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Midlife health in the 21st century

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

Photo
(compulsory)



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Background

- Many postmenopausal women choose hormone therapy (HT) with natural progesterone (P4)
- TX-001HR is an investigational, oral, combined, 17 β -estradiol (E2)/micronized P4 softgel capsule being developed for treating moderate-to-severe vasomotor symptoms (VMS) in menopausal women with a uterus
 - In the REPLENISH trial, women randomized to continuous oral TX-001HR (100 mg of P4 with E2 doses of 0.5 or 1 mg, or 50 mg with 0.25 or 0.5 mg) did not have endometrial hyperplasia or cancer with 12 months of use, and had a favourable bleeding profile¹
- Serum P4 levels required to prevent endometrial hyperplasia with HT have not been well characterized

1. Lobo R, et al. *Obstet Gynecol* 2018. In press

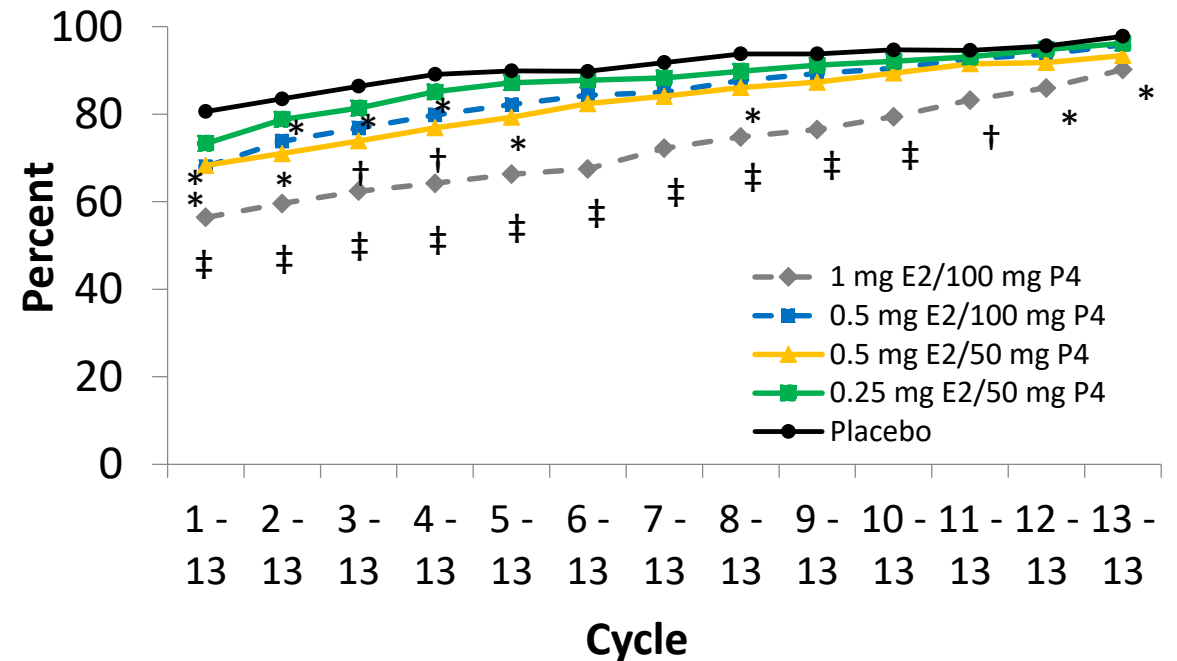
REPLENISH Trial: Endometrial Hyperplasia and Cumulative Amenorrhea

No endometrial hyperplasia or endometrial malignancies detected with any TX-001HR dose or placebo at 12 months

**Cumulative amenorrhea from cycle 1 to 13 was 56-73% with TX-001HR vs 81% with placebo
>90% had amenorrhea during cycle 13**

Hyperplasia rate at 12 months

| E2/P4 | n | Incidence rate | 1-sided upper 95% CI |
|---------------|-----|----------------|----------------------|
| 1 mg/100 mg | 280 | 0 (0) | 1.06% |
| 0.5 mg/100 mg | 303 | 0 (0) | 0.98% |
| 0.5 mg/50 mg | 306 | 0 (0) | 0.97% |
| 0.25 mg/50 mg | 274 | 0 (0) | 1.09% |
| Placebo | 92 | 0 (0) | 3.20% |

