Novel Oral, Continuous-Combined Solubilized 17β-estradiol and Natural Progesterone Provided Endometrial Protection: Comparison of Two Randomized Controlled Trials

James H. Pickar, MD, FACOG[1]
Brian Bernick, MD, FACOG[2]
Sebastian Mirkin, MD[2]

[1]Columbia University Medical Center, New York, NY
[2]TherapeuticsMD, Boca Raton, FL

Disclosures

- Consults for:
  - Pfizer
  - Shionogi
  - TherapeuticsMD
- Has stock options with TherapeuticsMD

Disclaimers

- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an oral combination of 17β-estradiol (E2) and progesterone (P4) in a single, softgel capsule not yet approved by the U.S. FDA

Question

- Is the incidence of endometrial cancer different between medroxyprogesterone acetate (MPA) and natural P4 when used with estrogens for endometrial protection?

Archer DF et al. *Endocr Rev* 2017;38(Suppl 1):3.

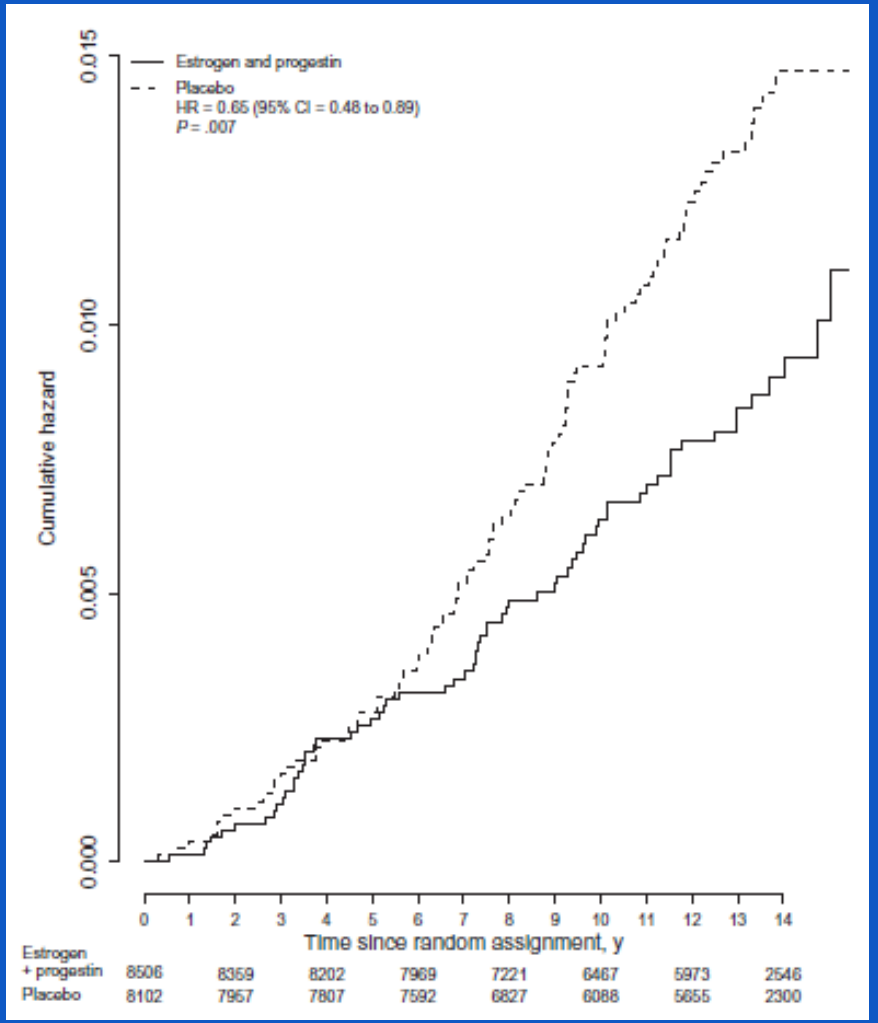
Background: WHI Endometrial Cancer Extended Follow Up

- Randomized 16,608 in the CEE/MPA clinical trial
- 5.6 years median intervention
- 12,788 consented for extended follow up
- 13 years median cumulative follow up
- CEE/MPA vs Placebo: 66 vs 95 case patients

CEE: conjugated equine estrogens; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative.
Chlebowski RT et al. *J Natl Cancer Inst* 2016;108:djv350.

