New Oral Testosterone Undecanoate (TU) Formulation Improve Testosterone Concentrations, as well as, Psychosexual, Well-Being, and Body Composition and Bone Density Parameters in Hypogonadal Men

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Introduction

Various routes of administration have been employed to ameliorate the signs and symptoms of male hypogonadism. Of the current testosterone replacement therapies (TRTs), there are transdermal applications, either by a gels or patches; intramuscular (IM) or subcutaneous (SC) injections; surgically implanted pellets; intranasal administration; and oral capsules, methyltestosterone in the US. All these therapies have certain drawbacks, such as the potential for transference with gels, application site reactions with patches, injection site pain with the IM or SC injections, or hepatotoxicity for oral methyltestosterone.

The address the need for a safe and efficacious oral TRT, a testosterone undecanoate (TU) formulation that utilizes a unique self-emulsifying drug delivery system was developed. This recently approved, novel, oral TU formulation has undergone and passed the safety and efficacy requirements that is mandated by the US FDA for new TRT products. During the process, two phase 3 clinical trials were conducted. In addition to the standard pharmacokinetic endpoints, the clinical trials also measured certain secondary endpoints, including changes in psychosexual and general well-being, changes in body composition, and changes in bone mineral density (BMD).

Methods

Hypogonadal men, with two morning serum total T < 300 ng/dL, were recruited into one of two phase 3 clinical trials. Both studies were open-label, active comparator trials. The inclusion and exclusion criteria were similar to other TRT registration studies. Both trials monitored safety throughout the study via physical exam and standard laboratory evaluations.

Trial 1:

- Hypogonadal men, aged 18 – 65, were randomized 3:1 to either oral TU (n=166) or a topical testosterone solution [Axiron] (n=55)
- Subjects were enrolled for 4-6 mo
- The starting dose was 237 mg TU bid. The dose was able to be titrated twice, during the first half of the study
- Total T was measured at the conclusion of the study
- Psychosexual Daily Questionnaire (PDQ) was completed by study subjects for 7 days prior to beginning the study and 7 day prior to the last study visit

Trial 2:

- Hypogonadal men, aged 18 – 75, were randomized 1:1 to either oral TU (n=162) or a topical testosterone gel [AndroGel 1%](n=161)
- Subjects were enrolled for 12 mo
- The starting dose was 316 mg TU bid. The dose was able to be titrated twice, during the first half of the study
- Total T was measured at the conclusion of the study
- The SF-36 Well-Being Questionnaire was administered throughout the study
- The PDQ was also administered for 7 day prior to the beginning of the study and throughout the study
- Body composition and BMD were assessed by DEXA on day 0, 180, and 365

Results

- Both the TU and transdermal TRT groups for both studies were similar (Table 1).

Table 1: Patient Demographics

Characteristic	Trial 1		Trial 2	
	TU (n=166)	Topical T (n=56)	TU (n=161)	T Gel (n=160)
Age, Years				
Mean	51.6	53.4	55.0	54.9
Range	24-65	31-65	20-75	20-75
Race, %				
Asian	1.8	3.6	0.0	1.6
Black or African American	17.5	19.6	11.2	12.8
White	80.1	75.0	87.6	83.8
Other	0.5	0.0	1.2	1.9
Body Mass Index, kg/m^2				
Mean	31.8	30.9	30.0	29.88
Range	17-38	21-38	17.1-38.5	19.6-37.4
Baseline Clinical Characteristics, %				
Prediabetic	36.1	33.9	38.5	35.0
Diabetes Mellitus	24.1	26.8	19.3	20.0
Hypertensive	52.4	46.4	41.0	47.5

T, testosterone; TU,testosteroneundecanoate

- Oral TU and the transdermal TRT products raised total T concentrations into the eugonadal range (Table 2).

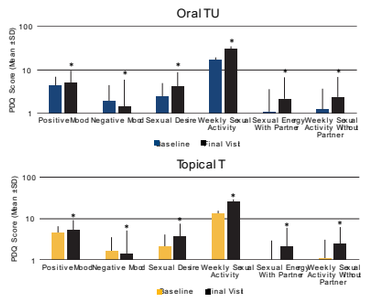
Table 2: Total Testosterone C_{avg} at Study End

	Serum TC_{avg} (mean ± SD)	Serum TC_{avg} (mean ± SD)
Trial 1	TU = 489 ± 155 ng/dL	Topical T = 473 ± 169 ng/dL
Trial 2	TU = 524 ± 215 ng/dL	T Gel = 425 ± 178 ng/dL

C_{avg}, time-weighted average concentration; CI, confidence interval; T,testosterone; TU,testosteroneundecanoate

- In Trial 1, both oral TU and transdermal TRT products statistically improved the parameters within the PDQ (Figure 1).

