IMS
16 WORLD CONGRESS ON MENOPAUSE
Midlife health in the 21st century
FAIRMONT HOTEL VANCOUVER, CANADA 6–9 JUNE 2018

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

Photo
(compulsory)

Rogerio A. Lobo, MD[1]; Frank Z. Stanczyk, PhD[2]; Ginger D. Constantine, MD[3]; James H. Pickar, MD[1]; Annette M. Shadiack, PhD[4]; Brian Bernick, MD[4]; Sebastian Mirkin, MD[4]

[1]Columbia University Medical Center, New York, NY
[2]University of Southern California, Keck School of Medicine, Los Angeles, CA
[3]EndoRheum Consultants, LLC, Malvern, PA
[4]TherapeuticsMD, Boca Raton, FL

Disclosures

- **Research grants**: TherapeuticsMD
- **Consulting** (within the past 3 years): Allergan, AMAG, JDS Therapeutics, Mithra, Pfizer, Teva, TherapeuticsMD

Background

- Many postmenopausal 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 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 profile[1]
- 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

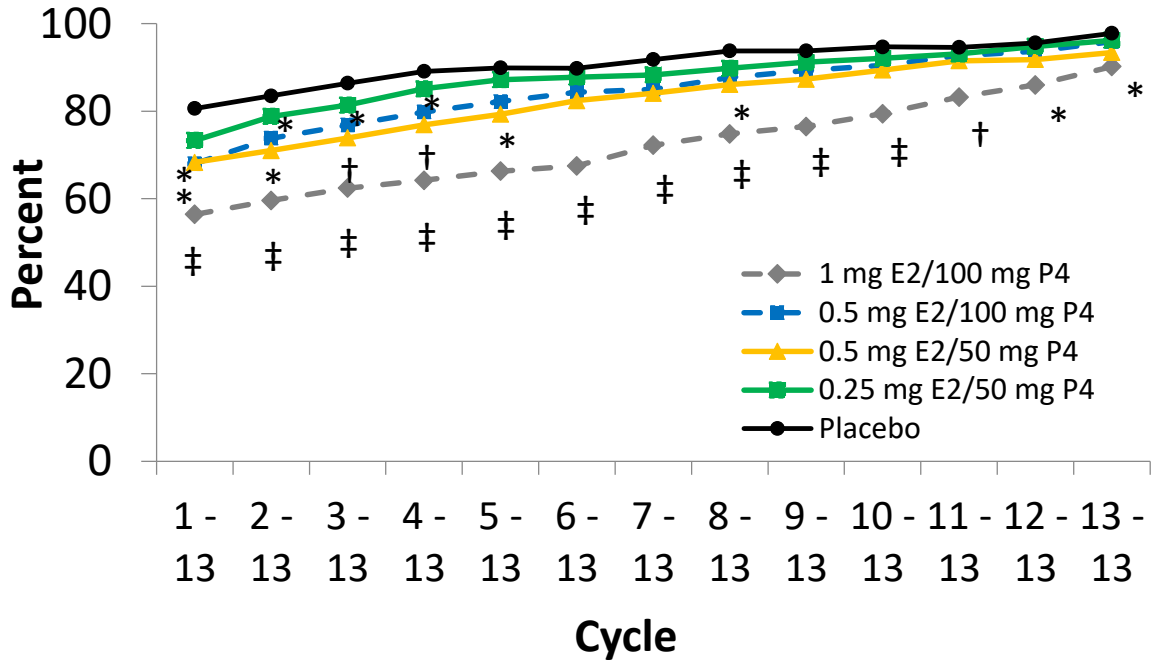
No endometrial hyperplasia or endometrial malignancies detected with any TX-001HR dose or placebo at 12 months

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%



Lobo RA et al. *Obstet Gynecol* 2018, In press.

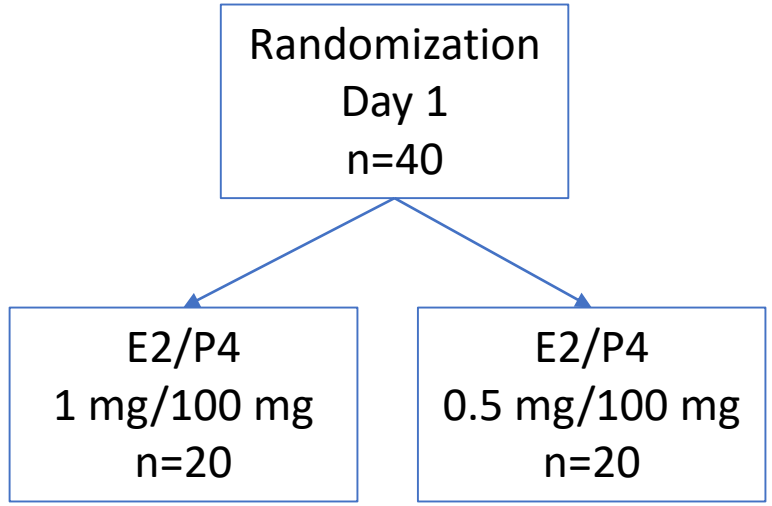
*P<0.05; †P<0.01; ‡P<0.001 vs placebo. Cycles are 28 days in length