MPA Protects the Endometrium

- In the WHI, endometrial cancer incidence was lower with daily 0.625 mg CEE/ 2.5 mg MPA than with placebo after 13 years of cumulative follow up (Figure)[1]
  - HR 0.65; 95% CI, 0.48–0.89
- The Women's HOPE study showed that MPA provided protection against endometrial hyperplasia with various CEE doses[2]



CEE: conjugated equine estrogens; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative.

1. Chlebowski RT et al. *J Natl Cancer Inst* 2016;108:djv350. **2.** Pickar JH et al. *Fertil Steril* 2001;76:25-31.

What About Progesterone?

- The PEPI trial showed that cyclic 200 mg P4 with 0.625 mg CEE, dosed separately, protected the endometrium from hyperplasia[1]
  - Incidence with CEE/cyclic P4 similar to that with placebo
- The REPLENISH trial showed for the first time in a large, randomized, controlled trial that P4 continuously combined with E2 provided adequate endometrial protection[2]
  - No endometrial hyperplasia or endometrial malignancy after 1 year

E2: 17β-estradiol; P4: progesterone; PEPI: Postmenopausal Estrogen/Progestin Interventions.

1. Writing Group for the PEPI Trial. *JAMA* 1996;275:370-375. **2.** Archer DF et al. *Endocr Rev* 2017;38(Suppl 1):3.

Objective

- To compare the separately conducted REPLENISH (E2/P4) and Women's HOPE (CEE/MPA) trials with regard to
  - Endometrial protection
  - Uterine bleeding

Women's HOPE Study: Study Design

- 12-month randomized, double-blind, placebo-controlled, multicenter trial in menopausal women with an intact uterus
- Evaluated the endometrial safety and uterine bleeding of daily doses of continuous combined CEE and MPA for 1 year

CEE	CEE/MPA
0.625 mg	0.625/2.5 mg
0.45 mg	0.45/2.5 mg
	0.45/1.5 mg
0.3 mg	0.3/1.5 mg
Placebo	

CEE: conjugated equine estrogens; MPA: medroxyprogesterone acetate; HOPE: Health, Osteoporosis, Progestin, Estrogen.

Pickar JH et al. *Fertil Steril* 2001;76:25-31.

REPLENISH Trial: Study Design

- 12-month, randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus
  - TX-001HR is an investigational combination of E2/P4 in a single, oral, softgel capsule
- Evaluated endometrial safety and uterine bleeding of continuous combined daily doses of E2/P4 (TX-001HR) to treat moderate-to-severe vasomotor symptoms

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

Goldstein SR, et al. *Menopause* 2017;24:1431-1432.

Endometrial Hyperplasia Assessment[1,2]

- Incidence of endometrial hyperplasia at year 1 was a primary endpoint of both trials
  - FDA guidance: ≤1% hyperplasia rate; upper bound of the one-sided 95% CI ≤4%
- Endometrial biopsies were performed at baseline and Month 12/end of treatment (as well as cycle 6 in the Women's HOPE Study)
- Biopsy specimens were processed by a central laboratory
  - Biopsy slides were reviewed by 2 or 3 pathologists
  - A consensus read of 2 of 3 pathologists was required to diagnose endometrial hyperplasia
  - No hyperplasia on biopsy at baseline for study eligibility
- Any patient who developed endometrial hyperplasia was withdrawn from the study and given the appropriate treatment

1. Pickar JH et al. *Fertil Steril* 2001;76:25-31. **2.** Archer DF et al. *Endocr Rev* 2017;38(Suppl 1):3; Poster available at https://ir.therapeuticsmd.com/static-files/5c87b506-fca2-45d4-a87f-789ddb23238a. Accessed on 25Jan2018.

