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

- Up to 75 million menopausal hormone therapy prescriptions (FDA-approved and compounded) containing progesterone (P4)/progestins were estimated to be filled in the US per year[1]
- The phase 3 REPLENISH trial, which evaluated the safety and efficacy of 4 doses of TX-001HR (17β-estradiol [E2]/P4: 1 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, 0.25 mg/50 mg), found no cases of endometrial hyperplasia or cancer with up to 12 months of continuous daily use, while significantly reducing the frequency and severity of moderate to severe VMS with most doses[2]
- Serum P4 levels required for endometrial protection in a continuous-combined regimen have not been well characterized

Objective

To describe serum P4 levels (when P4 dosed continuously) sufficient to counteract the potential estrogenic effects of 1 or 0.5 mg oral E2 on the endometrium. Serum levels of E2 and estrone (E1) were also examined.

Methods

- The serum levels of E2, E1, and P4 at select TX-001HR (E2/P4) doses were characterized in 2 separate studies
  - Single timepoint in the phase 3 REPLENISH trial
  - Multi-dose, multi-timepoint phase 1 trial
- In both trials, women were administered TX-001HR in the evening with food. Serum hormone levels were quantified at InVentiv Clinical Laboratories, Inc. (Princeton, NJ) using the same validated liquid chromatography (progesterone)- or gas chromatography (estradiol/estrone)-tandem mass spectrometry (LC/GC-MS/MS) methods
- Details on sampling time and assessments are found in **Table 1**

Phase 3 REPLENISH Trial

- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in non-hysterectomized, postmenopausal women (age 40–65 years; BMI ≤34 kg/m^2) with vasomotor symptoms[2]
- Women (n=1845) were randomized to 4 doses of TX-001HR or placebo administered orally, once daily for up to 12 months
  - Mean hormone levels for TX-001HR doses containing 1 mg E2 or 0.5 mg E2 are reported here

Phase 1 Multi-Dose Trial

- Phase 1, open-label, randomized, multi-dose study in healthy postmenopausal women (age 40–65 years; BMI 18–30 kg/m^2)
- Women (n=40) were randomized to 2 fixed-dose combinations of TX-001HR (1 mg E2/100 mg P4 [n=20] and 0.5 mg E2/100 mg P4 [n=20]) administered orally, once daily for 7 days
  - Pharmacokinetics (PK) parameters are reported here

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

Assessment	Phase 3 REPLENISH Trial	Phase 1 Multi-dose Trial
Doses*	• 1 mg E2/100 mg P4 (n=415) • 0.5 mg E2/100 mg P4 (n=424) • 0.5 mg E2/50 mg P4 (n=421)	• 1 mg E2/100 mg P4 (n=20) • 0.5 mg E2/100 mg P4 (n=20)
Time	Single-point collection (9-16 h after dose) for • P4 at baseline, week 12 and month 12 • E2 and E1 at baseline, weeks 4 and 12, and months 6, 9 and 12	Day 1 • 60, and 30 min before dosing (baseline) Days 1 and 7 • 0, 20, 40, 60, and 90 min, and 2, 3, 4, 6, 8, 12, 18, 24 h post dosing, and 36 and 48 h (day 7 only)
Parameters	Average serum concentrations	AUC$_\tau$, C_{avg}, C_{max}, t_{max}, C_{trough}, Accumulation ratio

Method	Progesterone	Estradiol	Estrone
Instrumentation	Validated LC-MS/MS	Validated GC-MS/MS	Validated GC-MS/MS
LLOQ	0.05 ng/mL	2.00 pg/mL	5.00 pg/mL
ULOQ	50 ng/mL	500 pg/mL	1000 pg/mL
Accuracy	2.08%	0%	2.50%
Precision, CV%	4.65%	3.51%	5.37%

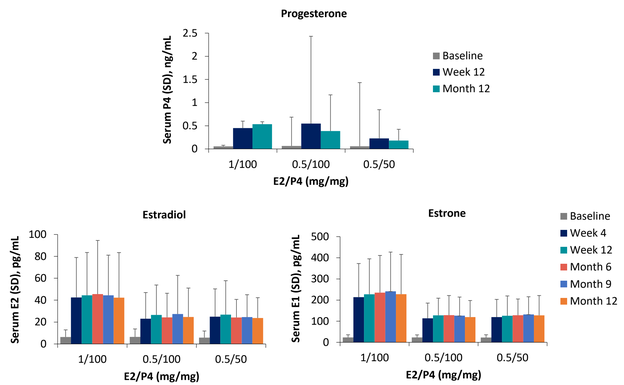
AUC$_\tau$: area under the curve calculated using the trapezoidal method; CV: coefficient of variation; GC-MS/MS: gas chromatography-tandem mass spectroscopy assay; LC: liquid chromatography; LLOQ: lowest limit of quantification; ULOQ: upper limit of quantification.
*Only TX-001HR doses containing 1 mg E2 or 0.5 mg E2 are reported here.