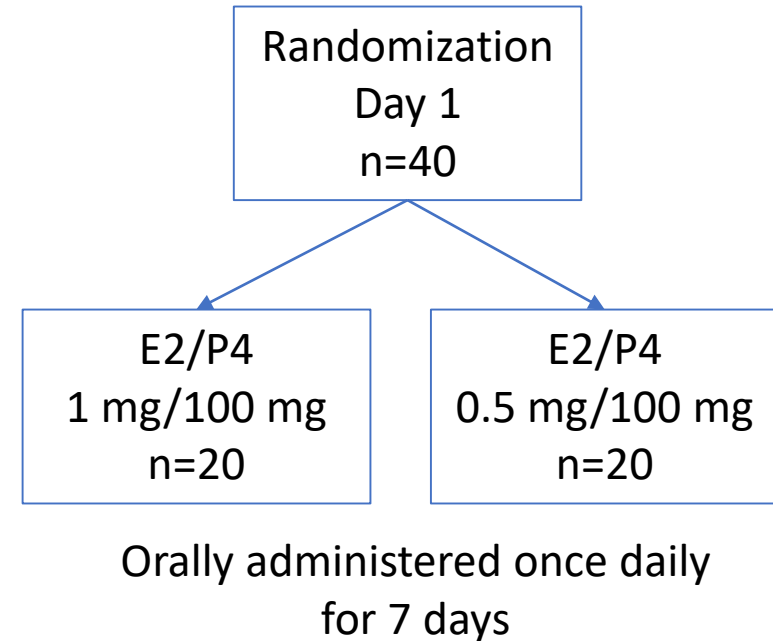


Objectives

- Characterize serum P4 levels with TX-001HR doses in 2 phase 1 studies
 - Multi-dose 7-day study (2 different doses were investigated)
 - Single-dose study under fasted vs fed conditions

Multi-Dose Study: Design

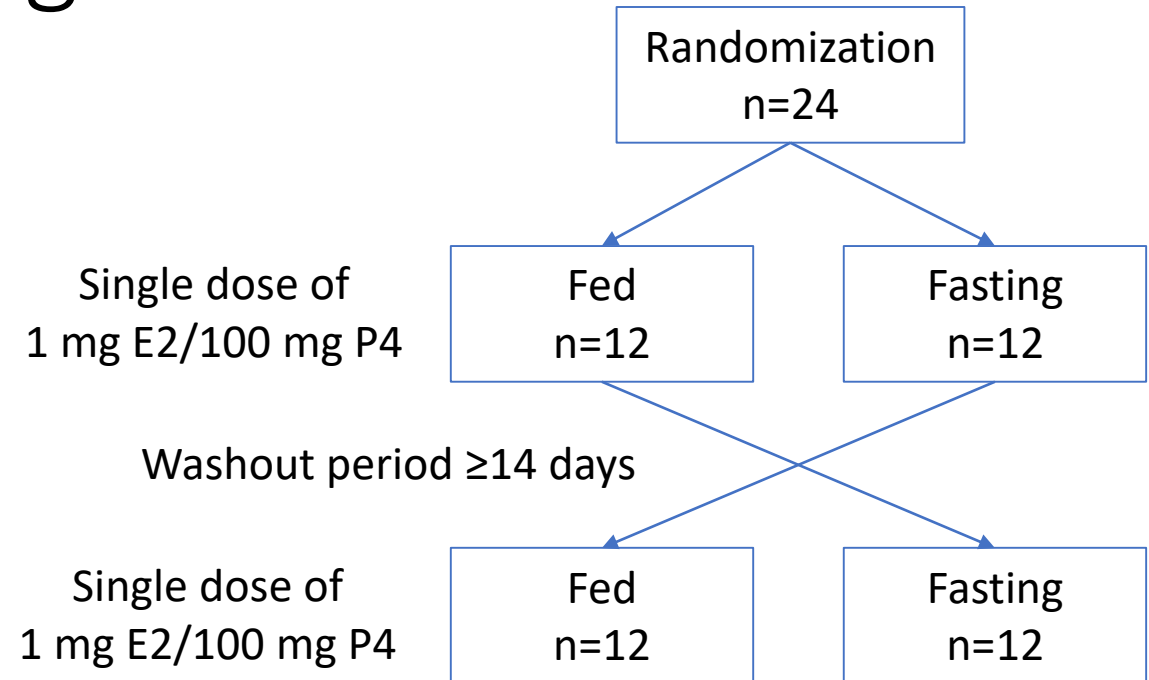
- Phase 1, open-label, randomized, trial in healthy menopausal women
 - Normal diet: 20%-35% fat
- 2 doses of TX-001HR (both containing 100 mg P4 with 1 mg or 0.5 mg E2) were administered orally, daily for 7 days (steady-state)
- Blood was collected on days 1 and 7 to assess PK parameters for P4
 - Prior to dosing [0-hour]
 - Post-dosing: 20, 40, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours



