Effects of Single-Capsule 17β-Estradiol/Progesterone (TX-001HR) on Metabolic Parameters and Cardiovascular Outcomes in Menopausal Women of the REPLENISH Trial

Rogerio A Lobo, MD[1]; James Liu, MD[2]; Andrew M Kaunitz, MD[3]; Brian Bernick, MD[4]; Shelli Graham, PhD[4]; Ginger D Constantine, MD[5]; Sebastian Mirkin, MD[4]

[1]Columbia University Medical Center, New York, NY
[2]University Hospital Cleveland Medical Center, Cleveland, OH
[3]University of Florida College of Medicine-*Jacksonville*, Jacksonville, FL
[4]TherapeuticsMD, Boca Raton, FL; 5EndoRheum Consultants, LLC, Malvern, PA

Disclosures

- **Consultant**: Multiple pharmaceutical companies including but not limited to TherapeuticsMD
- **Stock options:** TherapeuticsMD

Background

- Menopausal vasomotor symptoms (VMS) can be effectively treated with hormone therapy (HT), which reduces hot flush frequency and severity[1]
- However, HT can be associated with an increased risk of adverse events, such as venous thromboembolism (VTE), cardiovascular disease, and cerebrovascular disease[2-4]
- Evidence suggests that progesterone use in HT may not negatively affect VTE risk or cardiovascular outcomes, as with synthetic progestins[5-7]
- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone in a single, oral, softgel capsule[8]

1. NAMS. *Menopause*. 2017;24:728-753. **2.** Henderson VW and Lobo, RA. *Climacteric*. 2012;15:229-234. **3.** Renoux C, et al. *J Thromb Haemost*.2010;8:979-986. **4.** Hale GE and Shufelt CL. *Trends Cardiovasc Med*. 2015;25:540-549. **5.** Mirkin S. *Climacteric*. 2018;21:346-354. **6.** Canonico M, et al. *Arterioscler Thromb Vasc Biol* 2010;30:340-345. **7.** Canonico M, et al. *Stroke* 2016;47:1734-1741. **8.** Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

REPLENISH Trial

- Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus (NCT01942668)
  - 1-year endometrial and general safety study
  - 12-week efficacy substudy for the treatment of VMS
- **Additional safety endpoints**
  - Metabolic parameters
  - Cardiovascular outcomes

Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

Study Design: Randomization

VMS substudy (12 wks)

- ≥7/day or ≥50/week moderate-to-severe hot flushes
- Randomized 1:1:1:1:1

Treatment Groups

- 1 mg E2/100 mg P4
- 0.5 mg E2/100 mg P4
- 0.5 mg E2/50 mg P4
- 0.25 mg E2/50 mg P4
- Placebo

General study (12 mos)

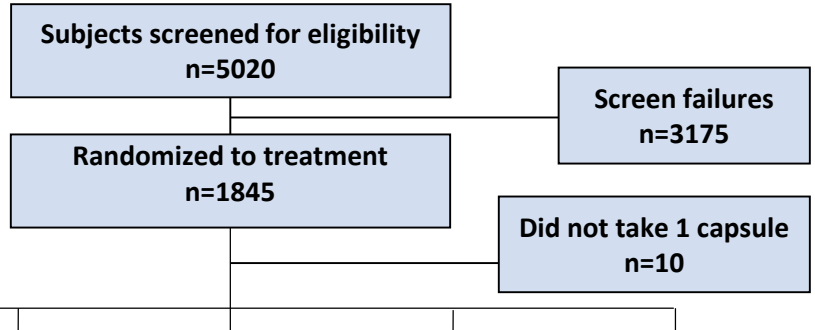
- Did not qualify for VMS substudy
- Randomized 1:1:1:1

- TX-001HR was taken daily for up to 12 months (VMS substudy was 12 weeks)
- All participants were assessed for general and endometrial safety
- All women completed a daily diary on the frequency and severity of their VMS through week 12

Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

Disposition and Demographics

- 69% completed at 52 weeks
- Mean age of 55 years (40–66)
- Mean BMI of 27 kg/m^2
- 65% were white, 32% African American



Population, n (%)	1 mg E2/ 100 mg P4	0.5 mg E2/ 100 mg P4	0.5 mg E2/ 50 mg P4	0.25 mg E2/ 50 mg P4	Placebo
Safety	415	424	421	424	151
Completed at 52 weeks	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)
Discontinued	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)
Adverse event	46 (11.1)	33 (7.8)	34 (8.1)	41 (9.7)	10 (6.6)
Lost to follow-up	27 (6.5)	30 (7.1)	26 (6.2)	38 (9.0)	17 (11.3)
Subject withdrawal	36 (8.7)	42 (9.9)	29 (6.9)	31 (7.3)	13 (8.6)
Other*	22 (5.3)	14 (3.3)	20 (4.8)	33 (7.8)	18 (11.9)
VMS substudy	141	149	147	154	135

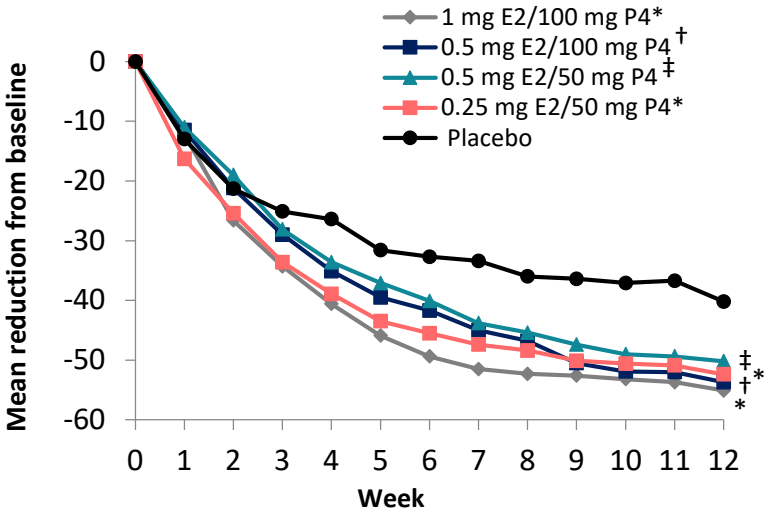
*Other included investigator decision, lack of efficacy, protocol deviation and other.

Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

VMS Frequency and Severity Substudy

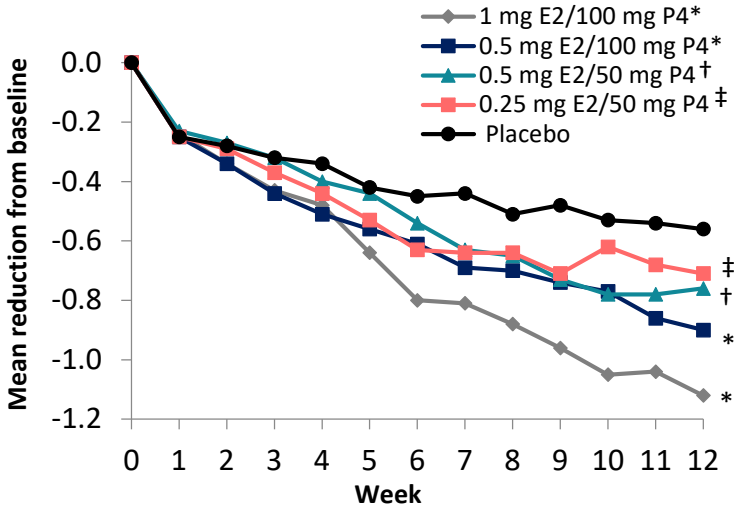
- Most TX-001HR doses significantly reduced the frequency and severity of moderate to severe VMS over 12 weeks; statistically significant reductions occurred as early as 4 weeks with the higher doses

Weekly Reduction in VMS Frequency



P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo.

