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ORIGINAL ARTICLE

Safety, efficacy, and pharmacokinetics of oral testosterone undecanoate in males with hypogonadism

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Abstract

Background: Testosterone deficiency results from insufficient testosterone production. Testosterone therapy may require dose titration to reach eugonadal serum testosterone concentrations.

Objective: The primary objective was the efficacy of oral testosterone undecanoate (TLANDO; Antares Pharma Inc.) in male patients with documented hypogonadism. Secondary objectives included a comparison of oral testosterone undecanoate safety and quality-of-life assessments to 1.62% topical testosterone gel (AndroGel 1.62%; AbbVie).

Materials and methods: In this phase 3 study, 315 patients were randomized 2:1 to oral testosterone undecanoate or 1.62% topical testosterone gel (NCT02081300). Patients received 225 mg oral testosterone undecanoate twice daily, and doses were adjusted by 75 mg/dose at weeks 4 and 8 based on average serum total testosterone concentration and maximum observed serum concentration. The primary endpoint was the proportion of patients receiving oral testosterone undecanoate with serum total testosterone concentration within the eugonadal reference range (300–1140 ng/dL). Secondary endpoints included the proportion of patients with maximum serum total testosterone concentrations within predetermined limits, safety parameters, and quality-of-life endpoints including the Short Form-36v2 Health Survey, Psychosexual Daily Questionnaire, and International Prostate Symptom Score.

Results: Overall mean ± SD baseline testosterone was 205.7 ± 71.6 ng/dL. For patients receiving oral testosterone undecanoate, 87.4% demonstrated a 24-h average serum total testosterone concentration within the reference range following titration. Oral testosterone undecanoate demonstrated a nominal statistically significantly greater mean change from baseline than 1.62% topical testosterone gel for Short Form-36v2 Health Survey measures of mental health (2.91 vs. -0.10; $p = 0.035$), and mental component summary (3.82 vs. 0.55; $p = 0.009$); and Psychosexual Daily

Questionnaire measure of weekly negative mood (-0.57 vs. -0.20; $p = 0.021$). Safety endpoints were comparable between therapies. No deaths or treatment-related serious adverse events were reported.

Discussion and conclusion: Male patients with hypogonadism receiving oral testosterone undecanoate 225 mg twice daily demonstrated improvements in libido and sexual frequency. Serum testosterone concentrations were within the reference range in 87% of patients without dose titration.

KEYWORDS
hypogonadism, oral testosterone, testosterone therapy, testosterone undecanoate, topical testosterone

1 | INTRODUCTION

Testosterone deficiency is a clinical disorder resulting from either a defect of the testes (primary hypogonadism) or failure of the hypothalamus or pituitary to produce sufficient gonadotropins (secondary hypogonadism).[1–3] Diagnosis of testosterone deficiency requires measurement of two early morning total testosterone levels < 300 ng/dL with associated signs and symptoms (sexual dysfunction, delayed sexual development, loss of body hair, or small testes [< 6 mL]).[2] The prevalence of symptomatic hypogonadism increases with age, and it has been estimated to be between 0.1% and 6% in the United States.[4,5]

Patients with testosterone deficiency who have signs and symptoms such as decreased energy, depressed mood, and reduced sexual desire should be considered for testosterone therapy, which may include intramuscular or subcutaneous injections, transdermal gels and patches, pellet implants, nasal gels, and oral capsules.[2,3] Many of these approved testosterone therapies may require dose titration to reach eugonadal serum testosterone concentrations.[6–8]

Oral administration of natural testosterone is ineffective due to inactivation in the liver via first-pass metabolism. Methyltestosterone was the first testosterone therapy available for oral use, although its use has been limited due to associations with liver toxicity.[9] Esterification of testosterone carbon 17-beta produced testosterone esters, such as testosterone propionate and testosterone enanthate, increasing native injectable testosterone half-life after intramuscular injection of testosterone. Further development resulted in oral testosterone undecanoate (TU) in different formulations, which predominantly circumvents the liver through absorption into the intestinal lymphatic system and avoids hepatic adverse effects seen with 17-alpha-alkyl androgens.[10]

A novel formulation of oral TU (TLANDO; Antares Pharma Inc.) that uses a self-emulsifying drug delivery system has been approved for the treatment of testosterone deficiency without dose adjustment.[11] A phase 3 study of oral TU 225 mg twice daily without dose adjustment demonstrated restoration of serum total testosterone to eugonadal ranges (300–1080 ng/dL) in 80% of men with testosterone deficiency ($N = 95$, NCT03242590).[12]

The goal of the Study of Oral Androgen Replacement (SOAR, NCT02081300) was to report the safety and efficacy endpoints of oral TU. Results of a comparison between oral TU and 1.62% topical testosterone gel for safety and quality-of-life assessments are also reported to affirm previously published findings of oral TU restoring serum total testosterone concentrations in patients with hypogonadism without dose adjustment.

2 | MATERIALS AND METHODS

2.1 | Patient population

Eligible patients included males 18–80 years of age with a diagnosis of documented symptomatic hypogonadism (primary or secondary) by the patient's physicians before age 65 years and confirmed serum total testosterone concentration of < 300 ng/dL based on two consecutive morning blood samples. Patients were either naïve to testosterone or had discontinued testosterone therapy and completed a washout period of 12 weeks after intramuscular testosterone, 4 weeks after topical or buccal testosterone, or 3 weeks after oral testosterone. Patients were excluded from this study if they met any of the following criteria: history of significant sensitivity or allergy to androgens or product excipients; abnormal prostate digital rectal exam; clinically significant abnormal laboratory values including chemistry, hematology, or urinalysis; positive results for hepatitis A, hepatitis B, hepatitis C, or human immunodeficiency virus; history of seizures, gastric surgery, cholecystectomy, vagotomy, bowel resection, or any surgical procedure that might interfere with gastrointestinal motility, pH, or absorption.

2.2 | Study design

SOAR was a multicenter, phase 3, randomized, open-label, active-controlled study of male patients with testosterone deficiency evaluating the efficacy and safety of oral TU. Safety and quality-of-life assessments were compared to 1.62% topical testosterone gel (AndroGel 1.62%; AbbVie). Forty sites in the United States participated

in this study from February 2014 to April 2015. All participants provided informed consent before initiation of any screening or study-specific procedures. All study sites received Institutional Review Board approval, and research was carried out in compliance with the Declaration of Helsinki as currently amended and consistent with Good Clinical Practices. This study was registered at ClinicalTrials.gov: NCT02081300.

Patients underwent screening to complete pre-study evaluations and to confirm hypogonadism, and those receiving testosterone therapy underwent a washout period before screening (Figure 1). Patients meeting eligibility criteria were enrolled and randomized 2:1 to either oral TU or 1.62% topical testosterone gel for 52 weeks. All patients receiving oral TU were administered 225 mg twice daily approximately 12 h apart with food. At weeks 4 and 8, doses were increased by 75 mg/dose if 24-h average serum total testosterone concentration ($C_{avg0\text{-}24\,h}$) < 300 ng/dL and decreased by 75 mg/dose if $C_{avg0\text{-}24\,h}$ > 1140 ng/dL or maximum observed serum concentration (C_{max}) > 1500 ng/dL regardless of $C_{avg0\text{-}24\,h}$.