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

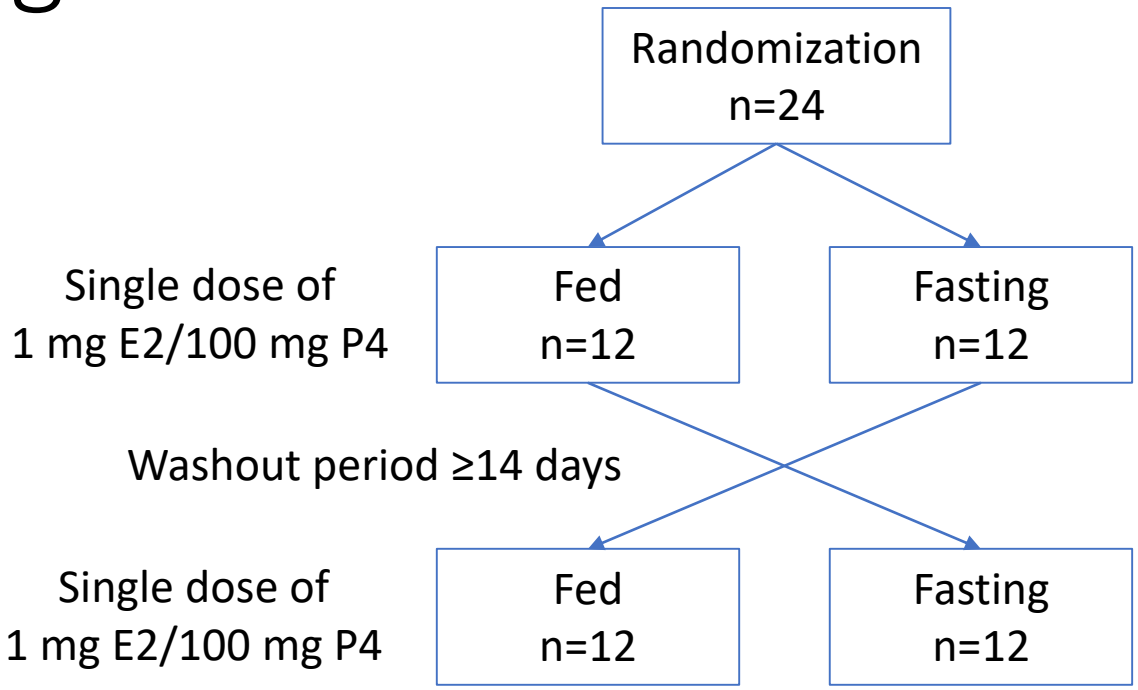


Orally administered once daily for 7 days

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
  - $AUC\tau_{trap}$, 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

$AUC\tau_{trap}$: 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/m^2
  - 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