Weekly Improvement in VMS Severity

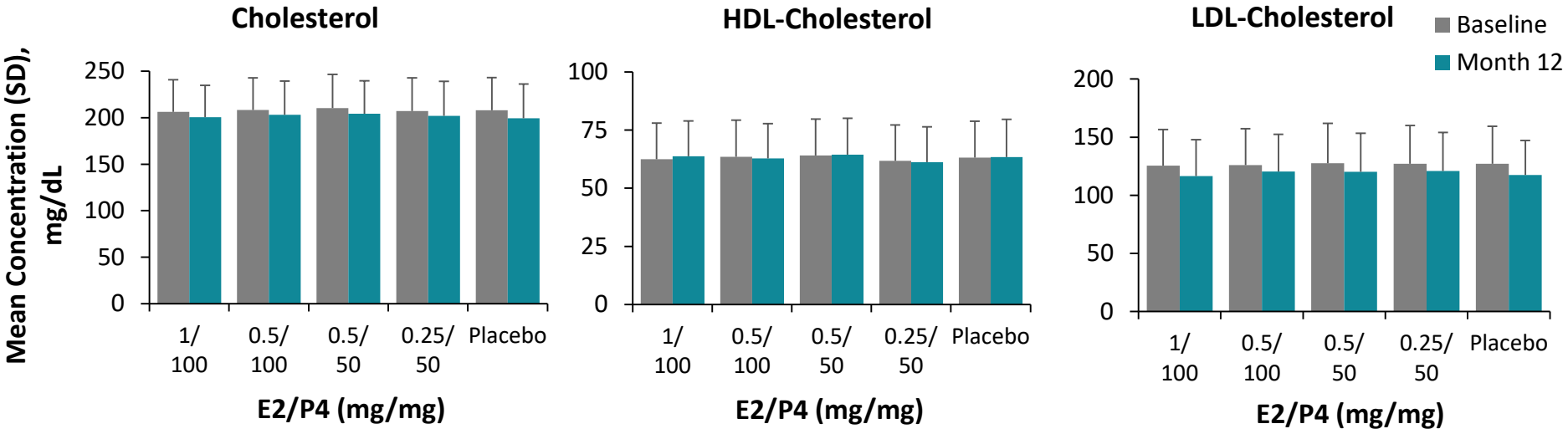


P<0.05 from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9 vs placebo.

Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

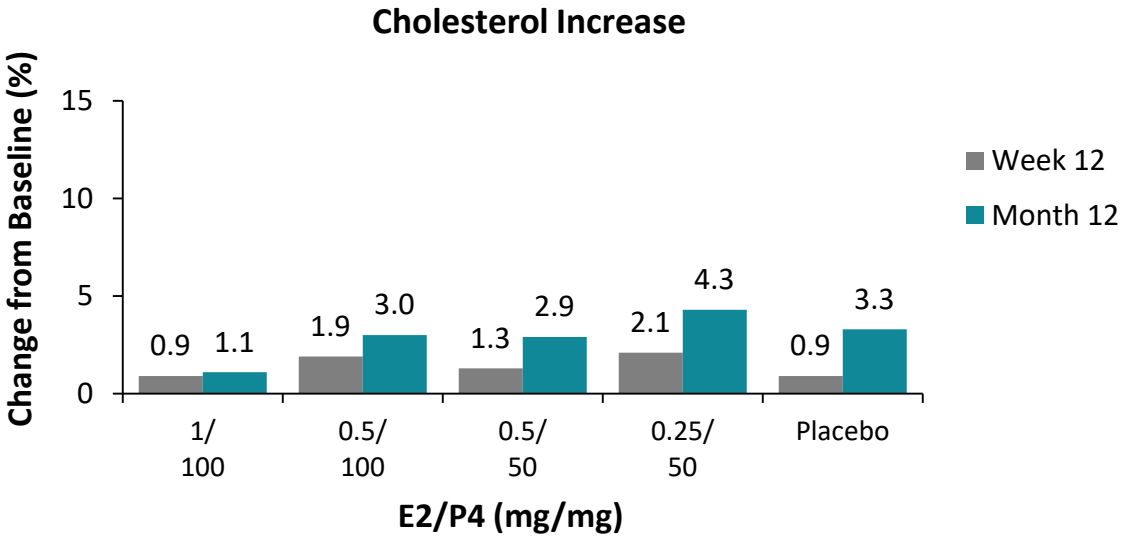
Cholesterol Parameters

- No clinically significant changes in cholesterol levels observed with TX-001HR or placebo