All patients receiving testosterone gel received 40.5 mg (two pump actuations) applied topically to the shoulders and upper arms once daily in the morning. Dose titration was based on a single serum total testosterone concentration measured in a morning blood sample obtained before 1.62% topical testosterone gel administration on weeks 2 and 4. Doses were decreased by 20.25 mg (one pump actuation) for patients with serum total testosterone concentration > 750 ng/dL and increased by 20.25 mg (one pump actuation) for those with serum total testosterone concentration < 350 ng/dL.

2.3 | Primary and secondary endpoints

The following data sets were analyzed in this study:

- Safety set: All patients who received at least one dose of study drug (n = 314). Patients were analyzed according to the treatment they received
- Full analysis set: All patients who received oral TU with at least one postbaseline efficacy variable response (n = 193)
- Efficacy population set: All patients in the full analysis set who did not have major protocol deviations (n = 151). Forty-two patients from the full analysis set were not included in the efficacy population set because they had at least one major protocol deviation. Major protocol deviations for patients receiving oral TU were generally related to dosing and included noncompliance with dosing regimen or incorrect dose titration
- Pharmacokinetics (PK) set: All patients in the full analysis set who did not have major protocol deviations that affected the PK analysis and had sufficient and interpretable PK data (n = 130)

The primary endpoint was the proportion of patients receiving oral TU that achieved a 24-h average serum total testosterone concentration within the predefined lab normal references range (300–1140 ng/dL) after approximately 13 weeks, with a target minimum acceptable percentage of 75% of patients achieving this testosterone concentration. A 95%, 2-sided binomial confidence interval (CI) surrounding the point estimate required a lower bound of ≥65% to conclude efficacy. Only patients receiving oral TU were used for the primary efficacy analysis at the recommendation of the US Food and Drug Administration (FDA).

Secondary endpoints included the proportion of patients receiving oral TU with maximum serum total testosterone concentrations ($C_{max0\text{-}24\,h}$, $C_{max0\text{-}12\,h}$, or $C_{max12\text{-}24\,h}$) within predetermined limits after approximately 13 weeks. Limits included the following: < 1500 ng/dL in ≥85% of all patients, 1800–2500 ng/dL in ≤5% of patients, and ≤2500 ng/dL in all patients. Safety endpoints included the incidence of adverse events (AEs); physical examination results; clinical laboratory test results; and changes in hematocrit (HCT), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, plasma lipoprotein-associated phospholipase A2, serum transaminases, and prostate-specific antigen (PSA). Any untoward medical occurrence in patients was considered an AE. Any AE resulting in conditions including the following were considered serious adverse events (SAE): death, life-threatening condition, hospitalization, or persistent disability. Cases of Hy's Law were defined as a ≥3-fold increase above the upper limit of normal in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) plus total bilirubin increases > 2-fold above the upper limit of normal without cholestasis and no other justification for the combined increase in liver enzymes and total bilirubin. These secondary endpoints were evaluated throughout the study on all patients based on AE reports, clinical laboratory data, electrocardiogram parameters, physical examinations, and vital sign measurements. A non-prespecified post hoc analysis was conducted comparing androgen-mediated laboratory parameters and serum total testosterone, free testosterone, and DHT concentrations at week 52 for patients who received oral TU or 1.62% topical testosterone gel. Patients were also evaluated for patient-reported outcomes (PROs) according to the Short Form-36v2 (SF-36), Psychosexual Daily Questionnaire (PDQ), and International Prostate Symptom Score (I-PSS).

Clinical laboratory tests including hematology, clinical chemistry, and urinalysis analytes were evaluated. A laboratory test value that required a patient to be discontinued from the study or to receive treatment was recorded as an AE. Blood and urine samples for clinical laboratory tests were collected for all patients at screening and weeks 7, 13, 26, 39, and 52. Samples for clinical laboratory tests were collected in the morning before meals and treatment administration. Laboratory tests were performed by Pharmaceutical Product Development Central Labs. To minimize the incidence of excessive HCT increases, patients with HCT > 54% were discontinued from the study.

Intensive PK sampling was only performed for patients receiving oral TU. Blood samples for PK analyses of testosterone and dihydrotestosterone (DHT) were collected from patients receiving oral TU at 0 (before the morning dose), 2, 3, 4, 5, 6, 8, 12 (before evening dose), 14, 15, 16, 17, 18, 20, and 24 h after the morning dose at weeks 3, 7, and 13. Approximately 384 mL of blood was collected for PK samples from patients receiving oral TU. A single blood sample