Results

Phase 3 REPLENISH Trial

- Baseline demographic characteristics were similar between all treatment groups, including overall mean age (54.6 years) and BMI (26.6 kg/m^2); 67% were White and 31% were African American
- Baseline serum P4 levels were below level of quantification (0.05 ng/mL) for the vast majority of subjects
- Mean baseline serum levels were 6.1 pg/mL for E2 and 23.3 pg/mL for E1
- Approximate dose proportionality was observed for all three analytes (**Figure 1**)

Figure 1. REPLENISH Trial: Unadjusted Mean Hormone Concentrations



Phase 1 Multi-Dose Trial

- Baseline demographics were comparable between the 2 treatment groups, including overall mean age (57.2 years) and BMI (25.7 kg/m^2); 82.5% were White and 17.5% were African American
- Baseline serum P4 levels were below level of quantification (0.05 ng/mL) for the vast majority of subjects
- Mean baseline serum levels were 13.2 pg/mL for E2 and 25.5 pg/mL for E1
- Mean serum concentrations for P4, E2, and E1 on day 1 and day 7 are in **Figure 2**
- Mean unadjusted PK parameters for P4, E2, and E1 are in **Table 2**
  - P4 PK parameters were similar between the 2 doses
    - Accumulation ratios for P4 levels were ~1.4 for both doses
  - Dose-dependent exposure was observed for E2 and E1 parameters (AUC$_\tau$ and C_{max}) on Days 1 and 7
    - Both doses had accumulation ratios of ~1.9 for E2 and ~1.6 for E1
- Steady states for P4, E2 and E1 were shown by consistent C_{trough} levels from pre-dose Day 6 through 24-h, post-dose Day 7 (**Table 3**). Thus, steady state was achieved within 1 week of daily dosing regardless of dose

