Estradiol and Progesterone Bioavailability for Moderate to Severe Vasomotor Symptom Treatment and Endometrial Protection with the Continuous-combined Regimen of TX-001HR (Oral Estradiol and Micronized Progesterone Capsules)

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Introduction

The efficacy and safety of oral contraceptive hormone therapy, particularly an EE approved and compounded, containing progesterone (P4)/progestins were estimated to be filled in the US per year.

Phase 1 Multi-Dose Trial

Women (n=1845) were randomized to 4 doses of TX-001HR or placebo administered orally, once daily for up to 12 months. The serum levels of E2, E1, and P4 at select TX-001HR (E2/P4) doses were characterized in 2 separate studies

Serum Hormone Concentration Methodology for P4, E2, and E1

Serum P4 levels (when P4 dosed continuously) sufficient to counteract the potential estrogenic effects of unopposed estrogens

Phase 3 REPLENISH Trial

To describe serum P4 levels (when P4 dosed continuously) sufficient to counteract the potential estrogenic effects of unopposed estrogens

Objective

Serum P4 levels required for endometrial protection in a continuous-combined regimen have not been well characterized

Methods

• The serum levels of E2, E1, and P4 at select TX-001HR (E2/P4) doses were characterized in 2 separate studies.

• Menopausal women in the phase 1 REPLENISH trial.

• Subjects who entered the study in the meeting with food. Serum hormone levels were quantified with validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) methods

• All data expressed as mean ± SD. an=19; bn=15. Accumulation ratio = AUC

Table 2: Serum Concentration Methodology for P4, E2, and E1

Table 3: Phase 1 Study: Unadjusted PK Parameters on Days 1 and 7

Table 4: Phase 1 Study: Unadjusted Steady-state (C∞) Hormone Levels

Results

Table 1: Serum Hormone Concentration Methodology for P4, E2, and E1

Table 5: Phase 1 Study: Unadjusted PK Parameters on Days 1 and 7

Table 6: Phase 1 Study: Unadjusted Steady-state (C∞) Hormone Levels

Conclusions

Levels of E2, as measured in the REPLENISH study, were associated with endometrial protection from endometrial hyperplasia and cancer. The steady-state levels of P4 and E2 were achieved within 7 days in phase 1 PK study.

Similar P4 levels were obtained in the phase 1 PK study.

Serum P4 levels were required for endometrial protection in a continuous combination regimen.

Steady-state levels for P4 and E2 were shown by consistent C∞ levels from pre-dose Day 6 through 24 h after dosing (Figure).

Serum Estrone

Serum Progesterone

Serum Estradiol

Figure 2. Phase 1 Multi-Dose Study Findings: Unadjusted Mean Serum Concentrations

Figure 1. REPLENISH Trial: Unadjusted Mean Hormone Concentrations

Figure 3. REPLENISH Trial Phase 3: Serum Estradiol, Estrone, and Progesterone