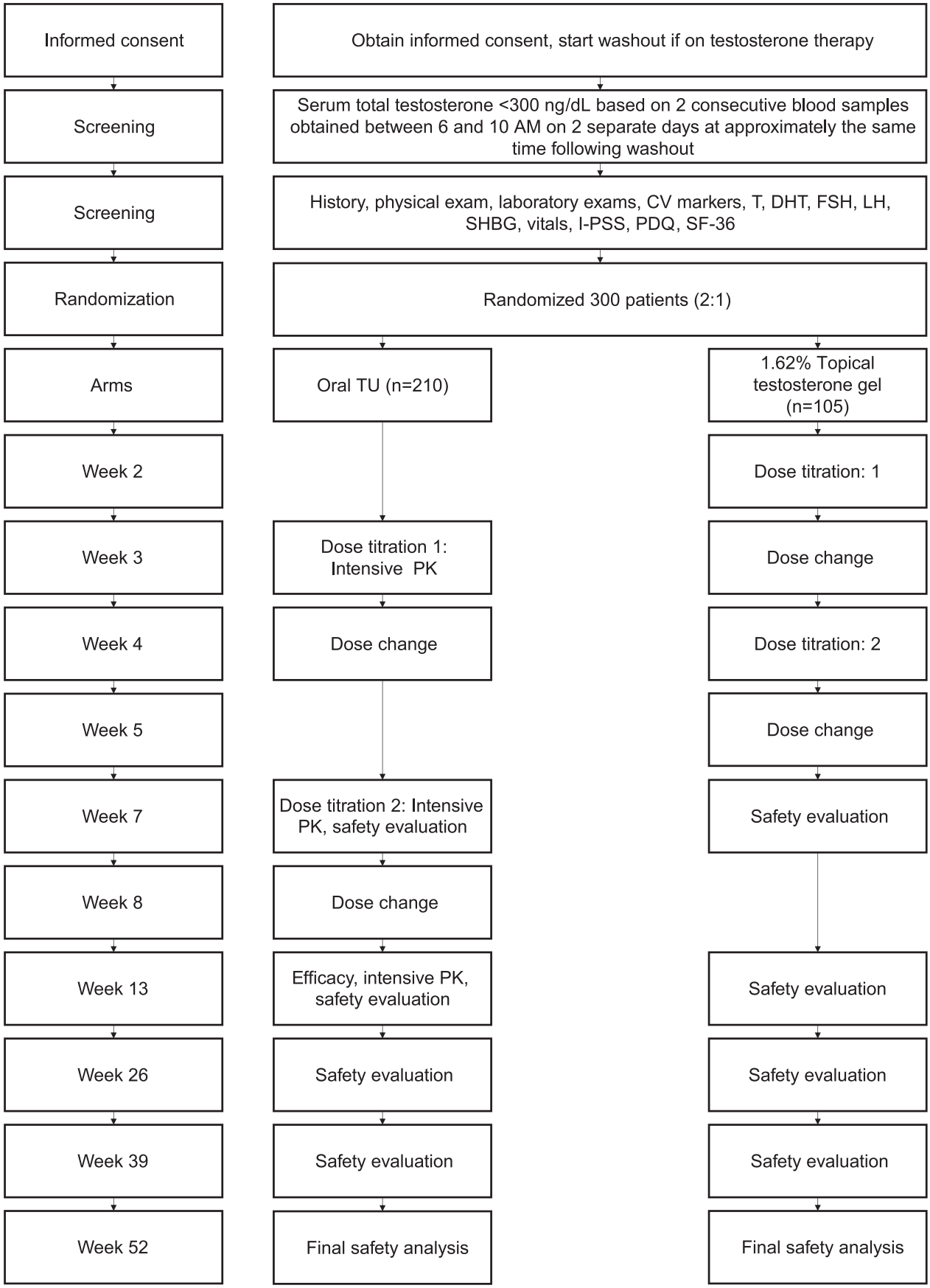

FIGURE 1 Study design. CV, cardiovascular; DHT, dihydrotestosterone; FSH, follicle stimulating hormone; I-PSS, International Prostate Symptom Score; LH, luteinizing hormone; PDQ, Psychosexual Daily Questionnaire; PK, pharmacokinetics; SF-36, Short Form-36v2 Health Survey; SHBG, sex hormone-binding globulin; T, testosterone; TU, testosterone undecanoate.

for the assay of testosterone and DHT was collected between 3 and 6 h after the morning dose at week 26, week 39, and week 52 or Early Termination for both oral TU and 1.62% topical testosterone gel groups. Serum total testosterone and serum DHT were determined using serum from whole blood samples and analyzed using a validated liquid chromatography-tandem mass spectrometry assay at the Pharmaceutical Product Development Bioanalytical Lab. These methods were validated for linearity, precision, accuracy, recovery, and specificity, and validations were adequate for the analysis of serum samples in this study. Analysis of these samples followed principles of Good Laboratory Practice. Free testosterone was calculated based on Vermeulen et al: free testosterone = total testosterone (1/[1 + KSHBG × SHBG + n*KALB × ALB]), where KSHBG is the association constant for binding to SHBG; n*KALB is the product of the number of binding sites per molecule and the association constant for albumin; and plasma albumin and SHBG values for each patient were used.[13]

Changes in sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were evaluated from baseline to weeks 7, 13, 26, 39, and 52.

2.4 | Statistical methods

The sample size for this study was based on the incidence and lower bound of the binomial CI for the 24-h average serum total testosterone concentration within the normal range (300–1140 ng/dL). Assuming the primary efficacy endpoint was achieved (≥75% of patients had testosterone concentrations within the reference range for adult men), the sample size of 200 patients exceeded the number needed to result in the lower bound of a 95%, 2-sided, binomial CI being no less than 65%. For analysis of PROs, *p* values were calculated using two-sample *t*-tests comparing change from baseline to end of study across patients receiving oral TU and 1.62% topical testosterone gel, and nominal *p* values were reported to account for multiple comparisons. For the non-prespecified post hoc analysis of androgen-mediated laboratory parameters and concentrations of serum testosterone, free testosterone, and DHT concentrations, *p* values were calculated using a two-sample *t*-test ($\alpha = 0.05$) comparing mean change from baseline for laboratory parameters and week 52 serum testosterone, free testosterone, and DHT concentrations between patients receiving oral TU and 1.62% topical testosterone gel; however, this analysis did not account for multiple comparisons.

3 | RESULTS

3.1 | Patient population

Of 326 patients enrolled in this study, 315 patients were randomized, of which 210 patients were randomized to oral TU, and 105 patients were randomized to 1.62% topical testosterone gel. One patient randomized to 1.62% topical testosterone gel did not receive treatment; therefore, 210 patients received oral TU, and 104 patients received 1.62% topical testosterone gel. Overall, 130 (62%) patients receiving oral TU and 71 (68%) patients receiving 1.62% topical testosterone gel completed the study. Early discontinuation rates were 38% (80/210) for patients randomized to oral TU and 32% (34/105) for patients randomized to 1.62% topical testosterone gel. Most patients who discontinued early did so due to withdrawal of consent (38/114) or loss to follow-up (25/114).

Baseline characteristics and demographics are in Table 1 and reported from all randomized patients unless otherwise specified. Overall, the mean age was 53 years, and the mean body mass index (BMI) was 31 kg/m^2. Baseline characteristics between treatment groups were similar, although more patients who received oral TU than 1.62% topical testosterone gel were considered obese (64% vs. 56%). The overall mean ± SD baseline testosterone level (205.7 ± 71.6 ng/dL) was below the normal male range in the safety set ($n = 314$).

In the full analysis set ($n = 193$), more patients had their dose of oral TU titrated only at week 4 (31.6% [61/193]) than only at week 8 (17.1% [33/193]). Oral TU doses were never titrated in 43.5% (84/193) of patients, and oral TU 225 mg BID was the last dose received in 51.8% (100/193) of patients. Dose distribution analysis demonstrated that the most common oral TU dose at weeks 3, 7, and 13 was 225 mg.

3.2 | Primary and secondary endpoints

For the efficacy population set ($n = 151$), 87.4% (95% CI, 81.7%–92.7%) of patients receiving oral TU demonstrated a 24-h average serum total testosterone concentration within the lab male reference range (300–1140 ng/dL) at week 13, which met the prespecified target of ≥75% of patients achieving a testosterone concentration within the adult male range. The lower bound of the CI was 81.7%, which met the prespecified target of ≥65% of patients achieving the adult male testosterone concentration range. Additional sensitivity analyses demonstrated that the primary efficacy endpoint was not sensitive to major protocol deviations.

The secondary efficacy endpoint target (≥85%) of the proportion of patients in the efficacy population set ($n = 151$) with $C_{max} < 1500$ ng/dL was met for $C_{max0\text{-}12\,h}$ (89.4%) and $C_{max12\text{-}24\,h}$ (89.4%), although $C_{max0\text{-}24\,h}$ resulted in proportions that were below the target (82.8%). The proportion of patients with C_{max} 1800–2500 ng/dL met the target (≤5%) for all three measures ($C_{max0\text{-}24\,h}$, 4.6%; $C_{max0\text{-}12\,h}$, 2.6%; $C_{max12\text{-}24\,h}$, 2.0%). Overall, all three measures had a small proportion of patients with $C_{max} > 2500$ ng/dL ($C_{max0\text{-}24\,h}$, 2.0%; $C_{max0\text{-}12\,h}$, 2.0%; $C_{max12\text{-}24\,h}$, 0.7%).

