 1, 6, 7, 12, 13, 18, 19, 26, 27, 38, 39, and 52 during the treatment titration and extended treatment phases.

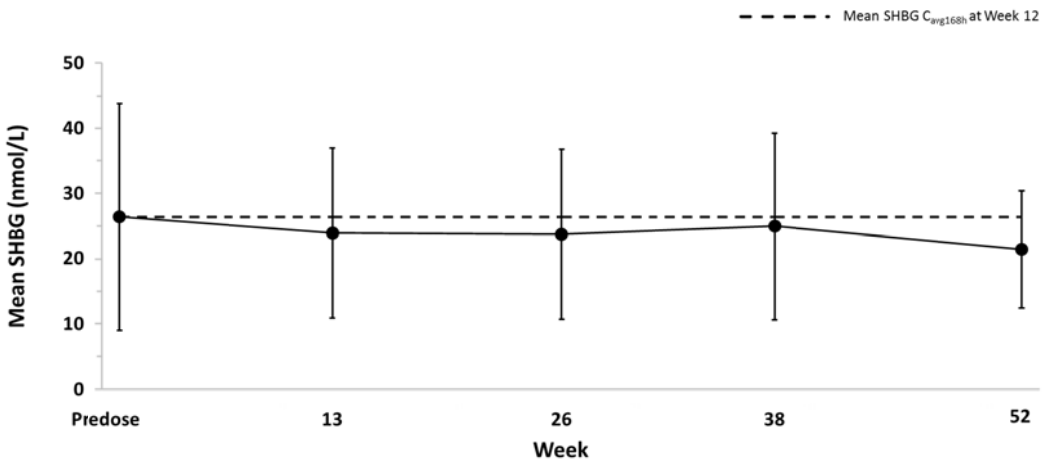


DHT, dihydrotestosterone; E2, estradiol; PK, pharmacokinetic; SD, standard deviation; TT, total testosterone.

Supplementary Figure 2. SCTE-AI PK profile by dose-titration group over first 7 days

(A) TT concentration by dose titration group (50, 75, or 100 mg); (B) DHT concentration by dose titration group (50, 75, or 100 mg); (C) E2 concentration by dose titration group (50, 75, or 100 mg).

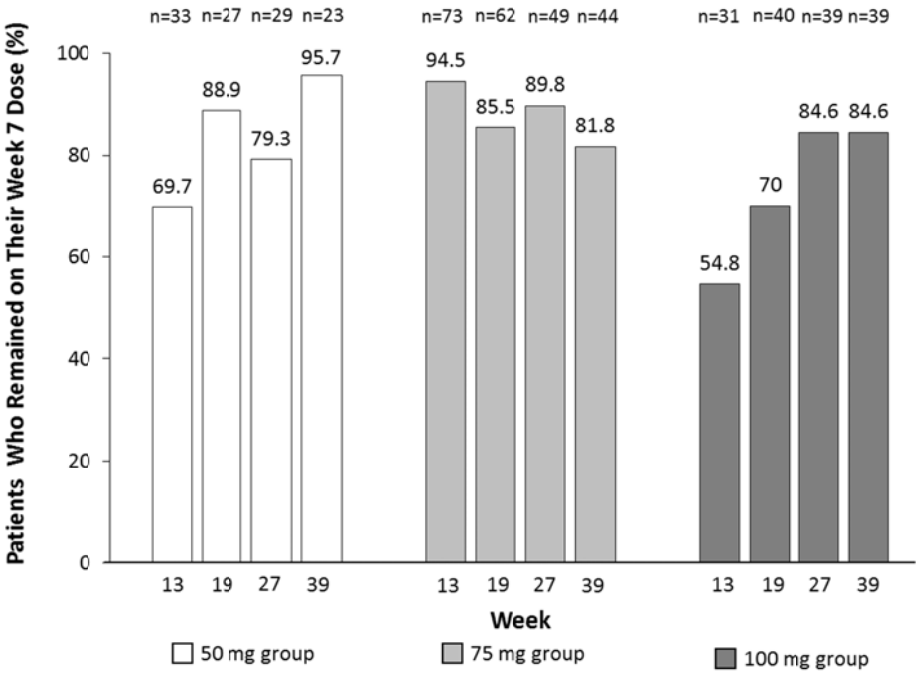
Blood samples were obtained pre-dose and 0.5, 1, 3, 6, 9, 12, 24, 26, 48, 72, and 168 hours post-dose. Error bars are standard deviations. Data are from the pharmacokinetic population.