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

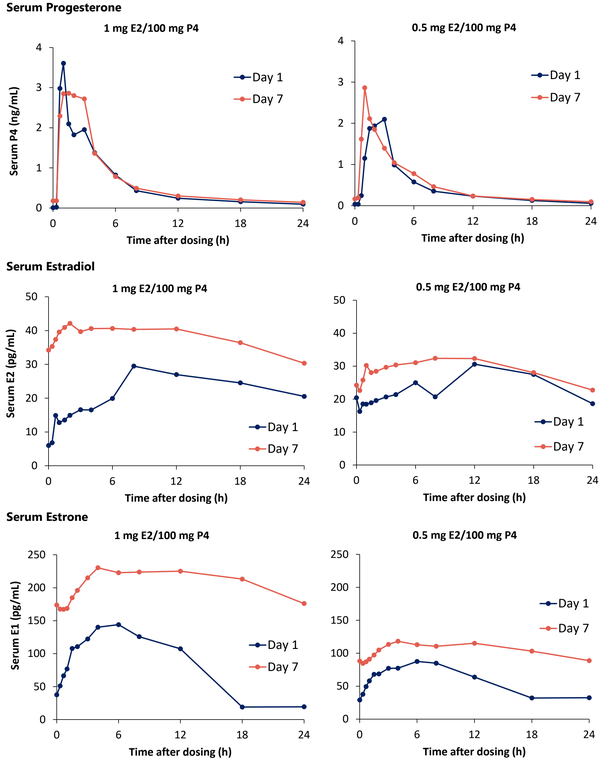


Table 2. Phase 1 Study: Unadjusted PK Parameters on Days 1 and 7

Parameters (Units)	Progesterone 1 mg E2/100 mg P4	Progesterone 0.5 mg E2/100 mg P4	Parameters (Units)	Estradiol 1 mg E2/100 mg P4	Estradiol 0.5 mg E2/100 mg P4	Estrone 1 mg E2/100 mg P4	Estrone 0.5 mg E2/100 mg P4
Day 1	(n=20)	(n=20)	**Day 1**	(n=20)	(n=20)	(n=20)	(n=20)
AUC$_\tau$ (h·ng/mL)	14.3 ± 9.9	10.6 ± 9.5	AUC$_\tau$ (h·pg/mL)	543 ± 250	559 ± 695	2860 ± 883	1754 ± 836
C_{max} (ng/mL)	6.5 ± 6.2	3.8 ± 3.2	C_{max} (pg/mL)	37.6 ± 35.5	33.8 ± 48.6	171 ± 67.3	99.2 ± 54.5
t_{max} (h)	2.2 ± 1.5	2.5 ± 1.9	t_{max} (h)	10.0 ± 6.8	11.1 ± 7.2	11.1 ± 5.8	11.8 ± 5.8
Day 7	(n=20)	(n=17)	**Day 7**	(n=20)	(n=17)	(n=20)	(n=17)
AUC$_\tau$ (h·ng/mL)	18.2 ± 15.5	12.5 ± 10.9	AUC$_\tau$ (h·pg/mL)	910 ± 339	699 ± 567	5046 ± 2155	2538 ± 1170
C_{avg} (ng/mL)	0.77 ± 0.64	0.53 ± 0.45	C_{avg} (pg/mL)	38.1 ± 14.2	29.2 ± 23.7	211 ± 90.1	106 ± 48.9
C_{max} (ng/mL)	11.3 ± 23.1	4.4 ± 5.7	C_{max} (pg/mL)	48.2 ± 15.8	37.2 ± 28.7	257 ± 101	131 ± 56.2
t_{max} (h)	2.6 ± 1.5	2.9 ± 2.3	t_{max} (h)	5.6 ± 5.6	5.9 ± 4.4	5.5 ± 3.5	8.5 ± 4.9
Accumulation ratio	**1.44 ± 0.95**	**1.36 ± 0.73**	**Accumulation ratio**	**1.81 ± 0.65**	**1.94 ± 1.96**	**1.72 ± 0.41**	**1.54 ± 0.25**

All data expressed as mean ± SD. [a]n=19; [b]n=15. Accumulation ratio = AUC$_\tau$ Day 7/AUC$_\tau$ Day 1

Table 3. Phase 1 Study: Unadjusted Steady-state (C_{trough}) Hormone Levels

C_{trough}	Progesterone (ng/mL) 1 mg E2/100 mg P4 (n=20)	Progesterone (ng/mL) 0.5 mg E2/100 mg P4 (n=17)	Estradiol (pg/mL) 1 mg E2/100 mg P4 (n=20)	Estradiol (pg/mL) 0.5 mg E2/100 mg P4 (n=17)	Estrone (pg/mL) 1 mg E2/100 mg P4 (n=20)	Estrone (pg/mL) 0.5 mg E2/100 mg P4 (n=17)
Day 6 (pre-dose)	0.15 ± 0.13[a]	0.16 ± 0.14[b]	28.4 ± 12.1	23.1 ± 36.3	171.5 ± 81.6	88.4 ±38.4
Day 7 (pre-dose)	0.18 ± 0.15	0.16 ± 0.14	34.2 ± 17.4	24.2 ± 21.5	173.7 ± 83.0	88.1 ± 40.6
Day 7 (24 h post-dose)	0.15 ± 0.11[c]	0.12 ± 0.07[d]	30.3 ± 12.9	22.7 ±18.7	176.0 ± 85.3	88.8 ± 50.5

All data expressed as mean ± SD. [a]n=18; [b]n=15; [c]n=19; [d]n=14.

Conclusions

- Levels of P4, as measured in the REPLENISH study, were associated with endometrial protection from estradiol administered at 1 mg or 0.5 mg daily over 1 year[2]
  - Similar P4 levels were observed in the phase 1 PK study
- Steady state levels of E2 and E1 with TX-001HR were achieved within 7 days in the phase 1 PK study
  - These estrogen levels were similar to those observed here for the REPLENISH trial[2]
  - In REPLENISH these levels reduced moderate to severe VMS frequency and severity by week 4[2]
- While E2 levels were well above the postmenopausal range in REPLENISH, women taking TX-001HR did not experience endometrial hyperplasia or cancer, which are experienced more frequently in women taking unopposed estrogens[3]
  - Continuous 50 mg or 100 mg P4 appears to be sufficient to counteract the endometrial estrogenic effect of 0.5 mg or 1 mg E2 for at least 1 year
- This evaluation helps to further our understanding of P4 levels required for endometrial protection

References

1. Pinkerton J, Santoro N. *Menopause* 2015;22:926-936. **2.** Lobo R, et al. *Obstet Gynecol* 2018;132:161-170. **3.** Pickar JH, et al. *Fertil Steril.* 2001;76:25-31.

Disclosures

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