3.3 | Pharmacokinetics

Figure 2 displays mean serum concentrations of testosterone (Figure 2A) and DHT (Figure 2B) at weeks 3, 7, and 13 versus time for the PK set ($n = 130$). Mean serum concentrations of testosterone

TABLE 1 Baseline characteristics and demographics.

Parameter	Oral TU ($n = 210$)	1.62% topical testosterone gel ($n = 105$)	Overall ($N = 315$)
Age, years, mean (SD)	52.6 (10.2)	54.2 (9.4)	53.1 (10.0)
Race, *n* (%)			
Asian	3 (1)	3 (3)	6 (2)
Black or African American	32 (15)	10 (10)	42 (13)
White	172 (82)	92 (88)	264 (84)
Other	3 (1)	0 (0)	3 (1)
Ethnicity, *n* (%)			
Hispanic or Latino	44 (21)	22 (21)	66 (21)
Not Hispanic or Latino	166 (79)	83 (79)	249 (79)
BMI, kg/m^2, mean (SD)	30.8 (3.9)	31.0 (3.9)	30.9 (3.9)
<25 kg/m^2, n (%)	12 (5.7)	5 (4.8)	17 (5.4)
≥25 and < 30 kg/m^2, *n* (%)	80 (38.1)	33 (31.4)	113 (35.9)
≥30 kg/m^2, *n* (%)	118 (56.2)	67 (63.8)	185 (58.7)
Baseline serum T, ng/dL, mean (SD)	208.6 (71.1)	199.9 (72.6)	205.7 (71.6)
Comorbidities, *n* (%)			
Diabetes	46 (22)	36 (34)	82 (26)
Lipid metabolism disorder	98 (47)	51 (49)	149 (47)
Cardiovascular disorder	111 (53)	53 (50)	164 (52)

Baseline serum total testosterone, as well as the number of patients with diabetes, cardiovascular disorder, and lipid metabolism disorder, are reported from the safety set ($n = 314$). All other values report results from all randomized patients ($N = 315$).
Abbreviations: BMI, body mass index; DHT, dihydrotestosterone; T, testosterone; TU, testosterone undecanoate.

were increased > 300 ng/dL within 2 h of each oral TU dose, reached peak concentration approximately 4–6 h after dosing, and declined to predose levels after approximately 12 h.

At week 3, before dose titration, patients in the PK set ($n = 130$) receiving oral TU demonstrated mean ± SD serum total testosterone $C_{avg0\text{-}24\,h}$ and $C_{max0\text{-}24\,h}$ values of 494.3 ± 192.6 and 1306.4 ± 652.2 ng/dL, respectively. At week 13, after dose titration, these patients demonstrated mean ± SD serum total testosterone $C_{avg0\text{-}24\,h}$ and $C_{max0\text{-}24\,h}$ values of 446.4 ± 171.5 and 1134.1 ± 526.2 ng/dL, respectively.

Concentrations of serum total testosterone, free testosterone, and DHT are reported in Figure 3A–C, respectively, at baseline and week 52 for both treatment groups. Mean ± SD serum total testosterone levels for oral TU (full analysis set, $n = 193$) and 1.62% topical testosterone gel (safety set, $n = 314$) remained within the adult male testosterone concentration range at week 26 (481.3 ± 371.2 [$n = 143$] vs. 596.4 ± 600.7 ng/dL [$n = 80$]), week 39 (543.2 ± 438.2 [$n = 137$] vs. 466.1 ± 277.8 ng/dL [$n = 74$]), and week 52 (538.5 ± 545.4 [$n = 143$] vs. 456.8 ± 255.6 ng/dL [$n = 77$]).

3.4 | Androgen-mediated laboratory parameters

The mean baseline and change from baseline for laboratory parameters commonly influenced by androgens for the safety set ($n = 314$) have been reported in Table 2. Mean HCT values at week 52 were comparable between patients receiving oral TU and 1.62% topical testosterone gel. Overall, HCT values ranged from 32% to 55% and demonstrated a mean ± SD change from baseline of 2.6% ± 3.4%.

All patients exhibited a mean ± SD decrease in HDL (−0.12 ± 0.22 mmol/L), LDL (−0.08 ± 0.71 mmol/L), and triglycerides (−0.16 ± 1.06 mmol/L) at week 52. Patients receiving oral TU demonstrated a greater mean ± SD decrease at week 52 in HDL (−0.15 ± 0.21 mmol/L) than those receiving 1.62% topical testosterone gel (−0.05 ± 0.23 mmol/L). Patients receiving 1.62% topical testosterone gel demonstrated a greater mean ± SD decrease at week 52 in LDL (−0.21 ± 0.74 mmol/L) than those receiving oral TU (−0.01 ± 0.68 mmol/L). Mean ± SD increases in PSA from baseline to week 52 were observed overall (0.21 ± 0.38 µg/L), and changes were similar between treatment groups. Patients receiving oral TU demonstrated a mean ± SD decrease in SHBG from baseline compared to an SHBG increase demonstrated with 1.62% topical testosterone gel (−8.91 ± 9.74 vs. 2.39 ± 7.91 nmol/L). Patients receiving oral TU and 1.62% topical testosterone gel both experienced mean decreases from baseline in FSH (−4.9 ± 9.5 vs. −3.9 ± 5.1 IU/L) and LH (−3.7 ± 7.2 vs. −2.9 ± 2.6 IU/L). For patients receiving oral TU and 1.62% topical testosterone gel, respectively, final mean ± SD (range) FSH values at week 52 were 3.97 ± 9.25 (0.15–84.90) versus 3.08 ± 4.44 (0.15–30.00) IU/L, and LH values were 2.35 ± 4.48 (0.05–37.00) versus 1.59 ± 2.42 (0.05–11.80) IU/L.

