Safety Analysis of an Oral Testosterone Undecanoate (TU) Formulation Following 2 Years of Administration in Hypogonadal Men

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Introduction: An oral testosterone (T) replacement therapy (TRT) would be the preferred choice for many hypogonadal men. Until recently, the only oral TRT approved in the US was methyl-T which has been associated with hepatotoxicity. The safety of a novel oral T undecanoate (TU) formulation was evaluated in hypogonadal men for up to 2 years.

Subjects and Methods: Two open-label, multicenter, dose-titration trials were conducted in hypogonadal men (serum T ≤ 300 ng/dL) age 18-75 years. Trial I was a randomized, active-controlled, 2-arm, 12-month study. Trial 2 was a long-term extension of those who completed Trial 1. Statistical analyses were only conducted with the subjects who completed Trial 1 and continued treatment in Trial 2, thus providing up to 2 full years of data. Safety was assessed by physical exam, AE reporting, and routine clinical laboratory measurements.

Results: Overall, up to 81 subjects were available for evaluation. T concentration increased from 208.3 ± 102.4 ng/dL (Mean ± SD) at baseline (BL) to 470.1 ± 396.5 ng/dL after 24 Mo of therapy with oral TU, and 84% of men achieved T in eugonadal range (300-1000 ng/dL) after 90 days of therapy. Mean T concentrations remained in the eugonadal range throughout Trial 2. There were no clinically significant changes in liver function tests - ALT (28.0 ± 12.3 to 26.6 ± 12.8 U/L), AST (21.8 ± 6.8 to 22.0 ± 8.2 U/L), and bilirubin (0.58 ± 0.22 to 0.52 ± 0.19 mg/dL) throughout the two studies. At Day 270, one subject had an ALT level of 227 U/L, which was > 4x the ULN (ULN for ALT = 45 U/L). Despite continued use of oral TU, ALT was measured again on Day 290, and the level dropped to 87 U/L, < 2x ULN. This was the only instance of an LFT elevation. There was a modest initial increase in prostate-related growth endpoints (i.e. PSA and prostate volume) that stabilized over time. There were not any significant changes in IPSS total score (-0.06 ± 3.9 vs BL). There were significant, yet modest, increases in mean HCT (+2.52 ± 3.7% vs BL, $p < 0.001$) and cuff systolic BP (+5.6 ± 15.0 mmHg vs BL, $p = 0.006$). The change in prostate-related growth variables and CV endpoints changed initially and stabilized throughout the 2 trials. For example, systolic BP consistently showed a mean increase from BL between 3 - 6 mmHg.

Conclusion: This oral TU formulation is an effective long-term therapy for hypogonadal men and has a safety profile consistent with other approved T products. Notably, no evidence of liver toxicity was observed. The long-term efficacy and safety profile of oral TU may provide a treatment option that avoids issues associated with other TRTs, such as injection site pain or transference to partners and children.