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Two-Year Analysis of a New Oral Testosterone Undecanoate (TU) Formulation in Hypogonadal Men: Efficacy, Impact on Psychosexual Function, and Safety

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ABSTRACT

Background: Long-term data evaluating the efficacy and safety of oral testosterone undecanoate (oral TU; JATENZO) in adult hypogonadal men provides important information for healthcare professionals who prescribe testosterone replacement therapy (TRT).

Aim: To determine the efficacy and safety of long-term oral TU therapy, including its impact on total testosterone (T) levels and psychosexual functioning.

Methods: Hypogonadal men, between 18 and 75 years old, (mean age 56.2; 87.2% white) who completed a 12-month, open-label, multicenter, randomized, active-controlled trial were given the opportunity to enroll in a 12-month extension study. Among the 129 eligible TU-treated subjects, 86 chose this option, and 69 completed 24 months of uninterrupted oral TU therapy.

Outcomes: The efficacy of oral TU was documented by measuring total serum T concentrations; sexual function was measured using the Psychosexual Daily Questionnaire (PDQ). For safety, liver function tests, cardiovascular endpoints, and prostate health were measured.

Results: Over 2 years, total serum T concentrations for patients treated with oral TU were in the eugonadal range (300−1,000 ng/dL [10−35 nmol/L]; mean ± SD: 617 ± 427 ng/dL [21 ± 15 nmol/L]) and increased significantly from baseline ($P < .0001$). For sexual function, mean score changes versus baseline for all PDQ domains at all time points were significantly improved ($P < .0011$ for all). For the sexual activity and sexual desire components, patient scores were consistently greater than validated thresholds for clinically meaningful change. Typical T-induced safety changes were observed, including a 3−6 mm Hg increase in systolic blood pressure ($P < .05$); a slight increase in hematocrit ($P < .0001$) that stayed <48% throughout the study; no clinically significant changes in prostate-specific antigen levels; and decreased high-density lipoprotein cholesterol (-9.8 ± 0.9 mg/dL from baseline; $P < .0001$). There were no clinically significant changes from baseline in liver function tests.

Clinical Implications: Over 2 years of treatment, this novel oral TU formulation maintained total T concentrations in mideugonadal ranges, with improvements in sexual function and no clinically significant changes in liver function or other safety concerns previously associated with oral TRT.

Strengths & Limitations: These are the first long-term data to evaluate the efficacy and safety of a novel formulation of oral TU; the comparative long-term safety of oral TU would be strengthened by confirmatory studies versus other TRT formulations.

Conclusion: Oral TU offers a safe and effective long-term treatment option for men with hypogonadism. **Honig S, Gittelman M, Kaminetsky J, et al. Two-Year Analysis of a New Oral Testosterone Undecanoate (TU) Formulation in Hypogonadal Men: Efficacy, Impact on Psychosexual Function, and Safety. J Sex Med 2022;XX:XXX−XXX.**

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INTRODUCTION

Testosterone (T) is the primary androgenic hormone responsible for the normal growth, development, and maintenance of male sex organs and secondary sex characteristics.[1] Deficient production of T with associated symptoms may occur due to various etiologies including structural and genetic defects, metabolic perturbations (eg, metabolic syndrome), and disease (eg, type 2 diabetes, chronic kidney disease). To ameliorate the effects of low T production, there are a variety of different testosterone hormone replacement therapies (TRT)[2] that include intramuscular injections, transdermal applications, and implantable pellets. More recently, T can be delivered by subcutaneous administration, nasal gel, and buccal mucoadhesive formulations.[3,4] Each mode of administration is associated with recognized drawbacks, such as injection site pain, skin irritation, and risk of T transference. Until recently, a safe and effective oral treatment option was not available in the U.S.[4] Oral T is subject to extensive first-pass metabolism in the gastrointestinal tract and the liver.[5] Currently, there are 2 available oral TRT formulations approved for the treatment of hypogonadism by the U.S. Food and Drug Administration (FDA).[6] The first, methyltestosterone, is a C-17 alkylated T analog that is resistant to first-pass hepatic clearance but associated with significant hepatotoxicity.[4,6,7] Indeed, treatment guidelines for the management of T deficiency, published in 2018 by the American Urological Association and the Endocrine Society, recommend that clinicians avoid prescribing alkylated oral T analogs, such as methyltestosterone, due to associated liver toxicity.[3,7]