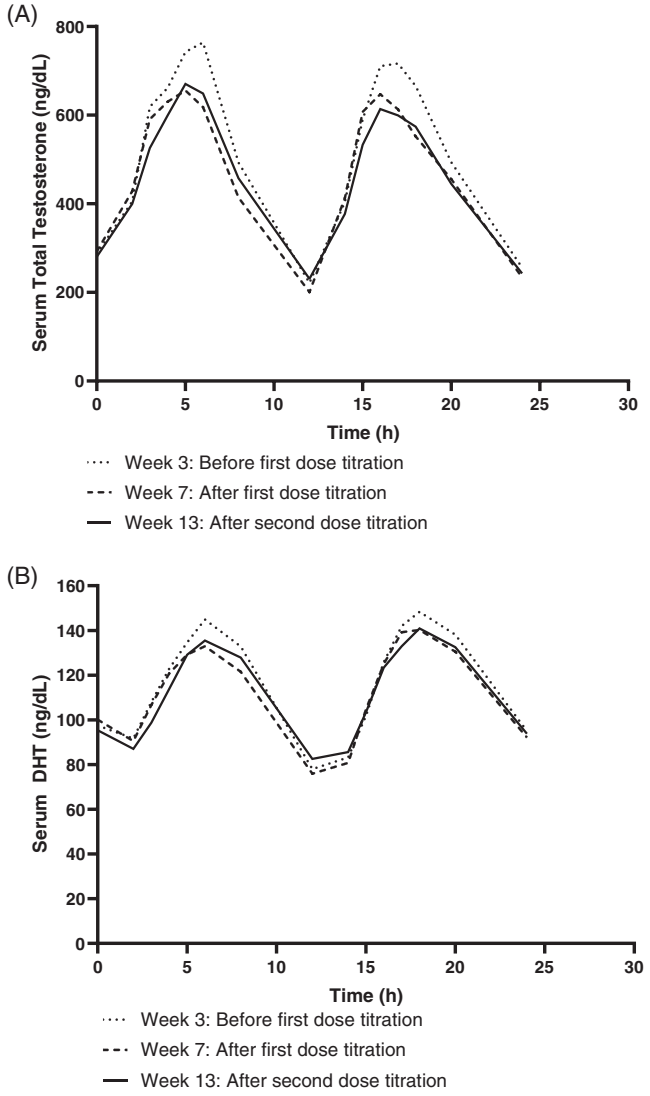

FIGURE 2 Mean (± SEM) serum total testosterone (A) and DHT (B) concentrations after 225 mg of Oral TU from 0 to 24 h at weeks 3, 7, and 13 in men with hypogonadism ($n = 130$). DHT, dihydrotestosterone; TU, testosterone undecanoate.

Both treatment groups demonstrated a decrease in ALT, AST, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) from baseline at week 52. No known cases of Hy's Law were observed.

3.5 | Patient-reported outcomes

Overall, patients in the safety set ($n = 314$) receiving oral TU and 1.62% topical testosterone gel exhibited improvements in SF-36 (Figure 4) and PDQ (Figure 5) PRO measures. For SF-36, oral TU demonstrated a nominal statistically significantly greater mean change from baseline than 1.62% topical testosterone gel for measures of mental component summary (3.82 vs. 0.55; $p = 0.009$) and mental health (2.91 vs. −0.10; $p = 0.035$), and numerically greater mean changes from baseline in vitality (6.89 vs. 3.82), social role functioning (2.17 vs. 0.64), emotional

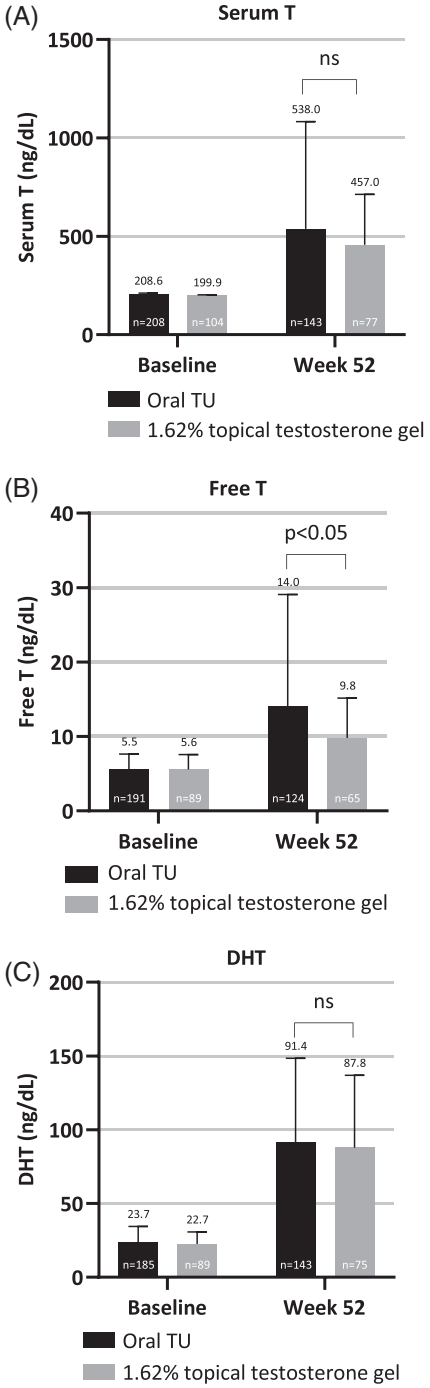

FIGURE 3 Serum total testosterone (A), free testosterone (B), and DHT concentrations (C) at baseline and week 52. For serum testosterone, n = number of patients receiving oral TU in the safety set at baseline ($n = 210$) and in the full analysis set ($n = 193$) at week 52; number of patients receiving 1.62% topical testosterone gel in the safety set ($n = 104$) at baseline and week 52. For free testosterone and DHT, n = number of patients receiving oral TU ($n = 210$) and 1.62% topical testosterone gel ($n = 104$) in the safety set at baseline and week 52. Baseline oral TU and 1.62% topical testosterone gel values were obtained in the morning between 6 and 10 AM before the dose. Week 52 oral TU and 1.62% topical testosterone gel values were obtained from a single blood draw 3–6 h after dose. Associated p values were not adjusted for multiplicity. DHT, dihydrotestosterone; NS, not significant; TU, testosterone undecanoate.

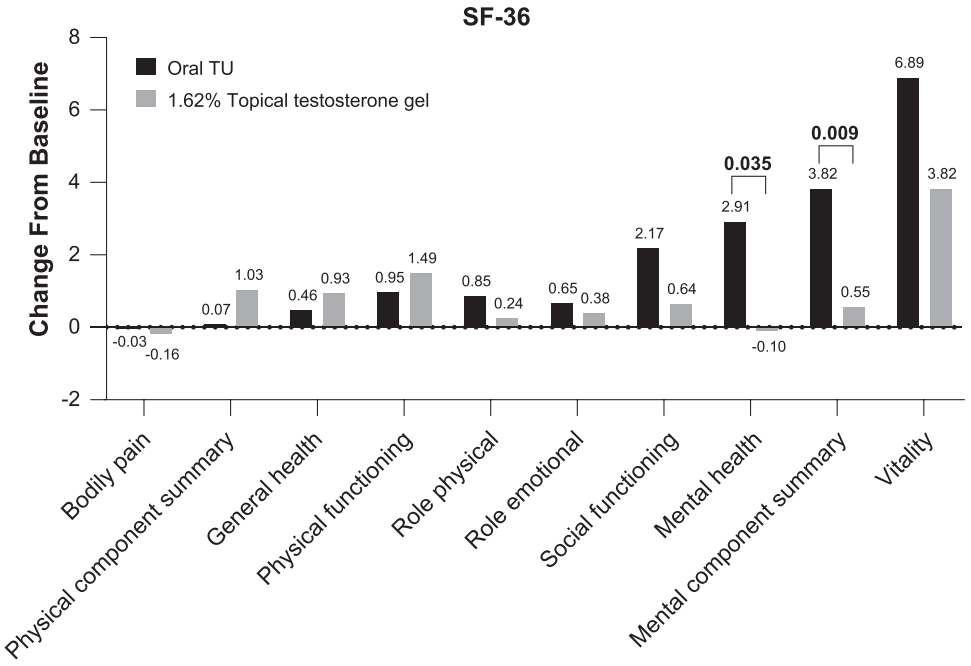

FIGURE 4 Mean change from baseline in SF-36 domains for oral TU and topical testosterone gel in the safety set ($n = 314$). The p values were calculated using a 2-sample t-test comparing change from baseline to end of study across patients receiving oral TU and 1.62% topical testosterone gel. SF-36, Short Form-36v2; TU, testosterone undecanoate.