SHBG, sex hormone–binding globulin

Supplementary Figure 3. SHBG over 52 weeks

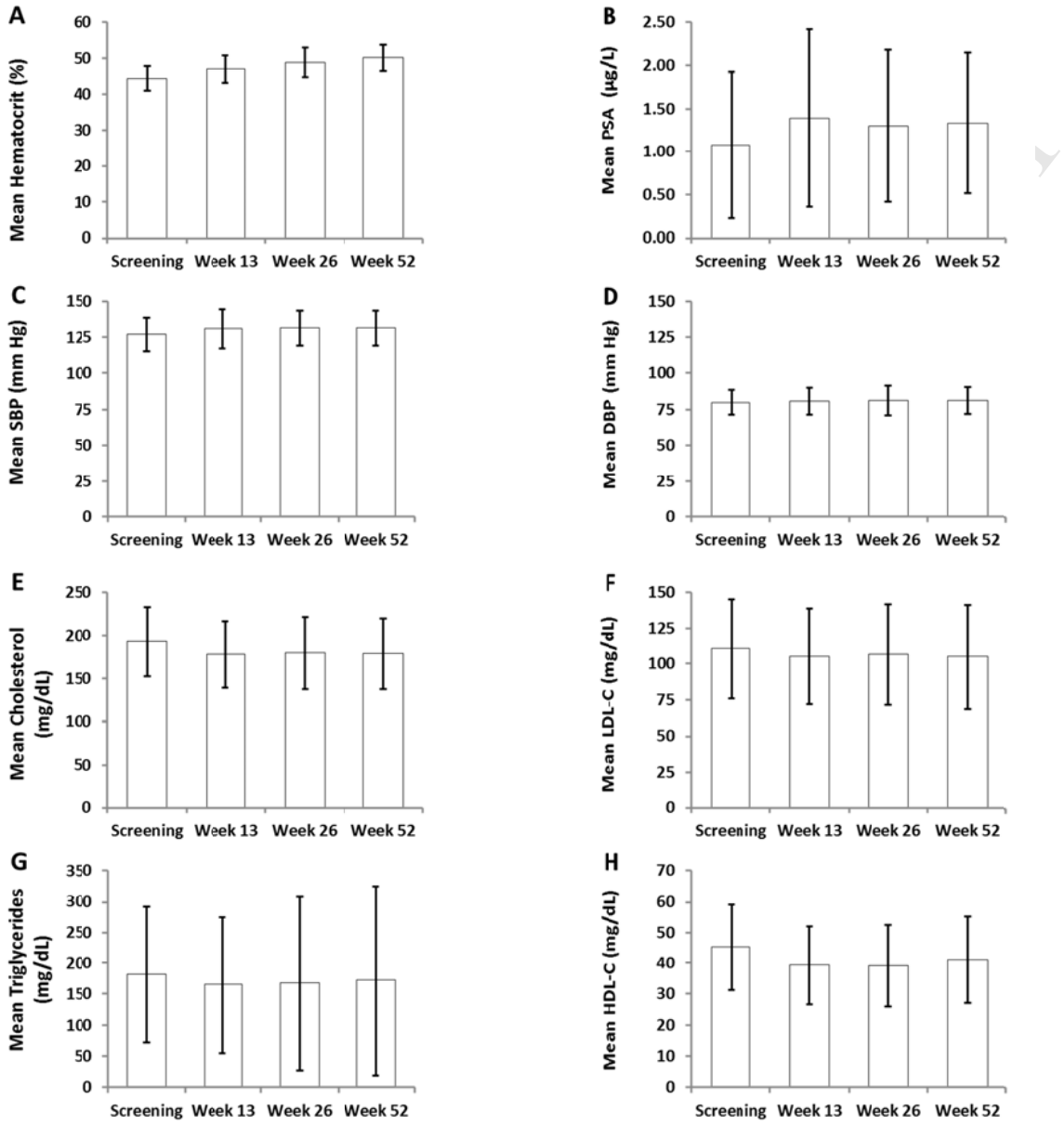
$C_{avg0–168h}$, average concentration over the 7-day dosing interval (0–168 h). Error bars are standard deviations. Data are from the safety population.



SCTE-AI, subcutaneous testosterone enanthate auto-injector.