The second FDA-approved oral TRT is JATENZO (oral TU capsules), a recently approved (2019) prodrug formulation of T undecanoate (TU),[8,9] To reduce first-pass hepatic clearance, oral TU is formulated in a self-emulsifying drug delivery system (SEDDS) that comprises a lipid and surfactant matrix designed to increase the absorption of TU- via intestinal lymphatics thus bypassing the liver. Upon dissolution of the TU SEDDS formulation in proximal gastrointestinal fluids, TU is encapsulated in lipid micelles that are exclusively absorbed into the intestinal lymphatics system which then delivers TU into the systemic circulation via the thoracic duct. The androgenic activity of TU results from the liberation of T by endogenous esterases. The improved bioavailability of this novel oral TU formulation allows for twice daily (BID) administration with a regular morning and evening meal.[8]

The efficacy and safety of oral TU has been previously demonstrated in two randomized, active-controlled, open-label, phase 3 clinical trials.[8,10] In the first trial (ClinicalTrials.gov identifier: NCT01403116), 161 men were treated with oral TU for up to 12 months[7]; in the second trial (ClinicalTrials.gov identifier: NCT02722278), 166 men received oral TU for 3−4 months.[10] At the completion of both studies, 83.6−87.3% of patients treated with oral TU, respectively, had achieved mean T concentrations (C_{avg}) in the eugonadal range. Oral TU was also generally safe and well tolerated and yielded clinical responses consistent with the known effects of TRT. Importantly, liver toxicity was not observed. Both studies evaluated patient sexual function, utilizing the Psychosexual Daily Questionnaire (PDQ).[8,10]

This study presents previously unpublished 2-year efficacy, including psychosexual functioning, and safety data from the above-mentioned 12-month trial and its 12-month extension. The primary efficacy objective was to measure changes in total serum T concentrations for patients receiving long-term oral TU treatment. Another key efficacy objective was to evaluate the effect of long-term oral TU administration on changes in sexual symptoms, as measured by the PDQ. The primary safety objective was to define the long-term safety profile of oral TU, focusing on liver function, evaluated by standard liver function tests, cardiovascular endpoints, evaluated by change in hematocrit, blood pressure, and lipid parameters, and prostate health, evaluated by change in prostate specific antigen (PSA) and voiding function as measured by the American Urological Association International Prostate Symptom Score (AUA-IPSS).

MATERIALS AND METHODS

Study Designs

The initial study was a phase 3, 12-month, open-label, multicenter (academic medical centers, private physician offices, and clinical research organizations), randomized, active-controlled, dose-titration study of men with hypogonadism treated with oral TU or an FDA-approved 1% transdermal T gel (AndroGel). This study was conducted between July 2011 and April 2013, and results have been previously published.[8] Patients who completed the initial study were eligible to enroll in the 12-month, open-label extension study. The current analysis evaluated the long-term efficacy and safety of oral TU over 2 years of treatment in patients who rolled into a 12-month extension study and completed 24 months of uninterrupted oral TU therapy. The primary efficacy endpoint was the change in total T concentrations over 24 months. In addition, a number of secondary endpoints were assessed including changes in psychosexual function and safety (eg, liver, prostate, and cardiovascular function; standard clinical biochemistry and hematology parameters).

Both clinical trials were approved by central or site-specific institutional review boards at each clinical site and were

conducted in accordance with the Declaration of Helsinki and/or all relevant national regulations, including Good Clinical Practice guidelines. Written informed consent was obtained from all trial participants before any study-related procedures were conducted.

Patient Populations and Treatment Regimen

Study inclusion and exclusion criteria have been previously described.[8] Briefly, eligible patients were males aged 18−75 years with hypogonadism, as confirmed by 2 morning serum T measurements ≤300 ng/dL, as well as signs and symptoms consistent with hypogonadism. Throughout the study, patients were required to remain off all forms of T except for the study medication. Patients were excluded if they had received T therapy (oral, topical gel/patch, or buccal) within the prior week, or an intramuscular short-acting T injection within the previous 4 weeks. Patients who used medications that could increase serum T or interfere with the study drug were excluded, as were those with significant intercurrent disease, including abnormal results for serum transaminases, bilirubin, creatinine, PSA, or abnormalities on prostate exam; hematocrit <35% or >48%; malabsorption syndrome; a recent history of stroke; body mass index (BMI) >38 kg/m^2; untreated, severe obstructive sleep apnea; known polycythemia (ie, erythrocytosis); history of breast or prostate cancer; psychiatric illness; or uncontrolled diabetes.

