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

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Introduction

- Poor aqueous solubility and significant first-pass liver metabolism limit the oral bioavailability of estradiol and progesterone[1-4]
- Hormone therapy formulations that contain solubilized estradiol and micronized progesterone can increase absorption and may improve bioavailability
- An investigational drug that combines solubilized 17β-estradiol with micronized progesterone (E2/P4) in a single, oral softgel capsule (TX-001HR; TherapeuticsMD, Boca Raton, FL) has been developed
- TX-001HR is currently being evaluated for the treatment of moderate-to-severe vasomotor symptoms in menopausal women with a uterus

Objectives

- Two primary objectives were evaluated in 2 pharmacokinetic (PK) studies
  - Assessing the effect of food on E2 and P4 levels after TX-001HR administration
  - Measuring E2 and P4 levels for two different doses of TX-001HR at steady state

Methods

- Two phase 1, open-label, randomized trials were conducted for this analysis. In both studies, healthy, postmenopausal women (40-65 years) with a body mass index (BMI) of 18-30 kg/m^2 were enrolled

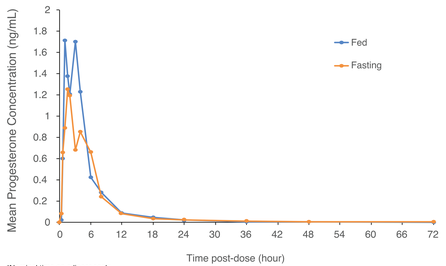
Food-Effect Study

- 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 (30 minutes after a standardized high-fat meal [52% fat calories]) conditions in a crossover design
- Blood was drawn -60, -30, and 0 minutes (averaged for baseline) and then 20, 40, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours after TX-001HR administration; PK parameters were compared under fasting and fed conditions
- After a 14-day wash-out period, subjects took TX-001HR under the opposite fasting-fed condition as per randomization

Multi-Dose Study

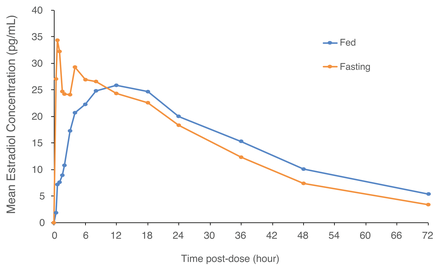
- Forty women were randomized to 2 doses of TX-001HR (1 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4), 20 women per TX-001HR dose, which was administered once daily for 7 days
- Blood was collected on Days 1 and 7 (prior to dosing [0-hour], and then 20, 40, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours after study drug administration) to assess PK parameters for E2, P4, and estrone (E1)
- Trough levels were collected prior to dosing on Day 6
- Baseline values were determined from the average of blood samples drawn at -60, -30, and 0 minutes prior to TX-001HR administration on Day 1

Figure 1. Mean Baseline-Adjusted Plasma Progesterone Levels versus Time: Food-Effect Study*



*Nominal time on a linear scale.

Figure 2. Mean Baseline-Adjusted Plasma Estradiol Levels versus Time: Food-Effect Study*



*Nominal time on a linear scale.

Results

Food-Effect Study

- The baseline-adjusted $AUC_{0\text{-}t}$ and C_{max} for P4 were significantly higher in the fed versus fasting state (**Table 1, Figure 1**)
- In contrast, the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ for E2 and E1 and the C_{max} for E1 were bioequivalent (**Table 1**)
- A transient E2 peak concentration at ~2.6 h was observed after dosing in the fasting state but not the fed state (**Figure 2**)
  - No early peak in E2 concentration was seen in the multi-dose study when TX-001HR was taken following a meal at steady state

Table 1. Baseline-Adjusted PK Parameters for Plasma Progesterone, Estradiol, and Estrone in the Food-Effect Study

	Adjusted Geometric Mean		Adjusted Geometric Mean Ratio for Fed/Fasting (%)
	Fed (n=23)	Fasting (n=23)	
Progesterone (P4)			
$AUC_{0\text{-}t}$ (ng·h/mL)	6.45	3.54	182.2
$AUC_{0\text{-}\infty}$ (ng·h/mL)	6.72	5.26	127.8
C_{max} (ng/mL)	2.50	0.92	270.9
Estradiol (E2)			
$AUC_{0\text{-}t}$ (pg·h/mL)	959.3	917.0	104.6
$AUC_{0\text{-}\infty}$ (pg·h/mL)	1144.6	1123.4	101.9
C_{max} (pg/mL)	27.7	60.4	45.9
Estrone (E1)			
$AUC_{0\text{-}t}$ (pg·h/mL)	3320.5	2983.9	111.3
$AUC_{0\text{-}\infty}$ (pg·h/mL)	3691.1	3227.1	114.4
C_{max} (pg/mL)	135.3	143.1	94.5