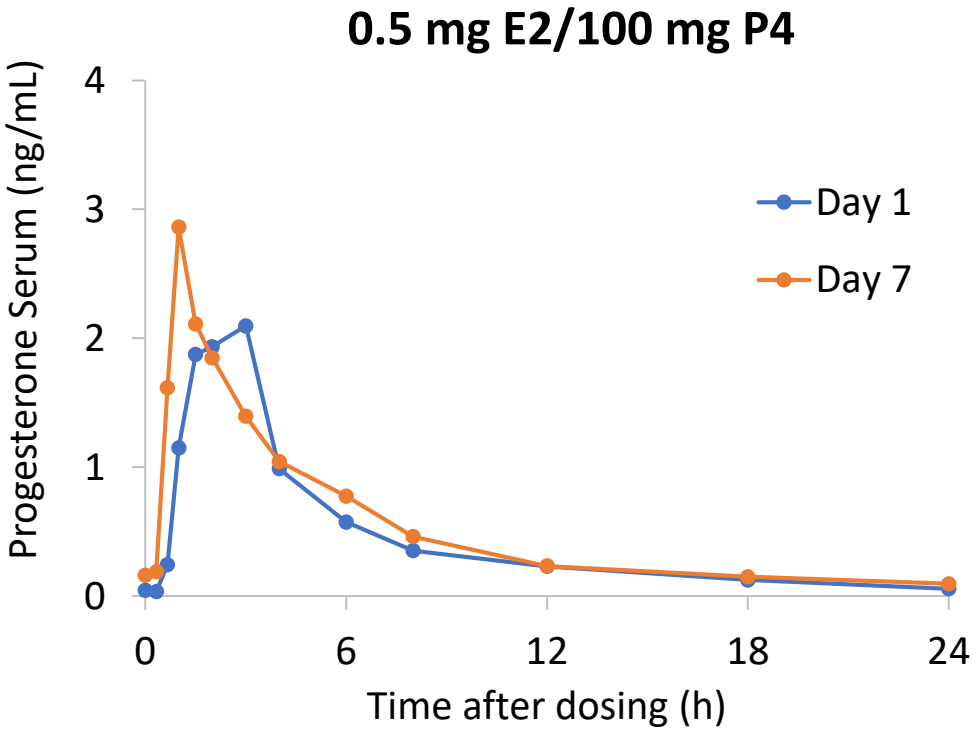
Progesterone Parameters	1 mg E2/ 100 mg P4 (n=20)	0.5 mg E2/ 100 mg P4 (n=20)*
Day 1		
$AUC\tau_{trap}$ (h·ng/mL)	14.1 (9.9)	10.1 (9.4)
C_{max} (ng/mL)	6.5 (6.2)	3.7 (3.2)
t_{max} (h)	2.2 (1.5)	2.5 (1.9)
Day 7		
$AUC\tau_{trap}$ (h·ng/mL)	18.1 (15.6)	12.2 (11.0)
C_{avg} (ng/mL)	**0.76 (0.65)**	**0.55 (0.45)**
C_{max} (ng/mL)	11.3 (23.1)	4.4 (5.7)
t_{max} (h)	2.6 (1.5)	2.9 (2.3)

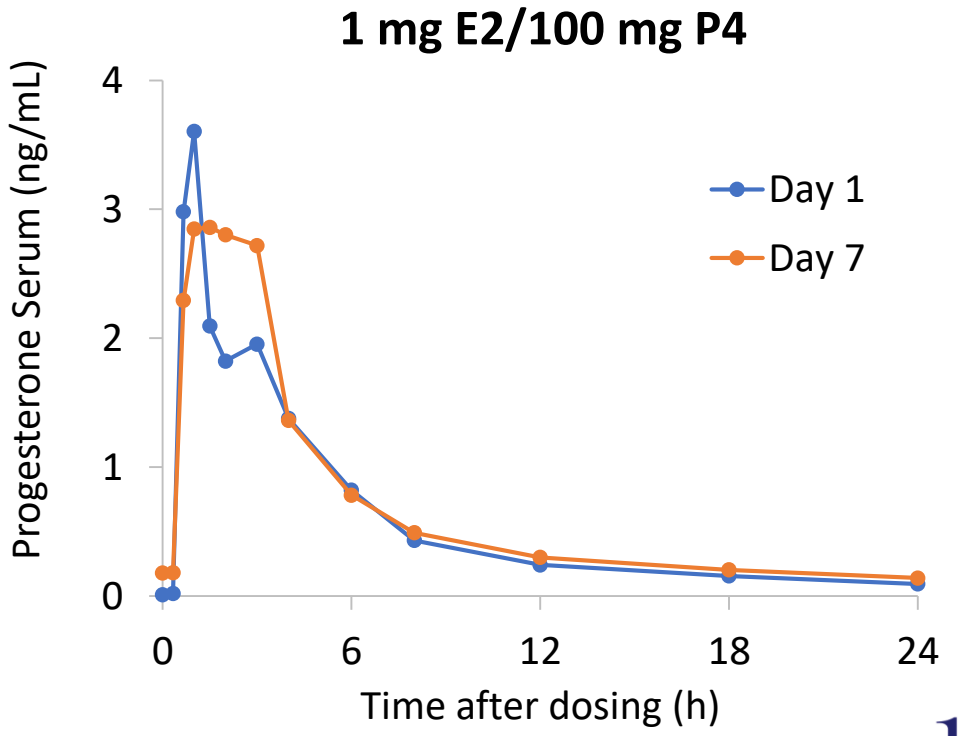
*n=17 at Day 7.