The starting dose of oral TU was 316 mg BID. Patients were instructed to take study medication within 30 minutes after a regular morning and evening meal, and their dose could be either titrated up or down twice during the first 60 study days. A description of the dose-adjustment paradigm has been previously published,[8] but briefly, patient's serum/plasma T C_{avg} was compared with predefined values to trigger either no change in oral TU dose or an upwards or downwards adjustment (Supplementary Figure 1 and Supplementary Figure 2).

Patients randomized to oral TU in the initial study who enrolled in the extension study continued taking oral TU. The need for dose titration was determined based on patient serum T concentrations at the final visit of the initial study (Day 365) (Supplementary Figure 3).

Efficacy Parameters

The primary efficacy variable was the change from baseline in total T levels among patients treated with oral TU. Serum T was collected 4−6 hours postdose. Based on studies conducted subsequent to the present trial, it was determined that serum T values collected in response to oral TU may overestimate mean serum T levels due to the action of nonspecific esterases in blood samples prior to centrifugation.[11,12] To account for this probable overestimate, a recently established conversion factor (0.82)[13] was applied as a posthoc adjustment to this analysis to increase its accuracy. Compliance with therapy was also captured based on the number of capsules consumed.

Patient sexual function was evaluated using the PDQ, a validated, patient-reported outcome measure developed to assess clinically meaningful changes in psychosexual function in men with hypogonadism. The 6-item PDQ is completed daily over a 7-day period and assesses the following domains: sexual desire, sexual enjoyment (with a partner), sexual enjoyment (without a partner), mood (both positive and negative), sexual activity score, satisfaction with erection (percentage score), and satisfaction with erection (total score).[14−16] Recent validation analyses have identified clinically meaningful score change thresholds for the sexual desire and sexual activity components of the PDQ. For sexual activity, score increases ≥0.7 were found to be clinically significant[15]; for sexual desire, score increases ≥0.6 were deemed clinically significant.[14]

Safety Parameters

Key safety variables were change in liver function tests (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin [BILI]); systolic and diastolic cuff blood pressure (SBP, DBP); hematocrit; lipid parameters (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol [TC], and triglycerides); and prostate health (digital rectal exam [DRE], PSA and AUA-IPSS).[17] Prior to clinical laboratory tests for liver function and lipid parameters, patients were asked to fast for ≥8 hours; fasting was not required for hematocrit and PSA.

All study end points were evaluated at baseline and various pre-determined time points, including Days 30, 90, 180, 270, and 365 of the initial study, continuing into Days 455, 545, 635, and 730 of the extension study. Not all variables were measured at all time points.

Statistical Methods

To be included in the efficacy and safety analyses, patients were required to have valid (protocol-defined) baseline data from the initial 12-month study for each variable, as well as scheduled (where noted) follow-up data at Days 30, 60, 90, 180, 270, 365, 455, 545, 635, and/or 730. AEs are reported for all patients who were treated with ≥1 dose of oral TU during the initial 12-month study and continued into the extension study.

All efficacy and safety analyses, except for adverse event analyses, were carried out using change from baseline data. In these analyses, only actual data obtained from each scheduled visit were used, and missing data for any study visit resulted in missing changes from baseline for that parameter. To ensure that missing patient data did not affect study conclusions, a separate confirmatory observed data analysis was conducted using the final recorded data obtained from the 12-month extension study. These final recorded data represented a hybrid of scheduled-visit data and data collected outside of visit windows (eg, during

otherwise unscheduled visits, as the result of repeated lab testing, or obtained at early study termination).