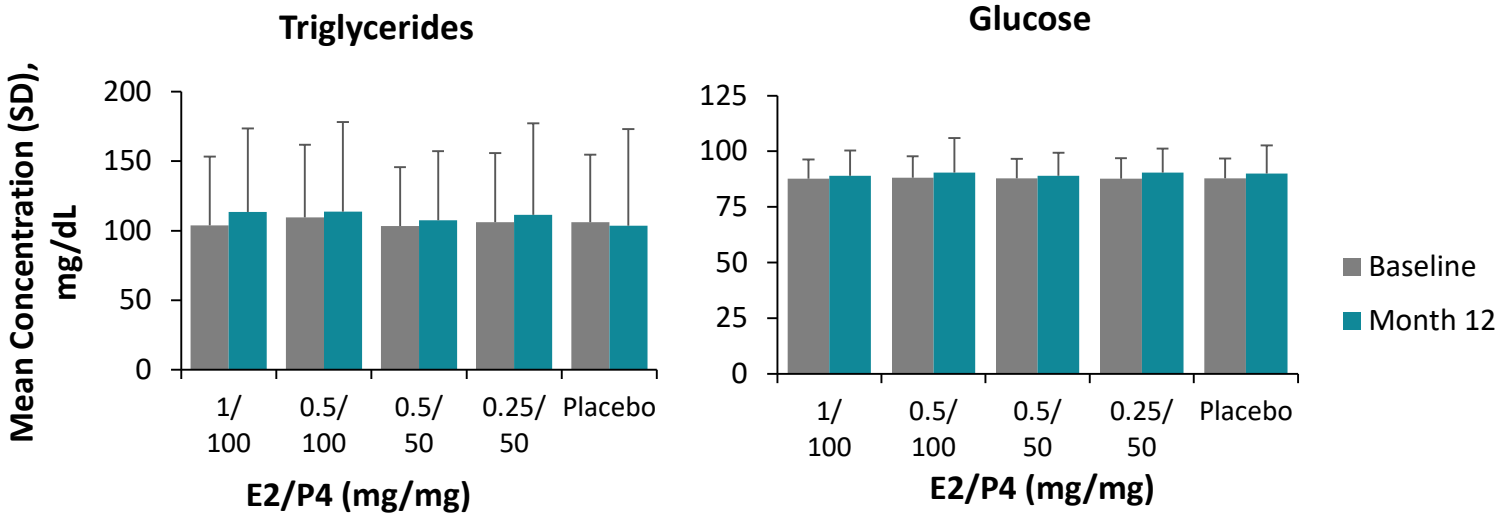
Cholesterol

- 36 of 1269 women (2.8%) had potentially clinically important cholesterol increases (≥50 mg/dL or above normal levels) at 12 months
  - Comparable between TX-001HR (2.8%) and placebo (3.3%) groups