Supplementary Figure 4. Percent of patients who remained on their week 7 dose

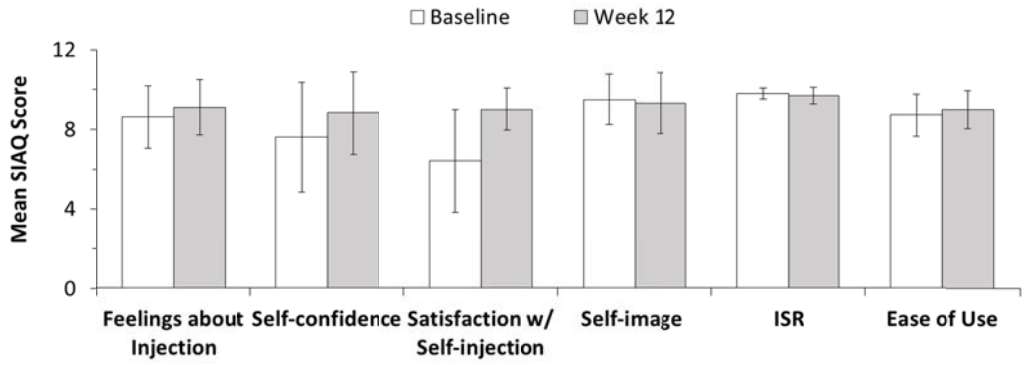
For those patients dose titrated to 50 mg at week 6, 30.3%, 11.1%, 20.7%, and 4.3% increased their dose to 75 mg at weeks 13, 19, 27, and 39, respectively, with no patients receiving 100 mg SCTE-AI at any time point. For those who remained on 75 mg at week 6, 1.4%, 11.3%, 6.1%, and 6.8% reduced their dose to 50 mg at weeks 13, 19, 27, and 39, respectively, and 4.1%, 3.2%, 4.1%, and 11.4% increased their dose to 100 mg at weeks 13, 19, 27, and 39, respectively. For those dose titrated to the 100-mg group at week 6, 45.2%, 30.0%, 15.4%, and 15.4% decreased their dose to 75 mg at weeks 13, 19, 27, and 39, respectively, with no patients receiving 50 mg at any time point. Data are from the safety population.



DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PSA, prostate-specific antigen; SBP, systolic blood pressure.

Supplementary Figure 5. Clinical and laboratory evaluations

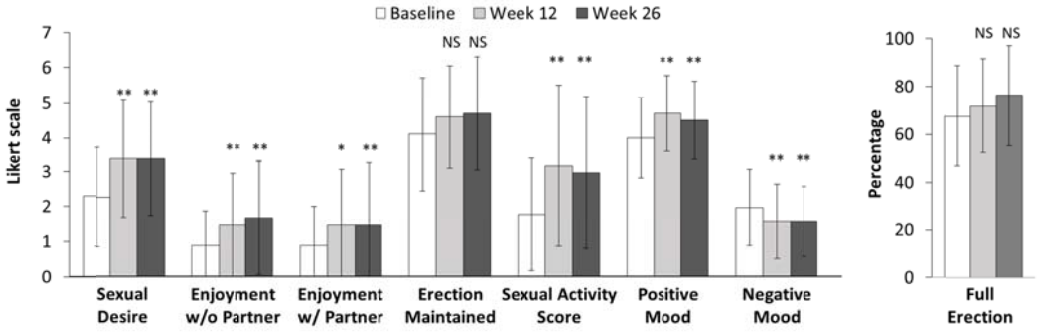
Error bars are standard deviations. Data are from the safety population.



ISR, injection site reactions; SIAQ, Self-Injection Assessment Questionnaire.

Supplementary Figure 6. SIAQ results

For all SIAQ domains, it was prospectively planned that a minimal clinically-important change of 0.5 standard deviations (SDs) would indicate satisfaction. Error bars are standard deviations. Data are from the safety population.



NS, not significant; PDQ, Psychosexual Daily Questionnaire.

**P*=0.0002 compared with baseline.
***P*<0.0001 compared with baseline.

Supplementary Figure 7. PDQ results

Sexual desire and enjoyment were rated on a scale from 0 (none) to 7 (very high). Percent full erection and erection satisfactorily maintained were answered only if the patient experienced an erection. Whether the erection was maintained for a satisfactory duration was rated on a scale from 0 (not satisfactory) to 7 (very satisfactory). Sexual activity was assessed using a checklist format (Yes = 1, No =

0). The composite sexual activity score was the sum of 0–12 items, such as sexual daydreams, orgasm, masturbation, etc. If more than one individual item was missing, the total composite score was set to missing. If one individual item was missing, the composite score was normalized to a 12-point scale. Moods were assessed on a scale from 0 (not at all true) to 7 (very true). Positive mood was the average of the four positive mood scores (alert, full of pep/energy, friendly, and well/good). Negative mood was the average of the five negative mood scores (angry, irritable, sad or blue, tired, and nervous). If more than one individual score was missing, the mood score was set to missing. For all domains, daily scores were averaged to weekly scores. For post-baseline scores, a minimum of five of seven daily scores per week was required, and at least 50% of the daily diary questions must have contained responses for the entry to be considered complete. Error bars represent standard deviations. Error bars are standard deviations. Data are from the safety population.