For each efficacy and safety variable, a parametric repeated-measures analysis of covariance (ANCOVA) model was used to evaluate mean changes from baseline over time, with the baseline value used as a covariate. Changes from baseline at each study visit day were assessed using paired-data *t*-tests embedded within the ANCOVA framework. Least-squares findings (LS), consisting of means and standard error (SE) adjusted for model terms, were reported for each analysis, as were the *P*-values for the covariate (baseline), overall time effect, and by-visit results. The testing procedure evaluated all nonmissing data available for any parameter. A condition for nonmissingness was the ability to calculate a change from baseline at any time point. If the baseline value did not exist for a patient for some parameter, then that patient was excluded from the analysis of the parameter. If a follow-up observation was missing at any time, then that patient was excluded from analysis at that time point but was included in the overall analysis and testing of remaining visits with nonmissing data. Summary tables also included patient counts, raw means, and standard deviation (SD). All confirmatory analyses were conducted separately using paired-data *t*-tests to evaluate changes from baseline. Note that no specific examination of normality or use of data transformations was performed in keeping with the original statistical methods of analysis used for the product registration studies.

SAS (2016, SAS Institute, Inc, Cary, NC, USA) version 9.4 software was used for all data analysis.

RESULTS

Of the 161 hypogonadal men randomized to oral TU in the initial 12-month study, 86 enrolled in the 12-month extension. Of these, 5 had no follow-up efficacy or safety data in the extension study, leaving 81 evaluable patients. Patients with missing baseline values were excluded from analysis for the parameter in question. Among the evaluable patients, baseline HDL-C, total cholesterol, and triglyceride values were missing for 1 patient each; baseline LDL-C values were missing for 2 patients, and baseline PSA values were missing for 1 patient. AUA-IPSS total score data during the 12-month extension study were obtained only on Days 545 and 730; 3 evaluable patients discontinued the study prior to Day 545 and were excluded from the analysis of that parameter. Patient disposition information, including reasons for discontinuation, is shown in Figure 1.

Demographics for all patients who had efficacy or safety data in the extension study are detailed in Table 1. A total of 69 patients completed 24 months of uninterrupted oral TU therapy. Most evaluable patients stayed on their initial TU dose for the duration of the study: 71.6% (58/81) did not need to be titrated from the starting dose, 24.7% (20/81) needed a lower TU dose, and 3.7% (3/81) needed a higher TU dose. Mean ± SD and median doses at study end were 283 ± 69.2 mg and 316 mg TU

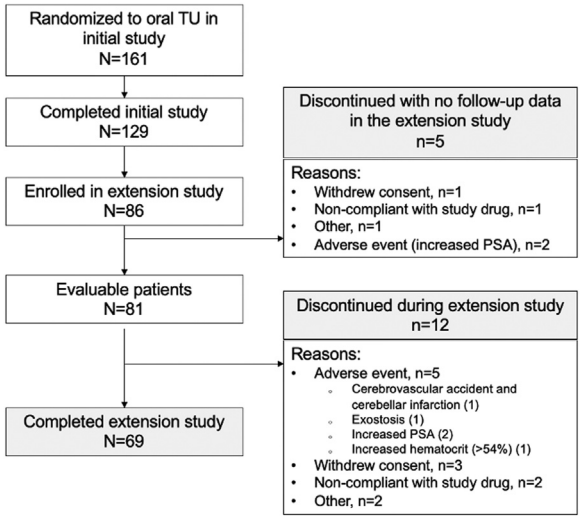

Figure 1. Patient disposition diagram. PSA = prostate-specific antigen.

BID, respectively. Mean patient compliance to oral TU (calculated as the number of capsules consumed/the number of capsules expected to be consumed) over 24 months was 94.0% (median 95.9%).

At all study evaluation time points, serum T concentrations were significantly increased compared to baseline and were in the eugonadal range (300−1000 ng/dL; 10−35 nmol/L) (Figure 2). The mean ± SD overall serum T concentration was 617 ± 427 ng/dL (21 ± 15 nmol/L), or 506 ± 350 ng/dL (18 ± 12 nmol/L) when the posthoc conversation factor was used to account for probable postcollection conversion of TU to T.[13−15] In the confirmatory analysis (Supplementary Table 1), mean ± SE serum T concentration was in the eugonadal range, at 431 ± 42.2 ng/dL (15 ± 13 nmol/L), with a mean ± SE change from baseline of 232 ± 44.2 ng/dL (8 ± 14 nmol/L) ($P < .0001$).

Table 2 summarizes patient sexual function data as measured by the PDQ at baseline and all subsequent study time points. In

Table 1. Demographics at trial initiation for patients treated with oral TU

Baseline characteristic	Oral TU (N=81)*
Age (SD), years	56.0 (9.8)
Race, n (%)	
Black or African American	11 (13.6%)
White	70 (86.4%)
BMI (SD), kg/m^2	30.4 (4.0)
Pre-diabetic	35 (43.2)
Diabetes mellitus	12 (14.8)
Hypertension	34 (42.0)

BMI = body mass index; SD = standard deviation; TU = testosterone undecanoate.
*All patients in the initial 12-month study who enrolled in the 12-month extension study and had at least 1 follow-up visit.