Multi-Dose Study

- 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-dependent exposure was observed with mean baseline-adjusted PK parameters ($AUC\tau_{trap}$ and C_{max}) on Days 1 and 7 for E2 (**Table 2**), as well as E1 (data not shown)
- Steady states for E2 and P4 were shown by consistent C_{trough} levels from pre-dose Day 6 through 24 h post-dose Day 7 (**Table 3**), and thus, 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

Table 2. Dose Dependence of Serum Estradiol and Progesterone Levels with TX-001HR at Days 1 and 7

Parameters (Units)	1 mg E2/ 100 mg P4	0.5 mg E2/ 100 mg P4
Estradiol		
Day 1	(n=20)	(n=20)
$AUC\tau_{trap}$ (h·pg/mL)	400.5 (157.9)	167.8 (100.0)
C_{max} (pg/mL)	31.5 (29.7)	13.5 (9.3)
Day 7	(n=20)	(n=17)
$AUC\tau_{trap}$ (h·pg/mL)	772.4 (384.1)	386.8 (356.6)
C_{avg} (pg/mL)	34.0 (14.5)[a]	16.6 (14.5)
C_{max} (pg/mL)	42.3 (18.6)	24.0 (16.9)
Progesterone		
Day 1	(n=20)	(n=20)
$AUC\tau_{trap}$ (h·ng/mL)	14.1 (9.9)	10.1 (9.4)
C_{max} (ng/mL)	6.5 (6.2)	3.7 (3.2)
Day 7	(n=20)	(n=17)
$AUC\tau_{trap}$ (h·ng/mL)	18.1 (15.6)	12.2 (11.0)
C_{avg} (ng/mL)	0.76 (0.65)	0.55 (0.45)
C_{max} (ng/mL)	11.3 (23.1)	4.4 (5.7)

All data expressed as mean (SD). [a]n=19.

Table 3. Baseline-Adjusted Steady-State (C_{trough}) Levels for Serum Estradiol and Progesterone with 2 Doses of TX-001HR

C_{trough}	1 mg E2/ 100 mg P4 (n=20)	0.5 mg E2/ 100 mg P4 (n=17)
Estradiol (pg/mL)		
Day 6 (pre-dose)	22.9 (12.9)	10.6 (7.9)
Day 7 (pre-dose)	28.6 (18.1)	11.4 (9.6)
Day 7 (24 h post-dose)	24.4 (14.4)	11.0 (9.9)
Progesterone (ng/mL)		
Day 6 (pre-dose)	0.14 (0.13)[b]	0.15 (0.14)[a]
Day 7 (pre-dose)	0.17 (0.15)	0.15 (0.14)
Day 7 (24 h post-dose)	0.14 (0.11)[c]	0.10 (0.08)[a]

All data expressed as mean (SD). [a]n=15; [b]n=18; [c]n=19.

Table 4. Accumulation Ratios for Baseline-Adjusted Serum Estradiol and Progesterone Levels with 2 Doses of TX-001HR

Parameters (units)	1 mg E2/ 100 mg P4	0.5 mg E2/ 100 mg P4
Estradiol	(n=20)	(n=15)
$AUC\tau_{trap}$ (h·pg/mL)		
Day 7	772.4 (384.1)	335.6 (222.8)
Day 1	400.5 (157.9)	198.2 (90.4)
Accumulation ratio ($AUC\tau_{trap}$ Day 7/ $AUC\tau_{trap}$ Day 1)	2.05 (0.96)	1.81 (0.9)
Progesterone	(n=20)	(n=17)
$AUC\tau_{trap}$ (h·ng/mL)		
Day 7	18.1 (15.6)	12.2 (11.0)
Day 1	14.1 (9.9)	10.8 (10.0)
Accumulation ratio ($AUC\tau_{trap}$ Day 7/ $AUC\tau_{trap}$ Day 1)	1.44 (0.95)	1.36 (0.73)

All data expressed as mean (SD).
$AUC\tau_{trap}$ = area under the curvet calculated using the trapezoidal method.

Conclusions and Discussion

- Consistent with other progesterone studies,[5,6] 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 E2/P4 as formulated in TX-001HR and demonstrated in these studies are important
  - 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 while protecting the endometrium from hyperplasia[7]
- If approved, TX-001HR may be an important option for 2.5 million women who use unapproved, inadequately regulated, compounded bioidentical hormone therapy (CBHT).[8] Such CBHT has not been rigorously evaluated in clinical studies.[9] Thus, food effects and other potential risks have not been systematically determined.

References

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Disclosures

JL consults for Therapeutics MD, Ascend Therapeutics, and Allergan. GC consults to pharmaceutical companies including but not limited to TherapeuticsMD and has stock options with TherapeuticsMD. AMS, SG, BB, and SM are employees of TherapeuticsMD (with stock/stock options). BB is also on the Board of TherapeuticsMD. TherapeuticsMD sponsored the study and analysis, and supported the medical writing assistance provided by Kathleen Chieth, PhD, CMPP (Precise Publications, LLC).

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