The Bioavailability of TX-001HR ( Estradiol and Micronized Progesterone Capsules): Effects of Food and Varying Dosing Profiles

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Methods

- **Introduction**
  - Baseline values were determined from the average of blood samples drawn at -60, -30, and 0 Trough levels were collected prior to dosing on Day 6
  - After a 14-day wash-out period, subjects took TX-001HR under the opposite fasting-fed condition
- **Objectives**
  - Poor aqueous solubility and significant first-pass liver metabolism limit the oral bioavailability of as per randomization
  - Measuring E2 and P4 levels for two different doses of TX-001HR at steady state
- **Design**
  - Multi-Dose Study
    - Twenty-four women were randomized to receive a single dose of TX-001HR (1 mg E2/100 mg P4) administered under fasting for at least 10 h and fed (20 minutes after a standardized high-fat meal [32% fat content]) in a crossover design across 2 periods
    - Blood was drawn -60, -30, and 0 minutes (baseline for E2) and then 20, 40, 60, and 90 minutes, and 2, 4, 6, 8, 12, 18, 24, 48, and 72 hours after TX-001HR administration; hematocrits were monitored to assess E1 (data not shown)
    - A 14-day wash-out period, subjects took TX-001HR under the opposite fasting-fed condition as per randomization
  - Dose-Dependent Exposure was observed with mean baseline-adjusted PK parameters (AUC_0-24, AUC_0-144, and C_max) on Days 1 and 7 for E2 (Table 2, A and B), as well as E1 (data not shown)
  - Steady-state for E2 and P4 were shown by consistent C_max levels from pre-dose Day 6 through 24 h post-dose Day 1 (Table 3, A and B), and this was achieved within 1 week of therapy regardless of dose
  - Baseline-adjusted mean accumulation ratio for (Table 4)
    - E2 concentrations were approximately 2 for both 1 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4
    - P4 concentrations were lower (~1.4 for both doses) than that of E2, which is likely due to its short half-life
  - Baseline demographic characteristics were comparable between the 2 treatment groups, including overall mean age (57.2 years) and BMI (25.7 kg/m^2)
  - Dose Dependence of Serum Estradiol and Progesterone Levels with TX-001HR
  - Estradiol and Progesterone levels from pre-dose Day 6
  - Adequate systemic absorption of estradiol and progesterone is necessary for relieving moderate-to-severe, menopausal VMS, and protecting the endometrium from hyperplasia
  - In a phase 3 study, the investigational E2/P4 formulation of TX-001HR reduced the frequency and severity of VMS and protected the endometrium from hyperplasia
  - If approved, TX-001HR may be an important option for 2.5 million women who use unapproved, inadequately regulated, compounded bioidentical hormone therapy (CBHT).

Results

- **Baseline-adjusted AUC_0-144 and C_max for P4 were significantly higher in the fed versus fasting state** (Table 1, Figure 1)
  - Baseline-adjusted AUC_0-144 for E2 and C_max for E1 were bioequivalent (n=19).

Conclusions and Discussion

- Consistent with other progesterone preparations, the trials demonstrated that food ingestion prior to TX-001HR administration increased the bioavailability of P4
  - In contrast, little to no effect of food was observed on E2 and E1 levels
  - E2 achieved steady state within 7 days in the multidose PK study
  - The PK characteristics of E4/4 P4 as formulated in TX-001HR and demonstrated in these studies are important
  - Alternate systemic absorption of estradiol and progesterone necessitates remodeling to estradiol, menopausal VMS, and protecting the endometrium from hyperplasia
  - If approved, TX-001HR may be an important option for 2.5 million women who use unapproved, inadequately regulated, compounded bioidentical hormone therapy (CBHT) that has not been rigorously evaluated in clinical trials.

References