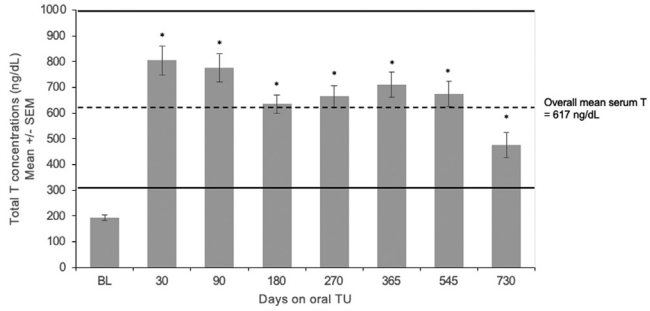

Figure 2. Total testosterone response over 2 years of oral TU therapy.

Solid line denotes upper and lower limits of eugonadal serum T (300–1000 ng/dL); dashed line denotes the overall mean total serum T.

*Denotes statistical significance at $P < .0001$ compared to baseline.

BL = baseline; SEM = standard error of the mean; T = testosterone; TU = testosterone undecanoate.

patients treated with oral TU, mean score changes vs baseline for each PDQ domain was statistically significant at all time points ($P \leq .0011$ for all). Specific domain changes included increased sexual enjoyment and improvement in erectile function. Both sexual activity and sexual desire PDQ components were both clinically and statistically, starting on Day 30 and for the entire study, improved throughout the study.

Over 24 months of oral TU exposure, patients experienced no clinically significant changes in liver function tests (Table 3). At Day 730, mean change ± SE from baseline in liver parameters among patients receiving oral TU were as follows: ALP, -11.1 ± 1.5 U/L; ALT, -1.7 ± 1.4 U/L; AST, +0.1 ± 0.8 U/L; and BILI, -0.03 ± 0.03 mg/dL.

Mean ± SE patient hematocrit (%) increased significantly at all time points ($P < .01$ at Day 30 and $P < .0001$ from Day 90 onward) compared to baseline (44.3 ± 0.3) but remained <48% . Hematocrit levels stabilized after Day 180 (46.8 ± 0.4) and for the remainder of the study (46.6 ± 0.5). Throughout the study, there were no clinically significant changes in PSA levels, with an overall increase in mean PSA of 0.3 ng/mL. Similarly, there were no significant changes in AUA-IPSS scores (mean ± SE change from baseline: -0.06 ± 3.9).

Patients treated with oral TU experienced a small, but statistically significant ($P < .05$), increase in mean SBP, ranging from 3 to 6 mm Hg throughout the study when compared to baseline. No statistically nor clinically meaningful changes in DBP were noted. HDL-C decreased over the first 30 days of treatment (LS mean change ± SE of -11.3 ± 0.8 mg/dL [$P < .0001$]) and then stabilized. On Day 730, the mean change ± SE from baseline in HDL-C was -9.8 ± 0.9 mg/dL ($P < .0001$). LDL-C levels were unchanged. There was a significant decrease in triglyceride and TC levels throughout the study. At Day 730, the mean changes ± SE from baseline in triglyceride and TC levels were -27.6 ± 8.2 mg/dL ($P = .0012$) and -16.7 ± 4.5 mg/dL ($P = .0005$), respectively. The results for all liver function, cardiovascular, and safety biomarkers were consistent with the confirmatory analyses (Supplementary Table 1).

Table 4 details all treatment-emergent adverse effects (TEAEs) occurring in ≥2% of patients who enrolled in the extension study over 2 years of treatment. A total of 70 of 86 (81.4%) patients experienced ≥1 TEAE, most commonly enlargement of prostate, as determined by DRE: 9 of 86 (10.5%); polycythemia (defined as hematocrit >54%), 6 of 86 (7.0%); and hypertension, 5 of 86 (5.8%). Of the men with an enlarged prostate, the majority were considered to have a slight or mild increase in prostate size (7/9; 77.8%). There were no TEAEs that were associated with increased prostate, such as urinary retention. There were no reported incidences of priapism. Serious adverse events (SAEs) included cholelithiasis (n = 1 patient), neck injury/wound (n = 1), exostosis (n = 1), cerebellar infarction and cerebrovascular accident (n = 1, both in the same patient), syncope (n = 1), Prinzmetal angina (n = 1), and basal cell carcinoma (n = 1). Of the SAEs, only the cerebellar infarction/cerebrovascular accident was considered by the Investigator as possibly related to oral TU. No reported TEAEs led to death.