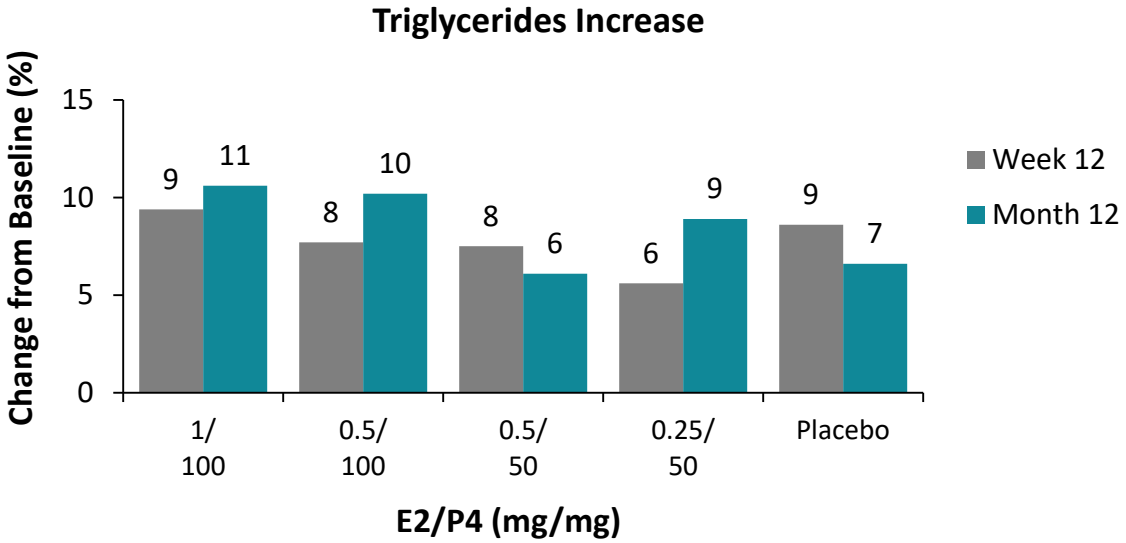
Triglyceride and Glucose Parameters

- No clinically significant changes in triglycerides and glucose levels observed with TX-001HR or placebo



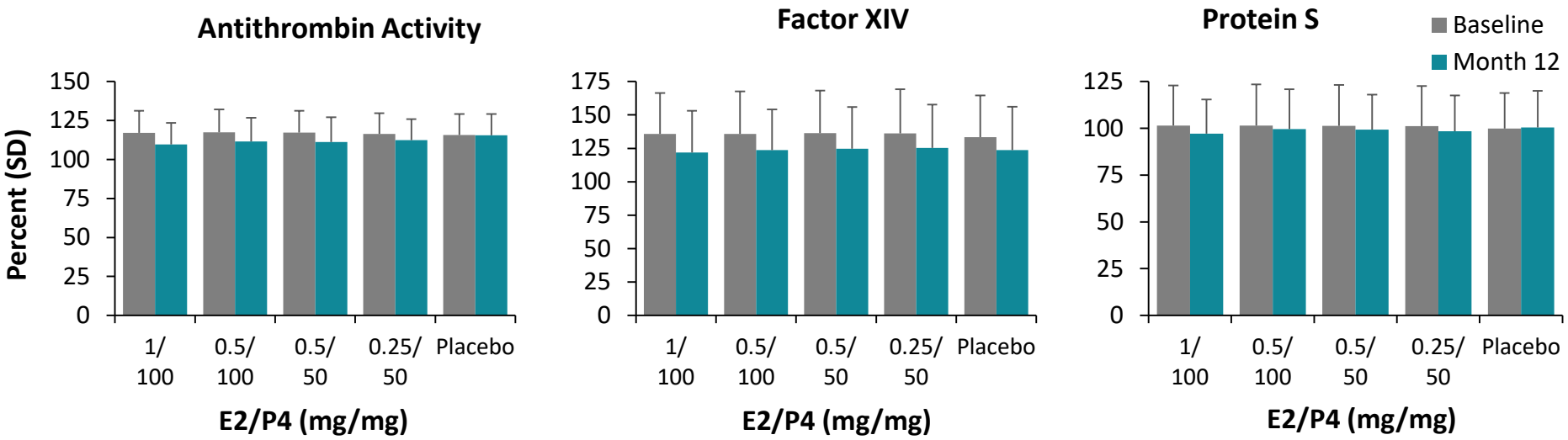
Triglycerides

- 111 of 1269 women (8.7%) had potentially clinically important triglycerides increases (≥50 mg/dL or above normal levels) at 12 months
  - Comparable between TX-001HR (8.9%) and placebo (6.6%) groups