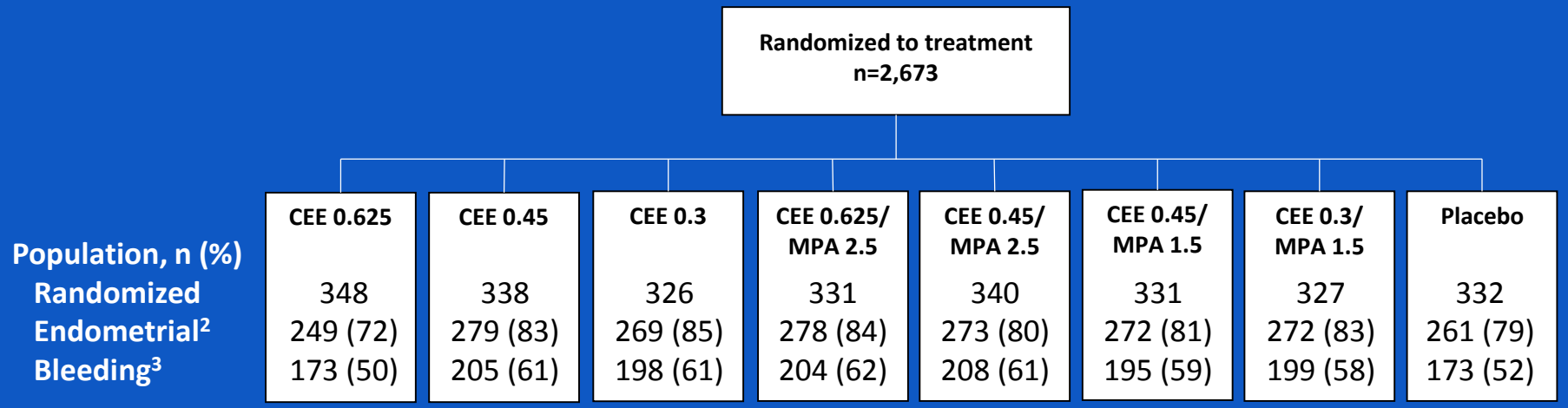
Bleeding and Spotting Assessment[1,2]

- Women in both studies completed diaries of daily vaginal bleeding and spotting up to month 12
  - Bleeding: required sanitary protection
  - Spotting: did not require sanitary protection
- Bleeding profiles, including cumulative amenorrhea (no bleeding or spotting) were assessed between treatment groups over thirteen 28-day cycles

1. Archer DF et al. *Fertil Steril* 2001;75:1080-1087. **2.** Goldstein SR et al. *Menopause* 2017;24:1431-1432.

Women's HOPE Study: Disposition and Demographics[1]

- Mean age: 53 years
- Mean BMI: 24 kg/m^2
- 88% were white, 6% African American, 4% Hispanic
- 19% of women withdrew from the study