Food-Effect Study: Design

- Phase 1, open-label, randomized, crossover trial in menopausal women
- TX-001HR dose: 1 mg E2/100 mg P4

Fasting: ≥ 10 h
Fed: 30 min after a high-fat meal [52% fat calories]



- Blood was collected to assess PK parameters for P4 under fasting and fed conditions
 - Prior to dosing [0-hour]
 - Post dosing: 20, 40, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours

Analysis and Statistics

- Samples analyzed for progesterone using validated LC-MS/MS assays
- Multi-dose study
 - LLOQ 0.05 ng/mL; inter-day accuracy 1.76% bias; inter-day precision 4.35% CV
 - $AUC_{\tau_{\text{trap}}}$, C_{avg} , C_{max} , t_{max} were assessed for progesterone
 - Summarized descriptively
- Single-dose food study
 - LLOQ 0.1 ng/mL; inter-day accuracy 1.53% bias; inter-day precision 4.53% CV
 - AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} were assessed for progesterone
 - Baseline-adjusted geometric mean reported
 - Fasted treatment served as the reference
 - Tested for bioequivalence with geometric mean ratios and 90% CI

$AUC_{\tau_{\text{trap}}}$: area under the concentration-time curve during the dosage interval (τ) calculated using the trapezoidal methods

Multi-Dose Study: Results

- Participants had a mean age of 57.2 years and mean BMI of 25.7 kg/m²
 - 82.5% were White and 17.5% African American
- On Day 7 (pre-dose), C_{trough} ranged from 0.15–0.17 ng/mL
- After 7 days of dosing with TX-001HR doses containing 100 mg P4
 - Mean P4 serum concentration ranged from 0.55–0.76 ng/mL (Table)