Table 2. Psychosexual daily questionnaire scores following 2 years of oral testosterone undecanoate (TU)

		Sexual enjoyment		Mood			Satisfaction with erection	
Study day	Sexual desire	With partner	Without partner	Positive	Negative	Sexual activity	Percentage	Total
Baseline	2.1 ± 0.2	1.1 ± 0.2	0.9 ± 0.1	4.5 ± 0.1	1.7 ± 0.1	1.9 ± 0.2	60.7 ± 4.0	3.7 ± 0.3
30	3.8 ± 0.2	2.2 ± 0.2	2.0 ± 0.2	5.0 ± 0.1	1.3 ± 0.1	3.8 ± 0.3	69.4 ± 3.5	4.5 ± 0.3
90	3.8 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	5.2 ± 0.1	1.3 ± 0.1	3.7 ± 0.3	71.8 ± 2.6	4.6 ± 0.2
180	3.9 ± 0.2	2.3 ± 0.2	2.1 ± 0.2	5.2 ± 0.1	1.4 ± 0.1	4.0 ± 0.3	73.4 ± 3.1	4.9 ± 0.2
270	3.7 ± 0.2	2.2 ± 0.2	1.9 ± 0.2	5.2 ± 0.1	1.4 ± 0.1	3.8 ± 0.3	71.6 ± 3.3	4.7 ± 0.2
365	3.8 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	5.1 ± 0.1	1.4 ± 0.1	3.7 ± 0.3	69.5 ± 3.1	4.4 ± 0.2
545	3.9 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	5.2 ± 0.1	1.3 ± 0.1	3.6 ± 0.3	72.4 ± 2.6	4.6 ± 0.2
730	3.5 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	5.3 ± 0.1	1.2 ± 0.1	3.8 ± 0.4	72.4 ± 3.1	4.6 ± 0.3

Changes from baseline for study days 30–730 were analyzed using a repeated measures analysis of covariance model run for each domain. Changes at each study visit were statistically significantly different from Baseline/D 0 and were $P \leq .0011$ in all cases.

Table 3. Liver function tests following two-years of oral testosterone undecanoate (TU)

Study day	ALP ± SEM (U/L)	ALT ± SEM (U/L)	AST ± SEM (U/L)	BILI ± SEM (mg/dL)
Baseline	64.05 ± 1.95	27.81 ± 1.40	21.58 ± 0.76	0.58 ± 0.026
D 30	54.45 ± 2.01	21.75 ± 1.02	20.41 ± 0.80	0.46 ± 0.024
D 90	54.91 ± 1.83	22.42 ± 1.03	21.18 ± 0.76	0.43 ± 0.022
D 180	54.23 ± 1.84	25.26 ± 1.10	22.55 ± 1.08	0.56 ± 0.023
D 270	55.05 ± 1.83	25.54 ± 1.23	21.86 ± 0.98	0.55 ± 0.024
D 365	52.40 ± 1.63	25.44 ± 1.28	21.78 ± 0.87	0.51 ± 0.020
D 455	52.52 ± 1.71	26.81 ± 1.23	22.73 ± 0.79	0.54 ± 0.021
D 635	53.18 ± 1.81	29.93 ± 3.16	22.73 ± 0.95	0.55 ± 0.025
D 730	53.74 ± 1.86	26.65 ± 1.59	22.00 ± 1.03	0.52 ± 0.023

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; SEM = standard error of the mean.