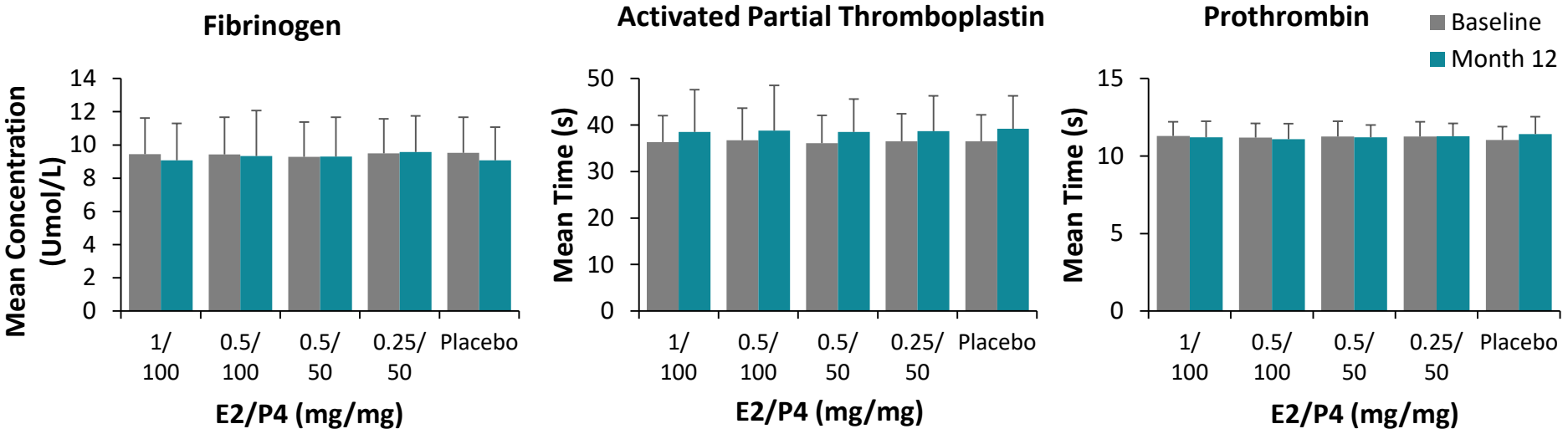
Coagulation Parameters

- No clinically significant changes in antithrombin activity, factor XIV and protein S were observed with TX-001HR compared with placebo



Coagulation Parameters

- Fibrinogen levels, time for activated partial thromboplastin and prothrombin, and prothrombin INR (ratio of 1) remained similar to baseline at 12 months



INR: international normalized ratio.

Vascular Disease Outcomes

- Cardiovascular disease
  - Two women experienced “coronary heart disease” adverse events considered not related to treatment
    - Unstable angina (0.5 mg E2/50 mg P4)
    - Angina and coronary artery disease (1 mg E2/100 mg P4)
    - Observed CHD event rate of 2/1684 was less than the expected annual rate of 2-3/1000 in women of this age[1]
  - There were no stroke events
- Venous thromboembolism (VTE)
  - One case of deep vein thrombosis (DVT) with 0.5 mg E2/50 mg P4, deemed possibly related to treatment, occurred in a woman with a family history of DVT
    - Observed VTE event rate of 1/1684 was less than the expected annual rate of 1.7/1000 in women of this age[2]

1. Lobo RA et al. *Arch Intern Med* 2004;164:482-484. **2.** Cushman M, et al. *JAMA* 2004;292:1573-1580.

Conclusions

- After 12 months of treatment with TX-001HR, no clinically meaningful effects on lipid, glucose, or coagulation parameters were observed compared with placebo
  - Observed changes in triglyceride levels, antithrombin activity, factor XIV, and protein S were consistent with oral estrogen therapy
- Although this trial lacked statistical power to assess these outcomes, VTE, cardiovascular disease, and cerebrovascular events were as expected for a menopausal population
- If approved, TX-001HR may provide the first oral E2/P4 combination for the treatment of VMS in menopausal women with a uterus