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





IMS

16 WORLD CONGRESS ON MENOPAUSE

Food-Effect Study: Results

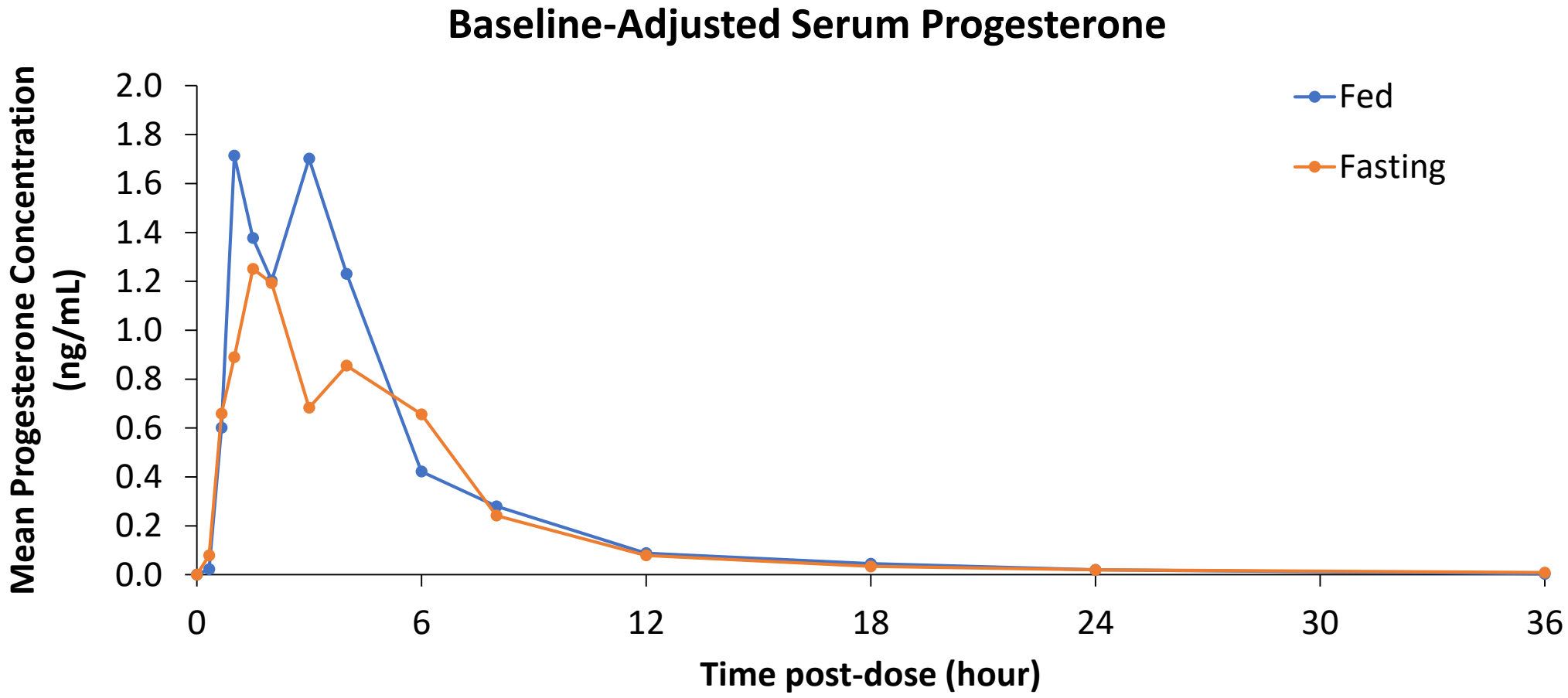
- Participants had a mean age of 57.5 years and mean BMI of 26.9 kg/m^2
  - 71% were White and 25% African American
- In the fed versus fasted state, ratios were significantly higher for P4 AUC_{0-t} and C_{max}
  - For bioequivalency, ratio had to be within 90% CI

Baseline-adjusted PK Parameters

Progesterone (P4)	Fed	Fasting	Fed/Fasting Ratio
AUC_{0-t} (ng·h/mL)	6.45	3.54	**1.8**
$AUC_{0-\infty}$ (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



IMS

16 WORLD CONGRESS ON MENOPAUSE

Conclusion

- In the 7-day, multi-dose study, oral TX-001HR with 100 mg P4 resulted in
  - $AUC\tau_{trap}$ 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]

IMS 16 WORLD CONGRESS ON MENOPAUSE

1. Lobo R, et al. *Obstet Gynecol* 2018. In press. **2.** Simon JA, et al. *Fertil Steril* 1993;60:26-33.

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