Baseline-adjusted PK Parameters at Days 1 and 7

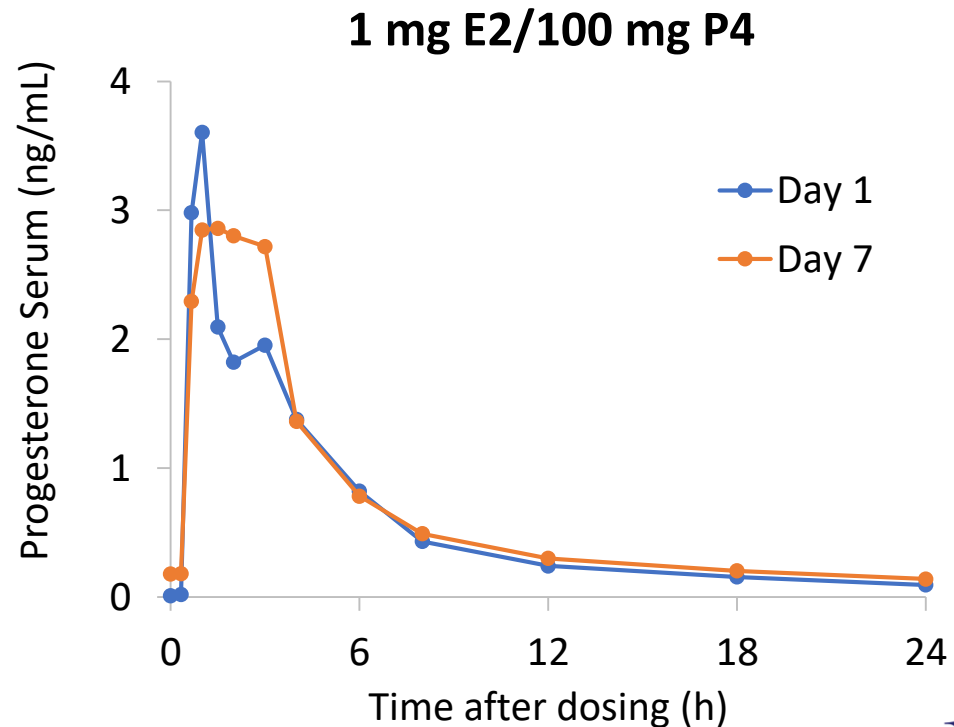
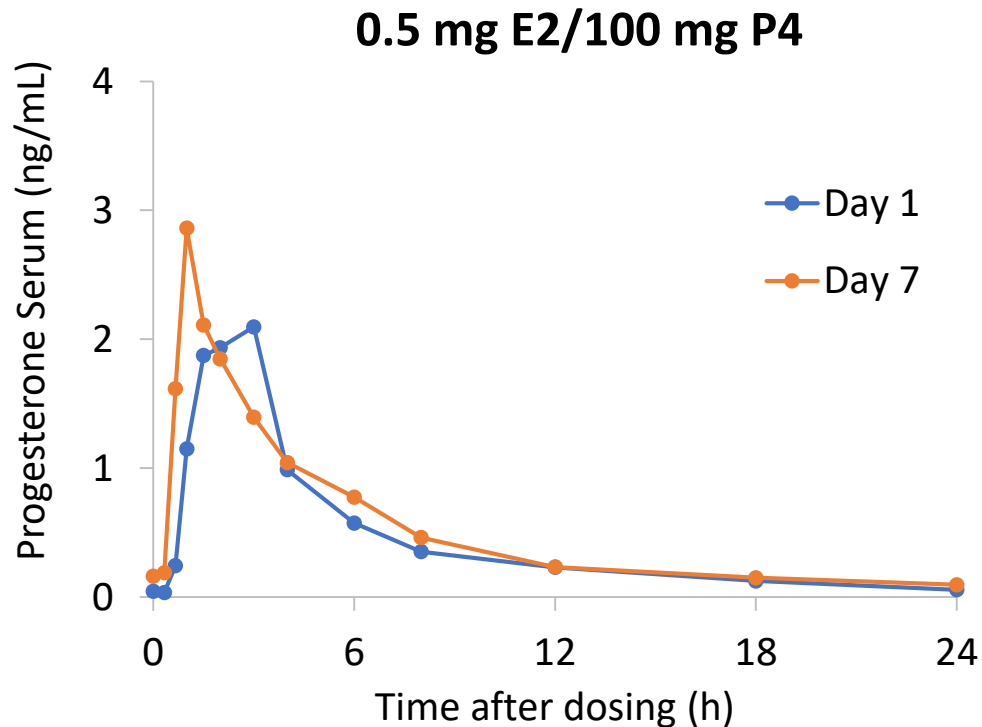
| Progesterone Parameters | 1 mg E2/ 100 mg P4 (n=20) | 0.5 mg E2/ 100 mg P4 (n=20)* |
|--|---------------------------------|------------------------------------|
| Day 1 | | |
| AUC _τ _{trap} (h·ng/mL) | 14.1 (9.9) | 10.1 (9.4) |
| C _{max} (ng/mL) | 6.5 (6.2) | 3.7 (3.2) |
| t _{max} (h) | 2.2 (1.5) | 2.5 (1.9) |
| Day 7 | | |
| AUC _τ _{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) |
| t _{max} (h) | 2.6 (1.5) | 2.9 (2.3) |

*n=17 at Day 7.

The LLOQ of the LC-MS/MS assay for progesterone was 0.050 ng/mL.

Multi-dose Study Findings

- No statistical difference in P4 levels or PK with E2 doses of 1 mg or 0.5 mg
- Accumulation ratio of 1.4 for Day 7 AUC/Day 1 AUC



Food-Effect Study: Results

- Participants had a mean age of 57.5 years and mean BMI of 26.9 kg/m²
 - 71% were White and 25% African American
- In the fed versus fasted state, ratios were significantly higher for P4 AUC_{0-t} and C_{max}
 - For bioequivalency, ratio had to be within 90% CI