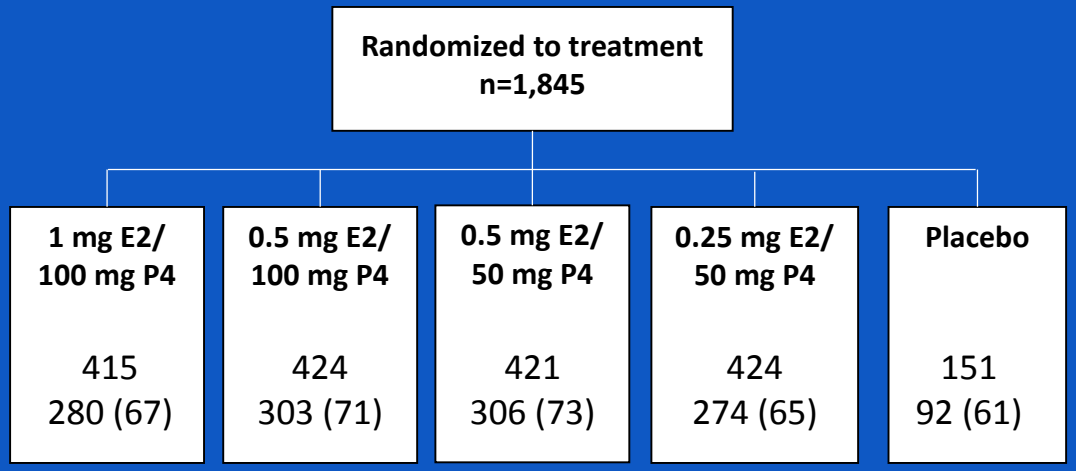


Population, n (%)	CEE 0.625	CEE 0.45	CEE 0.3	CEE 0.625/ MPA 2.5	CEE 0.45/ MPA 2.5	CEE 0.45/ MPA 1.5	CEE 0.3/ MPA 1.5	Placebo
Randomized	348	338	326	331	340	331	327	332
Endometrial[2]	249 (72)	279 (83)	269 (85)	278 (84)	273 (80)	272 (81)	272 (83)	261 (79)
Bleeding[3]	173 (50)	205 (61)	198 (61)	204 (62)	208 (61)	195 (59)	199 (58)	173 (52)

1. Utian WH et al. *Fertil Steril* 2001;75:1065-1079. **2.** Pickar JH et al. *Fertil Steril* 2001;76:25-31. **3.** Archer DF et al. *Fertil Steril* 2001;75:1080-1087.

REPLENISH Trial: Disposition and Demographics

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



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/Bleeding	415	424	421	424	151
Endometrial Safety	280 (67)	303 (71)	306 (73)	274 (65)	92 (61)

Goldstein SR et al. *Menopause* 2017;24:1431-1432. Presentation available at https://ir.therapeuticsmd.com/static-files/b3afa0c3-13a5-493b-a19a-ab8fc3f220ce. Accessed on 25Jan2018.

Women's HOPE Study: Endometrial Safety with CEE/MPA

- Endometrial hyperplasia incidence ranged from 0 to 0.37% with CEE/MPA after 1 year
  - Addition of MPA prevented the endometrial hyperplasia observed in women treated with CEE alone

Treatment (mg/mg)	n	Total no. of Hyperplasia	Hyperplasia Rate, %	95% CI
CEE 0.625/MPA 2.5	278	0	**0**	0.00–1.32
CEE 0.45/MPA 2.5	273	0	**0**	0.00–1.34
CEE 0.45/MPA 1.5	272	1	**0.37**	0.01–2.03
CEE 0.3/MPA 1.5	272	1	**0.37**	0.01–2.03
Placebo	261	0	**0**	0.00–1.40

Pickar JH et al. *Fertil Steril* 2001;76:25-31.