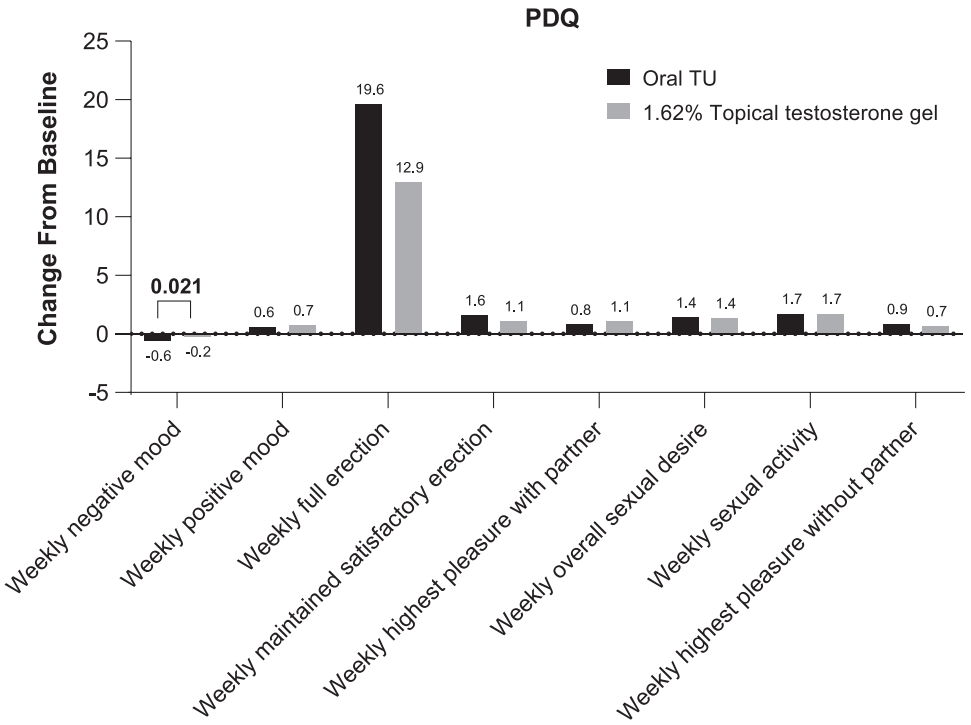

FIGURE 5 Mean change from baseline in PDQ domains for oral testosterone undecanoate and topical testosterone gel in the safety set ($n = 314$). The p values were calculated using a 2-sample t-test comparing change from baseline to end of study across patients receiving oral TU and 1.62% topical testosterone gel. NS, not significant; PDQ, Psychosexual Daily Questionnaire; TU, testosterone undecanoate.

TABLE 2 Change from baseline in androgen-mediated laboratory parameters in the safety set ($n = 314$).

Parameter	Oral TU	1.62% topical testosterone gel	*p* Value
HCT, %			
n	206	103	
Baseline	43.5 (3.2)	44.0 (3.4)	
Mean change from baseline	2.9 (3.5)	2.2 (3.4)	NS
HDL, mmol/L			
n	207	104	
Baseline	1.3 (0.3)	1.2 (0.3)	
Mean change from baseline	−0.2 (0.2)	−0.1 (0.2)	<0.05
LDL, mmol/L			
n	194	97	
Baseline	2.9 (0.8)	2.9 (0.9)	
Mean change from baseline	−0.01 (0.7)	−0.2 (0.7)	<0.05
PSA, µg/L			
n	208	104	
Baseline	0.7 (0.5)	0.6 (0.4)	
Mean change from baseline	0.2 (0.4)	0.2 (0.2)	NS
SHBG, nmol/L			
n	204	99	
Baseline	30.3 (15.0)	30.4 (11.8)	
Mean change from baseline	−8.9 (9.7)	2.4 (7.9)	<0.05
LH, IU/L			
n	207	104	
Baseline	5.8 (7.3)	4.8 (4.4)	
Mean change from baseline	−3.8 (7.2)	−3.0 (2.6)	NS
FSH, IU/L			
n	207	104	
Baseline	8.4 (10.3)	7.2 (7.6)	
Mean change from baseline	−4.9 (9.5)	−3.9 (5.1)	NS

Data are given as mean (SD) unless otherwise noted. *n* values report the number of patients with data available.
All parameters report mean change from baseline to week 52.
Associated *p* values were not adjusted for multiplicity.
Abbreviations: FSH, follicle-stimulating hormone; HCT, hematocrit; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; NS, not significant; PSA, prostate-specific antigen; SHBG, sex hormone-binding globulin; TU, testosterone undecanoate.

role functioning (0.65 vs. 0.38), and physical role functioning (0.85 vs. 0.24). For PDQ, oral TU showed a nominal statistically significantly greater mean change from baseline than 1.62% topical testosterone gel for measures of negative mood (−0.57 vs. −0.20; $p = 0.021$) and a numerically greater mean change from baseline in highest pleasure without a partner (0.85 vs. 0.65), sexual activity (1.72 vs. 1.71), overall sexual desire (1.38 vs. 1.35), maintained satisfactory erection (1.59 vs. 1.09), and full erection (19.62 vs. 12.93). Oral TU demonstrated a smaller change from baseline in I-PSS total symptom score than 1.62% topical testosterone gel (1.0 vs. 2.3; Table 3).

TABLE 3 Mean change from baseline in I-PSS for oral TU and topical testosterone gel in the safety set ($n = 314$).

Parameter	Oral TU ($n = 210$)	1.62% topical testosterone gel ($n = 104$)	Overall ($n = 314$)
I-PSS total score			
Baseline	5.6 (4.8)	4.6 (3.9)	5.3 (4.6)
Mean change from baseline	1.0 (4.2)	2.3 (5.1)	1.4 (4.5)

Data are given as mean (SD) unless otherwise noted.
Abbreviation: I-PSS, International Prostate Symptom Score; TU, testosterone undecanoate.

TABLE 4 Treatment-related adverse events in ≥1% of patients in the safety set ($n = 314$).