Supplementary Appendix

Inclusion criteria

1. Men ≥18 years of age with a documented diagnosis of hypogonadism. Past patient medical records included classical signs and symptoms at the time of diagnosis, however, ongoing signs and symptoms were not required or assessed at entry
2. Confirmed biochemical diagnosis of hypogonadism based on qualifying total testosterone (TT) levels. Specifically, per ENDO society Clinical Practice Guidelines,[1] patients were required to have ≥two morning TT values <300 ng/dL during the screening phase, obtained on separate visits spaced not <7 and not >9 days apart
    a. The first TT level was obtained after completion of washout from current testosterone replacement (TR) therapy, if applicable
    b. The washout period was dependent on patient's T therapy at time of screening
        i. Buccal, transdermal, and topical washout was a minimum of 2 weeks from the last application
        ii. Intramuscular washout was a minimum of 4 weeks from last application
        iii. Testopel washout was considered complete at the end of the dosing interval
    c. Patients who were naïve to treatment or who had discontinued T therapy with adequate washout before the initial screen were permitted to proceed to TT visit 1
    d. One repeat TT level was allowed if one of the two morning TT levels was ≥300 ng/dL. The repeat TT was required to be obtained not <7 and not >9 days after the second TT level was obtained
3. Good health as determined by the investigator and based on medical history, physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory tests
4. Agreed to practice effective contraception throughout the duration of the study and for 30 days after receiving the last dose of investigational product (IP)
5. Provided written informed consent and comply with all study requirements and restrictions including the study visit schedule
6. Had access to a reliable Internet connection

Exclusion criteria

1. Allergic or idiosyncratic reaction to sesame seeds, sesame products, or sesame oil
2. History of food anaphylaxis
3. History of intolerance, allergy, or idiosyncratic reaction to testosterone products
4. Body mass index (BMI) ≥40 kg/m^2
5. Hematocrit ≥52% at the initial screening visit
6. History or current evidence of prostate or breast cancer
7. Any malignancy, except for non-melanoma carcinoma of the skin diagnosed or treated within 5 years of the screening date
8. Elevated prostate-specific antigen (PSA) for age: >2.5 ng/mL in men 18–60 years and >4 ng/mL in men ≥61 years
9. Presence of prostate nodule or induration on digital rectal examination

10. Obstructive uropathy of prostatic origin and of a severity that, in the opinion of the investigator, contraindicated the use of testosterone
11. Poorly controlled diabetes. Patients on a stable dose and regimen of antidiabetic medications for at least 4 weeks and with hemoglobin A_{1c} ≤7.5% were permitted
12. New York Heart Association Class III or IV congestive heart failure
13. Myocardial infarction, unstable angina leading to hospitalization, percutaneous coronary intervention, coronary artery bypass graft, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 6 months of screening
14. History or current treatment for thromboembolic disease or use of anti-thromboembolic medications. Use of low-dose aspirin was permitted
15. Patients taking adrenocorticotropic hormone or oral or depot corticosteroids
16. History of severe, untreated sleep apnea
17. History or current evidence of any clinically significant disease or disorder that in the investigator's opinion could be detrimental to the patient or influence the results of the study
18. Positive serology for human immunodeficiency virus or hepatitis C antibodies or hepatitis B surface antigen at screening
19. Current evidence of alcohol or drug abuse
20. Any skin condition in the injection site area that could confound injection site assessments
21. Administration of any other investigational product within 1 month prior to screening or 5 half-lives of the IP (whichever was longer)
22. Use of estrogen, gonadotropin-releasing hormone agonists, or growth hormone within 12 months of screening
23. Use of other androgens (eg, dehydroepiandrosterone [DHEA]), anabolic steroids, other sex hormones, or other substances/medications, including dietary supplements, known to affect the pharmacokinetics of TE. Discontinuation was allowed if the half-life of the substance/medication allowed complete washout (at least 5 half-lives) during the washout phase of screening. DHEA was required to be washed out for a minimum of 4 weeks
24. Scheduled major surgical or dental procedure anticipated to be associated with significant blood loss (≥500 mL) during the study
25. Plasma or blood donation within 56 days or donation of >500 mL within 3 months of screening
26. Unable to understand verbal or written English or any other language in which a certified translation of the informed consent was available

Stopping criteria

Stopping criteria were developed to ensure patient safety. If any of the criteria were met, treatment with subcutaneous TE auto-injector (SCTE-AI) was discontinued and the patient was withdrawn from the study. The stopping criteria were:

1. Increase in PSA ≥1.4 ng/mL above the baseline value at study entry[1]
2. Elevated hematocrit >55% during the treatment titration or extended treatment phases
3. Occurrence of myocardial infarction, new-onset angina, unstable angina, cardiac revascularization (bypass, stenting, or endarterectomy), transient ischemic attack, or cerebrovascular accident
4. Anaphylaxis

5. Increased blood testosterone, defined as patients receiving 50-mg dose of SCTE-AI who required a dose reduction and who had a TT C_{trough} value ≥650 ng/dL

Supplementary Appendix References

1. Bhasin S, Cunningham GR, Hayes FJ et al: Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010; **95:** 2536.