DISCUSSION

This study summarizes the efficacy and safety of an oral TU SEDDS formulation over 2 years of treatment in hypogonadal men. Within 1 month of treatment initiation, total serum T concentrations reached the mideugonadal range, and this effect persisted over 24 months. Patients receiving oral TU reported better sexual function, evidenced by statistically significant and clinically meaningful improvements in PDQ scores that were initially observed on Day 30 and persisted over 24 months. Furthermore, oral TU exhibited a good safety profile that was both expected in context with prior research,[4,10] and consistent with other TRT formulations available to treat TRT.[18–21] Patients had no clinically significant changes in liver function tests, and while SBP increased slightly from baseline, this effect plateaued after several months. Additionally, oral TU did not result in a clinically meaningful increase in PSA and did not alter other prostate function parameters (consistent with the slight PSA increases observed with other TRTs, especially with intramuscular administration).[19]

Table 4. Treatment-emergent adverse events occurring in ≥ 2% of patients at any time during 2 years of oral TU treatment

Preferred term, n (%)	Oral TU, N = 86
Prostatomegaly	9 (10.5%)
Polycythemia	6 (7%)
Hypertension	5 (5.8%)
Bronchitis	4 (4.7%)
Hematocrit increased	4 (4.7%)
Prostatic specific antigen increased	4 (4.7%)
Sinusitis	4 (4.7%)
Back pain	3 (3.5%)
Blood pressure increased	3 (3.5%)
Depression	3 (3.5%)
Epistaxis	3 (3.5%)
Eructation	3 (3.5%)
Fatigue	3 (3.5%)
Headache	3 (3.5%)
Edema peripheral	3 (3.5%)
Rash	3 (3.5%)
Seasonal allergy	3 (3.5%)
Anxiety	2 (2.3%)
Basal cell carcinoma	2 (2.3%)
Benign prostatic hyperplasia	2 (2.3%)
Blood glucose increased	2 (2.3%)
Cardiac failure congestive	2 (2.3%)
Diabetes mellitus	2 (2.3%)
Gynecomastia	2 (2.3%)
High density lipoprotein decreased	2 (2.3%)
Hypercholesterolemia	2 (2.3%)
Renal failure chronic	2 (2.3%)
Upper respiratory tract infection	2 (2.3%)

TU = testosterone undecanoate.

These findings confirm the long-term efficacy of oral TU, initially established via two prior phase 3 evaluations of substantially shorter duration.[4,10] Specific to sexual function, current results are consistent with existing research showing improved libido and sexual satisfaction and function in hypogonadal men treated with TRT,[22,23] including research conducted using the PDQ instrument,[14,15] and prior research in patients treated with oral TU.[4,24] In addition to statistically significant improvements in all PDQ domains, treatment with oral TU was associated with significant and sustained clinical improvement in sexual activity and sexual desire, based on thresholds established by PDQ validation models of sexual activity (established sexual activity threshold ≥0.7: current analysis ~1.0−1.2; sexual desire threshold ≥0.6: current analysis ~1.5−1.8).[14,15]

In terms of safety, an important clinical finding from this study is the absence of liver toxicity in a continuously treated cohort over 24 months of follow up. Oral androgens have long been associated with hepatoxicity,[2,5] and although this effect is directly associated with the alkylation of T at the C-17 position (to avoid first-pass hepatic metabolism), oral administration of any TRT continues to be of potential concern.[4] The current data are also consistent with those observed in a placebo-controlled trial of a different

oral TU formulation administered for 15 months at a lower daily dose and at lower serum T concentrations.[18]

Although an increase in mean hematocrit occurred in men treated with oral TU, this remained below the ULN and stabilized after Day 180. Hematocrit increases were consistent with the TRT "class" effect. Among men undergoing TRT, T-induced hematocrit elevations are common, and the attendant risk of developing erythrocytosis is well-established. Polycythemia (defined as hematocrit >54%) is the most common dose-limiting adverse effect associated with TRT, particularly in response to parenteral TRT preparations,[25] and was the second most frequently observed TEAE in the present study, affecting 7.0% (6/86) of patients receiving oral TU over 24 months. Nonetheless, no patients ceased oral TU therapy due to high hematocrit.