Preferred Term, *n* (%)	Oral TU ($n = 210$)	1.62% topical testosterone gel ($n = 104$)	Overall ($n = 314$)
Acne	6 (2.9)	3 (2.9)	9 (2.9)
Headache	1 (0.5)	4 (3.8)	5 (1.6)
Weight increased	5 (2.4)	0	5 (1.6)
HCT increased	4 (1.9)	0	4 (1.3)
LP-PLA2 increased	3 (1.4)	0	3 (1.0)
Fatigue	1 (0.5)	2 (1.9)	3 (1.0)
Hypertension	1 (0.5)	2 (1.9)	3 (1.0)

Abbreviations: HCT, hematocrit; LP-PLA2, lipoprotein-associated phospholipase A2; TU, testosterone undecanoate.

3.6 | Safety

Overall, in the safety set, 67% (210/314) of patients experienced ≥1 treatment-emergent AE (TEAE). A total of 14 patients experienced treatment-emergent SAE during the study. Overall, the treatment-emergent SAEs were most frequently categorized as infections and infestations (four patients, 1.3%) and musculoskeletal and connective tissue disorders (three patients, 1.0%). Sixteen patients experienced 27 severe TEAEs, but none of these were determined by investigators to be treatment-related. The incidence of treatment-related TEAEs was similar between patients receiving oral TU compared to 1.62% topical testosterone gel (24.3% [51/210] vs. 22.1% [23/104]). Frequently reported treatment-related TEAEs for patients receiving oral TU were acne (6 [2.9%]), weight increase (5 [2.4%]), and HCT increase (4 [1.9%]; Table 4). Treatment-related TEAEs led to discontinuation in 11 (5.2%) patients receiving oral TU and three (2.9%) patients receiving 1.62% topical testosterone gel. All treatment-related TEAEs of HCT level increases occurred in patients receiving oral TU. Two patients receiving oral TU and one patient receiving 1.62% topical testosterone gel were

discontinued for having HCT > 54%. No patients experienced any serious cardiovascular TEAEs. Throughout this study, treatment-related AEs of hypertension occurred in one patient receiving oral TU and two patients receiving 1.62% topical testosterone gel, although no clinically meaningful trends in systolic or diastolic blood pressure change were demonstrated among patients receiving either treatment. No deaths or treatment-related serious AEs were reported during this study.

4 | DISCUSSION

In this study, 87% of patients receiving oral TU 225 mg twice daily demonstrated serum testosterone concentration within the adult male reference range (300-1140 ng/dL) at week 13, which met the primary efficacy endpoint definition of ≥75% of patients achieving the adult male testosterone concentration range. The percentage of patients with C_{max} < 1500 ng/dL generally met the targeted proportion (≥85%). At the recommendation of the FDA, only oral TU was included in the full analysis set, which was used for primary analysis. Therefore, a comparison of the percentage of patients reaching the adult male testosterone concentration range at week 13 was not completed for oral TU and 1.62% topical testosterone gel. Eligible patients included those with documented hypogonadism as determined by the patient's physicians, and no information on patient symptomatology resulting from testosterone deficiency is available. The incidence of treatment-related TEAEs was similar between patients receiving oral TU (24.3%) and 1.62% topical testosterone gel (22.1%), suggesting comparable safety. Furthermore, oral TU was not associated with clinically significant liver enzyme elevations, supporting findings that oral administration does not have clinically relevant adverse liver effects.[14]

Mean serum total testosterone concentrations before dose titration at week 3 were similar to concentrations after dose titration at week 13, affirming the currently recommended dosing of oral TU 225 mg twice daily without dose adjustment. Within 2 h of the oral TU morning dose, mean serum total testosterone concentrations increased above the lower threshold. Concentrations peaked approximately 4–6 h later and returned to predose concentrations after approximately 12 h. This concentration pattern was repeated following the evening dose. Endogenous serum total testosterone exhibits diurnal variation in healthy individuals, but this diurnal pattern is not seen in men with hypogonadism.[15] Additional research on the importance of diurnal endogenous testosterone variation is necessary to determine the clinical impact of circadian timing on testosterone concentrations. Furthermore, this population overall demonstrated an elevated average BMI (> 30 kg/m^2). Patients with elevated BMI have been shown to require higher doses of testosterone to achieve physiological total testosterone levels compared to patients with lower BMIs,[16] which suggests that the elevated average BMI in this study may have impacted PK results. Additional analyses on the effect of BMI on oral TU dosing are necessary to explore this further.

Despite being unable to compare oral TU and 1.62% topical testosterone gel for the primary endpoint, both therapies demonstrated mean serum total testosterone levels that remained within the adult male testosterone concentration range through week 52. This study reports the results of oral TU following dose titration, although this treatment was approved for administration without dose titration. PK findings for patients receiving oral TU demonstrated similar $C_{avg0\text{-}24\,h}$ and $C_{max0\text{-}24\,h}$ values before and after dose titration, and the most common oral TU dose at weeks 3, 7, and 13 was 225 mg. Furthermore, almost half (43.5%) of patients receiving oral TU never underwent dose titration. These results support the currently approved dose of 225 mg twice daily.

The PK properties of oral TU described here suggest elements that may be beneficial for patient adherence and ease of administration. Testosterone dosing titrations can be complex, and a fixed-dose formulation offers a simple schedule for both patients and physicians.[7,8,17] Peak concentrations within 4–6 h and a return to predose concentrations within 12 h allow patients to stop treatment quickly, which may be helpful if patients are trialing different routes of testosterone administration. Oral testosterone administration also avoids possible secondary transference with gels and needle injection with intramuscular or subcutaneous formulations. Oral TU is a lipophilic molecule transported by chylomicrons into the lymph system following administration. Chylomicrons are formed in response to lipid ingestion to facilitate the transport of lipophilic molecules.[18] Therefore, it is recommended that oral TU be taken with meals. However, a food effect study of oral TU showed mean testosterone C_{max} and AUC were bioequivalent following administration with low-, moderate-, or high-fat meals.[19] While oral TU should be administered with meals, there is currently no evidence to support increased absorption with greater meal fat content. This fixed-dose regimen and lack of concern for meal fat content during oral TU administration may be beneficial for patient compliance. A formulation of oral TU that uses a dose-adjustment strategy (JATENZO) has also been approved for adult males with testosterone deficiency.[8,20]

Increased HCT is a known effect of testosterone therapy, which may increase a patient's risk for thromboembolic events.[2,21,22] A network meta-analysis evaluating mean HCT change after various testosterone therapies, including gel and oral TU, demonstrated that all formulations led to a statistically significant increase in mean HCT compared to placebo.[23] Despite this, no formulation resulted in a pooled mean HCT increase > 4.3%, suggesting that the risk of thromboembolic events due to testosterone therapy may be mitigated by close monitoring and informed patient selection. Concerns about cardiovascular risk with testosterone therapy have been tempered by recent evidence suggesting a possible cardioprotective effect of testosterone.[24,25] In this phase 3 study of oral TU, changes in HCT were consistent between patients receiving oral TU and 1.62% topical testosterone gel, and only 3 patients overall discontinued this study due to HCT > 54%. Results of the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response (TRAVERSE) trial demonstrated that men with hypogonadism and preexisting or high risk of cardiovascular disease receiving testosterone exhibited an increased risk of thromboembolic events, although the occurrence of major cardiac events was comparable between patients receiving testosterone and placebo.[26] Testosterone therapy should be monitored closely in men with previous thromboembolic events.[2,3]

