Progesterone bioavailability for preventing endometrial stimulation with a continuous-combined regimen of TX-001HR (oral estradiol and micronized progesterone capsules)

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IMS 2018 (deadline January 12, 2018)
[CHARACTER LIMIT: 2000 including spaces; currently 1983]

Objective
Many menopausal women choose hormone therapy (HT) with natural progesterone (P4). TX-001HR is an investigational, oral, combined, 17β-estradiol (E2)/micronized P4 softgel capsule being developed for the treatment of moderate-to-severe vasomotor symptoms (VMS) in menopausal women with a uterus. In the REPLENISH trial, continuous use of 100 mg of P4 prevented endometrial hyperplasia with E2 doses of 0.5 or 1 mg, with a favorable bleeding profile. Serum P4 levels required to prevent endometrial hyperplasia with HT have not been well characterized.

Methods
Two phase 1, open-label, randomized trials were conducted in menopausal women. One evaluated the food effect on P4 bioavailability following a single TX-001HR dose (1 mg E2/100 mg P4) under fasted vs fed (high-fat, 52% fat calories) conditions in a cross-over design. The other, a multiple-dose study (normal diet, 20%-35% fat), assessed serum levels at steady state following 7 daily doses of TX-001HR (1 mg E2/100 mg P4).

Results
P4 $AUC_{0\text{-}t}$ and C_{max} were significantly higher (1.3- and 1.8-fold higher, respectively) in the fed versus fasted state. In the multi-dose study, C_{max}, C_{avg}, and AUC_{τ} were 11.3 ng/mL, 0.76 ng/mL, and 18.1 ng·h/mL, respectively, on day 7.

Conclusions
Consistent with other studies of natural P4 (e.g., Prometrium), TX-001HR taken with food enhanced P4 bioavailability. Systemic P4 levels found in these studies support continuous-combined E2/P4 (TX-001HR) allowing for adequate endometrial protection from hyperplasia, while improving VMS, as seen in REPLENISH. Further, a likely indirect effect of P4 in TX-001HR is the downregulation of endometrial estrogen receptors, thus, decreasing endometrial estrogen sensitivity and reducing breakthrough bleeding, without altering E2 effects on VMS. These characteristics of oral TX-001HR are important as sufficient systemic absorption is necessary for moderate-to-severe VMS relief in menopausal women, while keeping the endometrium protected.