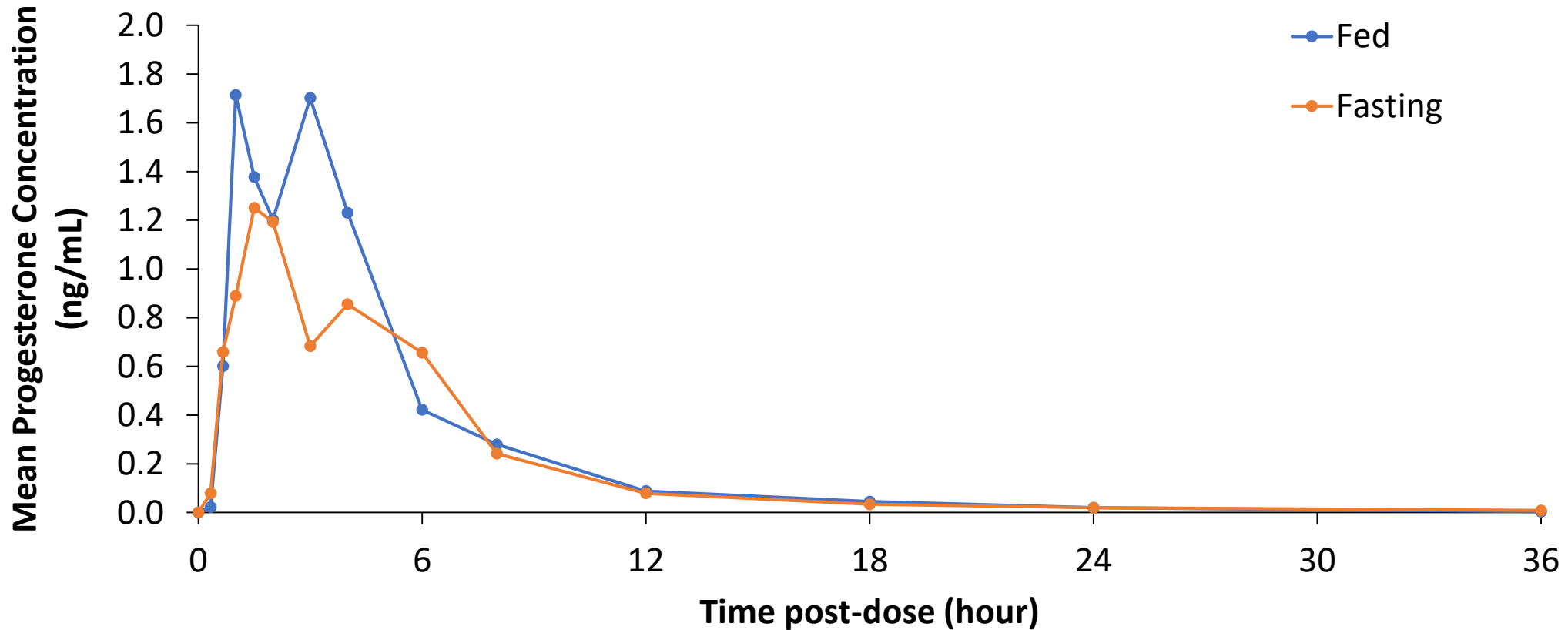
Baseline-adjusted PK Parameters

| Progesterone (P4) | Fed | Fasting | Fed/Fasting Ratio |
|------------------------------|-------------|-------------|-------------------|
| AUC _{0-t} (ng·h/mL) | 6.45 | 3.54 | 1.8 |
| AUC _{0-∞} (ng·h/mL) | 6.72 | 5.26 | 1.3 |
| C _{max} (ng/mL) | 2.50 | 0.92 | 2.7 |
| t _{max} (h) | 2.48 | 2.64 | 0.9 |

Data expressed as baseline-adjusted geometric means

Food-Effect Study: Serum Progesterone

Baseline-Adjusted Serum Progesterone



Conclusion

- In the 7-day, multi-dose study, oral TX-001HR with 100 mg P4 resulted in
 - $AUC_{\tau_{\text{trap}}}$ of 10.1–18.1 h·ng/mL
 - C_{avg} of 0.55–0.76 ng/mL
 - C_{max} of 3.7–11.3 ng/mL
- These systemic P4 levels result in adequate endometrial protection from hyperplasia with continuous-combined E2/P4 (TX-001HR) as observed in the REPLENISH trial,¹ while improving VMS
- In the single-dose, food study, P4 bioavailability was enhanced with food by approximately 2 fold, consistent with other studies of natural P4 (e.g., Prometrium)²

Discussion

- P4 in TX-001HR, by continuous delivery, may protect the endometrium by downregulating endometrial estrogen receptors and decreasing mitotic activity
- This effect of decreasing estrogen action may prevent endometrial hyperplasia and may decrease endometrial bleeding