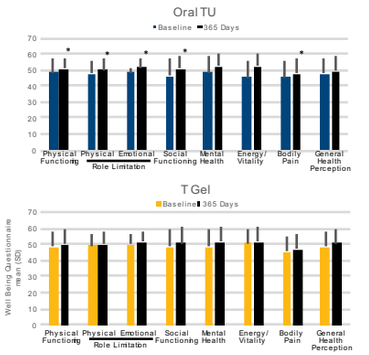
Figure 1: Change in PDQ from Baseline to Study End in Trial 1



ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; SD, standard deviation; TU,testosteroneundecanoate
* Denotes p< 0.05 when compared to baseline
LS mean difference, 95% CI, and P values are based on ANCOVA model with change from baseline as the dependent variable, treatment group as a factor, and baseline value as the covariate

- In Trial 2, significantly greater improvements in the SF-36 were observed in the oral TU group, when compared to the transdermal TRT group in physical functioning, role limitations/physical, role limitations/emotional, social functioning, and bodily pain (Figure 2).

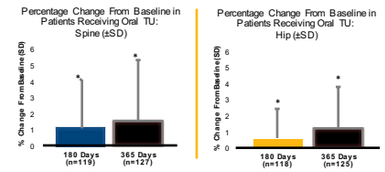
Figure 2: Figure 2. Change in General (SF-36) Well-Being Parameters in Trial 2



*Denotes statistical difference between the magnitude of improvement between TU and T Gel. All statistical differences showed a greater magnitude of increase for the TU group.
Treatment group, visit, and the interaction of treatment group and visit were included in the model as fixed effects and subject was included as a random effect.

- In Trial 2, significant increases in BMD in both hip and spine for the oral TU group, when compared to baseline (Figure 3).

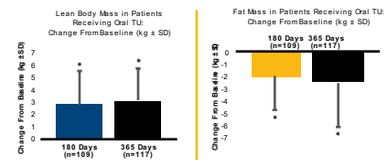
Figure 3: Change from Baseline of BMD in Trial 2



* Denotes p< 0.001 versus baseline
SD, standard deviation; TU, testosterone undecanoate

- In Trial 2, significant increase in lean body mass and significant decrease in fat mass in the oral TU group, when compared to baseline (Figure 4).

Figure 4: Change from Baseline of Body Composition Variables in Trial 2



* Denotes p< 0.001 compared to baseline.
kg, kilogram; SD, standard deviation; T, testosterone; TU,testosteroneundecanoate

- There was no significant change in liver function tests in either study (Table 3).

Table 3: Change from Baseline to End of Study in Liver Function Measurements

Trial 1

Liver Function Measurements	Change From Baseline to Final Visit*	
	TU (n=166)	Topical T (n=55)
ALT	−3.541 U/L	−4.078 U/L
AST	−0.365 U/L	−1.745 U/L
Bilirubin	−0.800 µmol/L	0.311 µmol/L

No significant changes in liver function tests were observed in either treatment group

Trial 2

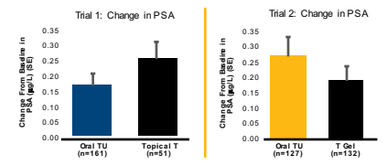
Liver Function Measurements	Change From Baseline to Final Visit*	
	TU (n=161)	T Gel (n=159)
ALT	-2.286 U/L	-2.132 U/L
AST	0.677 U/L	-0.876 U/L
Bilirubin	0.010 µmol/L	-0.034 µmol/L

No significant changes in liver function tests were observed in either treatment group

*Final visit was defined as either Visit 7 or date of last dose decision if terminated early.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; T, testosterone; TU,testosteroneundecanoate

- There was a slight increase in PSA, but stayed stable throughout Trial 1 and Trial 2 (Figure 5)

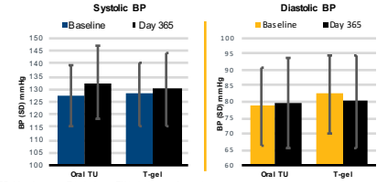
Figure 5. Change in PSA from Baseline to Study End



PSA, prostate-specific antigen; T, testosterone; TU, testosterone undecanoate

- In both studies, there was an increase in cuff sBP, which was more pronounced in the oral TU group when compared to the transdermal TRT group. In Trial 1, the cuff sBP increased 2.8 ± 11.84 (SD) mm Hg and 1.8 ± 10.76 mm Hg for the TU group and the transdermal TRT group, respectively. A similar trend was observed in Trial 2 (Figure 6).

Figure 6. Change in Cuff Systolic and Diastolic BP from Baseline to End of Study in Trial 2



BP, blood pressure; T, testosterone; TU,testosteroneundecanoate

Conclusions

Treatment of hypogonadal men with oral TU yielded:

- Total mean testosterone concentrations in the mid-eugonadal range
  - Improvements in psychosexual parameters
  - Improvements in general well being
  - Increased BMD in both the spine and hip
  - Increased lean body mass and reduced fat mass
- Safety parameters between oral TU and transdermal TRT products were similar

Disclosure

Study was supported by Clarus Therapeutics, Inc.