The effects of oral TU on lipid parameters were also consistent with the TRT class effect. Specifically, meta-analyses of hypogonadal men receiving TRT have generally shown that exogenous T lowers HDL-C and is associated with concomitant LDL-C and TC lowering.[26–28] In the present study, HDL-C decreased by approximately 23% over the first 30 days of treatment and then stabilized. TC levels decreased significantly throughout the study, and LDL-C was unaffected. The absence of increases in TC and LDL-C in response to long-term oral TU therapy is noteworthy, as significant elevations in these lipid fractions (particularly LDL-C) are unequivocal risk factors for cardiovascular disease.[29]

The modest increase in systolic blood pressure (SBP) observed in this analysis is consistent with subsequent findings from shorter-term studies of oral TU,[7,13] as well as SBP findings from clinical studies for different oral TU formulations[20,21] and parenterally administered T enanthate.[30] The mechanism for this pressor effect remains unclear; data from the initial 12 months of the current study were evaluated to identify factors potentially related to SBP (eg, estradiol and dihydrotestosterone concentrations, hematocrit, heart rate, hemoglobin, oral TU dose, potassium, and total and free T), but none of these correlated with increased SBP.[10] Therefore, per the package insert boxed warning, healthcare practitioners who prescribe oral TU should regularly monitor patient blood pressure.[9]

These safety findings are consistent with previous phase 3 studies showing that oral TU is generally safe and well tolerated.[4,10] In one study, over 3–4 months of follow-up, the most common TEAEs that occurred in patients receiving oral TU were headache (4.8%), increased hematocrit (4.8%), upper respiratory tract infection (3.6%), hypertension (3.0%), decreased HDL-C (3.0%), and nausea (2.4%).[10] Similarly, oral TU was found to be safe and tolerable in the first 12 months of the present study, where the most common TEAEs (occurring in ≥2% of patients) in the oral TU treatment group were elevated hematocrit (6.8%), enlarged prostate (5.6%), peripheral edema (5.5%), hypertension (3.7%), diarrhea (3.1%), elevated PSA (2.5%), and eructation (2.5%).[4] The incidence of these TEAEs decreased numerically over 24 months of oral TU therapy, aside from elevated PSA, which persisted at a similar rate throughout the study.

Oral TU formulated in a SEDDS formulation represents a therapeutic advance that may promote improved patient adherence in the treatment of male hypogonadism. A U.S. retrospective claims analysis (2007–2014) conducted in men initiating topical TRT (N = 3184) showed very low medication adherence rates; at 12 months, only 17% of remained treatment-adherent (defined as ≥80% proportion of days covered).[31] In contrast, a randomized controlled clinical study of an oral TU formulation (N = 237) approved in Europe found strong treatment adherence at 6 months with twice-daily dosing, with >90% of patients using ≥80% of their medication.[18] There are several reasons why oral TU may promote improved patient adherence. It is more straightforward to use than to injectable or transdermal T preparations, which are associated with administration site pain and T skin-to-skin transference, respectively.[4] Postmarketing surveillance of T gel has captured cases of secondary exposure to children, resulting in virilization[32] and has led to a boxed warning on product labeling in this regard. Furthermore, up to 12.7% of patients in clinical trials receiving T injections experience injection-site reactions (eg, bruising, hemorrhage, erythema, and induration).[33,34] The benefits of treatment adherence to T therapy in hypogonadal men observed over 12 months of follow up included improvements in fatigue, depression, sexual dysfunction, insomnia, and/or osteoarthritis.[32]

Strengths and Limitations

This study provides the first long-term data regarding the safety of a novel SEDDS formulation of oral TU. One potential limitation is that data in the current 2-year analysis were observational and not compared with a control or active-treatment group. However, this patient population was compared to a cohort treated with transdermal T in the initial 1-year randomized study. That analysis found similar efficacy and safety outcomes between the formulations.[4] Nonetheless, the comparative long-term safety of oral TU vs transdermal T gel and other T formulations would be strengthened by confirmatory studies. In addition, while the number of patients followed for 2 years in this study was modest in size, it is sufficiently large to derive comfort that the observations regarding the safety of oral TU are accurate, and thus reassuring for medical practitioners who may prescribe oral TU for appropriate hypogonadal patients.

In addition, the PDQ was utilized to evaluate multiple parameters of sexual function, more appropriate for evaluating patients who are treated with testosterone therapy. We did not evaluate erectile dysfunction with the IIEF questionnaire in this study.

CONCLUSION

Over 2 years, a novel oral TU formulation maintained total T concentrations in mideugonadal ranges and patients showed statistically significant and clinically meaningful improvements in sexual function based on the PDQ. Treatment with oral TU did not lead to any clinically significant changes in liver function or

other safety concerns previously associated with oral TRT. Oral TU may offer a safe and effective long-term treatment option for men with hypogonadism.

DATA AVAILABILITY

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jsxm.2022.09.002.