REPLENISH Trial: Endometrial Safety with E2/P4

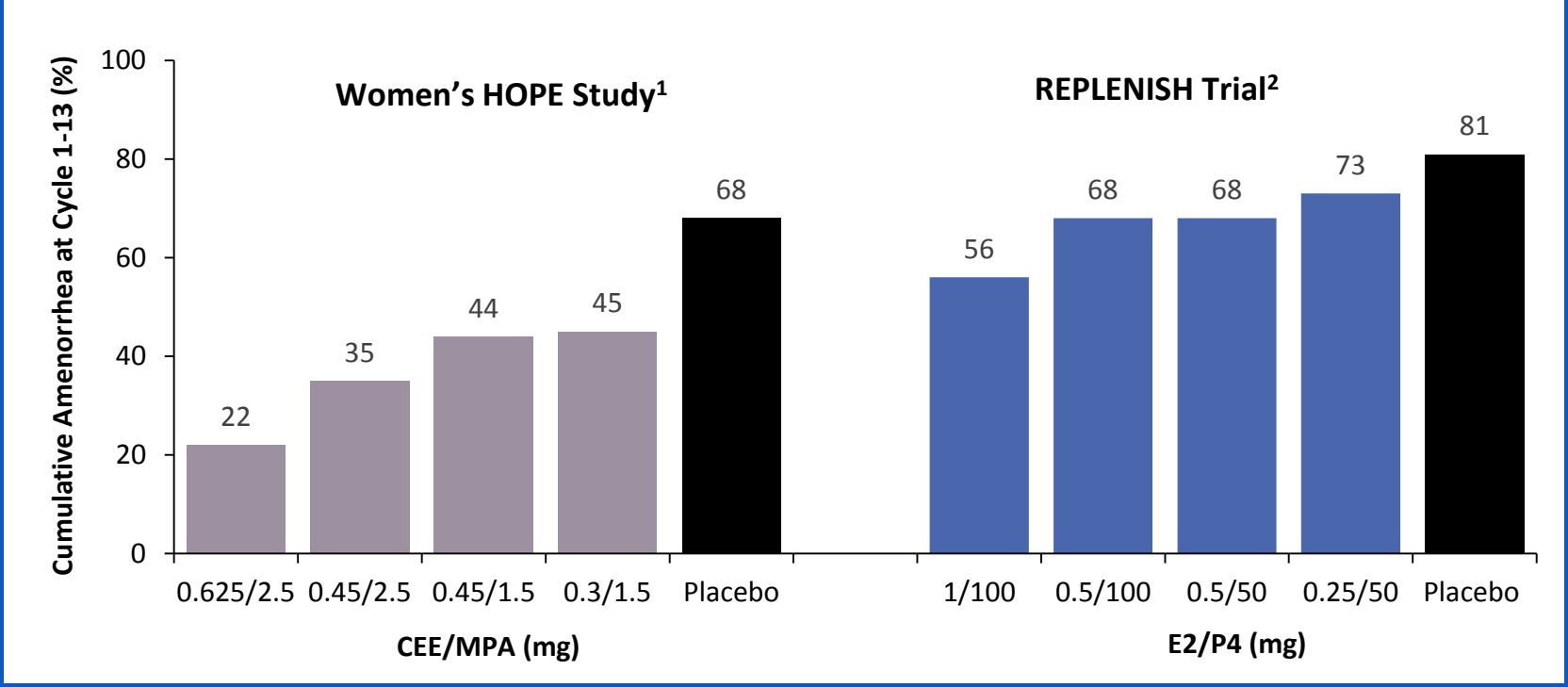
- Endometrial hyperplasia incidence was 0% after 1 year
- No endometrial malignancies detected with any TX-001HR dose or placebo

Treatment (mg/mg)	n	Total no. of Hyperplasia	Hyperplasia Rate, %	1-sided upper 95% CI
E2 1/P4 100	280	0	0	1.06%
E2 0.5/P4 100	303	0	0	0.98%
E2 0.5/P4 50	306	0	0	0.97%
E2 0.25/P4 50	274	0	0	1.09%
Placebo	92	0	0	3.20%

Goldstein SR et al. *Menopause* 2017;24:1431-1432. Presentation available at https://ir.therapeuticsmd.com/static-files/b3afa0c3-13a5-493b-a19a-ab8fc3f220ce. Accessed on 25Jan2018.

Cumulative Amenorrhea*

- Cumulative amenorrhea at cycle 1-13 ranged from 22–45% with CEE/MPA and 56–73% with E2/P4
- Increased over time
  - By cycle 13, amenorrhea was 76–89% with CEE/MPA and >90% with E2/P4



*CEE/MPA and E2/P4 doses were not directly compared in a head-to-head study

1. Archer DF et al. *Fertil Steril* 2001;75:1080-1087. **2.** Goldstein SR et al. *Menopause* 2017;24:1431-1432. Presentation available at https://ir.therapeuticsmd.com/static-files/b3afa0c3-13a5-493b-a19a-ab8fc3f220ce. Accessed on 25Jan2018.

Conclusions

- TX-001HR (E2/P4) provided endometrial protection in the 1-year REPLENISH study
  - Incidence rates of endometrial hyperplasia at 1 year with all P4 doses continuously combined with estradiol, were 0%
  - No cases of endometrial cancer were observed
  - Cumulative amenorrhea rates increased over time. At 12 months:
    - Rates were 56–73% with E2/P4 vs 81% with placebo
- If approved, TX-001HR (E2/P4) may be an appropriate alternative combination hormone therapy for treating moderate-to-severe vasomotor symptoms, while protecting the endometrium

Thank You