Increased PSA is also a known effect of testosterone therapy, although reported increases due to testosterone have been small (0.30–0.43 μg/L).[27,28] In this study, increases in PSA were observed for both treatment groups, and PSA changes were comparable between oral TU (0.2 ± 0.4 μg/L) and 1.62% topical testosterone gel (0.2 ± 0.2 μg/L) and consistent with the effects of testosterone treatment. Following a comparison of the mean change in baseline for PSA between oral TU and 1.62%, no statistical difference was determined. Furthermore, the TRAVERSE trial has reported a low risk of adverse prostate events, including cancer, in men with hypogonadism and PSA concentrations less than 0.3 μg/L receiving testosterone.[29] This suggests that low increases in PSA seen with testosterone pose minimal prostate cancer risk to patients already at low risk for prostate cancer.

Mean baseline SHBG values were similar between treatment groups. However, patients receiving oral TU demonstrated a notable decrease in SHBG, while SHBG increased among patients receiving 1.62% topical testosterone gel. Serum total testosterone at week 52 was comparable for patients receiving oral TU and 1.62% topical testosterone gel, but free testosterone at week 52 was higher in patients receiving oral TU compared to 1.62% topical testosterone gel. With the oral administration of testosterone, there is a small but noticeable first-pass effect on the liver, allowing suppression of SHBG and HDL by androgens.[20] The results of this phase 3 study support the suppression of SHBG by free testosterone, but additional studies on the mechanism and the clinical significance of small decreases in SHBG are necessary to make further conclusions.

Although this study did not specifically analyze the effects of treatment on spermatogenesis, measurements of LH and FSH are key components of spermatogenesis and may serve as surrogate markers. Mean baseline LH and FSH values were similar between treatments, and both groups exhibited a comparable decrease at week 52. However, a comparison of mean change in the baseline for LH and FSH between oral TU and 1.62% determined no significant difference between these therapies. Future studies on the effect of oral TU on LH and FSH as well as semen parameters will improve our understanding of how this treatment affects spermatogenesis.

Oral TU, along with other testosterone therapies, bears a black box warning for blood pressure increases.[22] In this study, neither treatment group exhibited meaningful changes in systolic or diastolic blood pressure. The effect of oral TU 225 mg twice daily on ambulatory blood pressure monitoring (ABPM) was evaluated in a single-arm study of patients with hypogonadism.[30] For 138 men, ABPM assessments were completed at baseline and following 4 months of therapy. Patients exhibited a mean increase in 24-h systolic/diastolic BPs of 3.8/1.2 mmHg, and 4.3% of patients demonstrated HCT > 54%. Analyses concluded that greater increases in BP were seen in patients with greater increases in HCT, suggesting that HCT may be a key biomarker predicting the development of BP increases in patients receiving testosterone therapy.

Patients receiving oral TU did not exhibit any markers of clinically meaningful liver AEs. These results were consistent with findings of a 16-week, single-arm study of another oral TU prodrug (LPCN 1144) in male patients with hypogonadism (N = 36).[14] In this study, 66% of patients were determined to have nonalcoholic fatty liver disease (NAFLD), which resolved in 33% of patients following 16 weeks of oral TU. Furthermore, most patients with NAFLD demonstrated improvements in AST, ALT, ALP, and GGT. These results suggest that oral TU does not worsen adverse liver effects.

Nominal statistically significant improvements for oral TU compared to 1.62% topical testosterone gel were observed for SF-36 measures of mental health and mental component summary and the PDQ measure of weekly negative mood. Changes in physical and sexual parameters of both SF-36 and PDQ were comparable between oral TU and 1.62% topical testosterone gel, but mental parameters were generally improved over 1.62% topical testosterone gel in patients receiving oral TU. However, analyses of PROs used small patient populations and did not show significant changes from baseline for most domains of SF-36 and PDQ for oral TU compared to 1.62% topical testosterone gel. In the TRAVERSE trial, patients receiving 1.62% topical testosterone gel demonstrated greater improvements in mood and energy compared to placebo.[31] Additional research is necessary to determine the effect of oral TU on mood and energy.

5 | CONCLUSION

This study provides a head-to-head safety comparison of novel oral TU to a widely used testosterone gel. Concentrations of serum testosterone were similar before and after dose titration, confirming current dosing recommendations for oral TU 225 mg twice daily without dose adjustment. While the change from baseline for oral TU compared to 1.62% topical testosterone gel in most domains of SF-36 and PDQ was not significant, both therapies were beneficial in improving libido and sexual frequency. Oral TU also demonstrated comparable safety to 1.62% topical testosterone gel and, specifically, showed similar changes in HCT. The results of this study are consistent with current literature, which has found oral testosterone formulations to be well tolerated in patients with hypogonadism and effective at improving testosterone levels and sexual symptoms.[32] Thus, both 1.62% topical testosterone gel and oral TU offer viable solutions, avoiding needles and dose titration, for patients with hypogonadism.

AUTHOR CONTRIBUTIONS

Concept and design: Christina Wang and Nachiappan Chidambaram; *Provision of study materials or patients*: Christina Wang, Jed Kaminetsky, and Irwin Goldstein; *Collection of clinical data*: Christina Wang, Jed Kaminetsky, and Irwin Goldstein; *Analysis and interpretation of clinical data*: Martin Miner, Christina Wang, Jed Kaminetsky, Mohit Khera, Irwin Goldstein, Culley Carson III, Nachiappan Chidambaram, and Adrian Dobs; *Manuscript writing & revision*: Martin Miner, Christina Wang, Jed Kaminetsky, Mohit Khera, Irwin Goldstein, Culley Carson III, Nachiappan Chidambaram, Shelby King, and Adrian Dobs; *Statistical expertise*: Christina Wang and Nachiappan Chidambaram; *Obtained funding*: Nachiappan Chidambaram; *Other administrative, technical, or material support*: Shelby King; *Review and final approval of manuscript*: Martin Miner, Christina Wang, Jed Kaminetsky, Mohit Khera, Irwin

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CONFLICT OF INTEREST STATEMENT

Martin Miner: Consultant, Halozyme, Inc, Janssen; Speaker's Bureau, Halozyme. Christina Wang: Investigator, Lipocine, Inc. Mohit Khera: Consultant, AbbVie, Endo, Halozyme, Inc, Marius, Tolmar, Inc. Culley Carson: Speaker, Endo. Nachiappan Chidambaram: Employee, Lipocine, Inc. Shelby King: formerly with Antares Pharma and Shareholder of Halozyme Therapeutics. The rest of the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used for the analyses in this manuscript are available on request from the corresponding author.

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