

TX-001HR (17 β -estradiol/progesterone) is Associated with a Clinically Meaningful Effect on Vasomotor Symptoms

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Disclosures

- **Consultant:** TherapeuticsMD as well as other pharmaceutical companies
- **Stock options:** TherapeuticsMD

What Reduction in Vasomotor Symptom (VMS) Frequency is Clinically Meaningful?

- VMS in menopausal women are effectively treated with HT
- Reductions in VMS frequency with HT¹⁻³
 - By 50% to 86% from baseline
 - By 5.5 to 9.0 hot flushes per day
- Placebo response in VMS studies is known to be high^{1,4-6}
 - 17% to 61% reduction from baseline in VMS frequency
 - Cochrane review of 9 studies of oral estrogens showed that placebo groups have a mean reduction of 58% in hot flush frequency¹
 - Pooled analysis of 10 clinical trials showed reduction in hot flush frequency ranged from 27% to 52% with placebo^{2,4}

The REPLENISH Trial

- **Presentation Objective:** To present the clinical meaningfulness of reductions in moderate-to-severe VMS frequency with four doses of TX-001HR (TherapeuticsMD, Boca Raton, FL) versus placebo
 - TX-001HR is an investigational combination of 17 β -estradiol [E2] combined with progesterone [P4] in a single oral softgel capsule versus placebo
- **Study Design:** Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in postmenopausal women with an intact uterus
 - 12-week efficacy substudy for the treatment of vasomotor symptoms
 - 1-year endometrial and general safety analyses

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

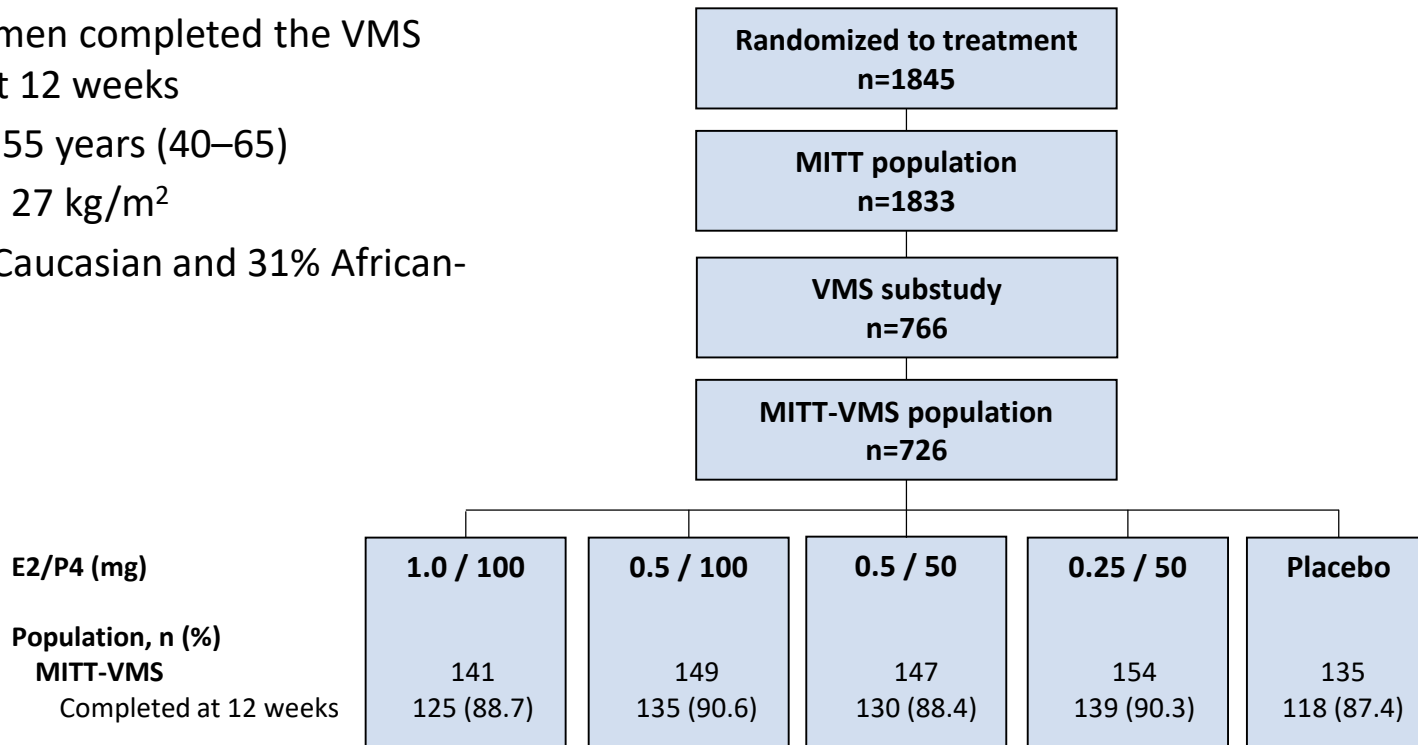
- 1.0 mg E2/100 mg P4
- 0.5 mg E2/100 mg P4
- 0.5 mg E2/50 mg P4
- 0.25 mg E2/50 mg P4
- Placebo

General study (12 mos)

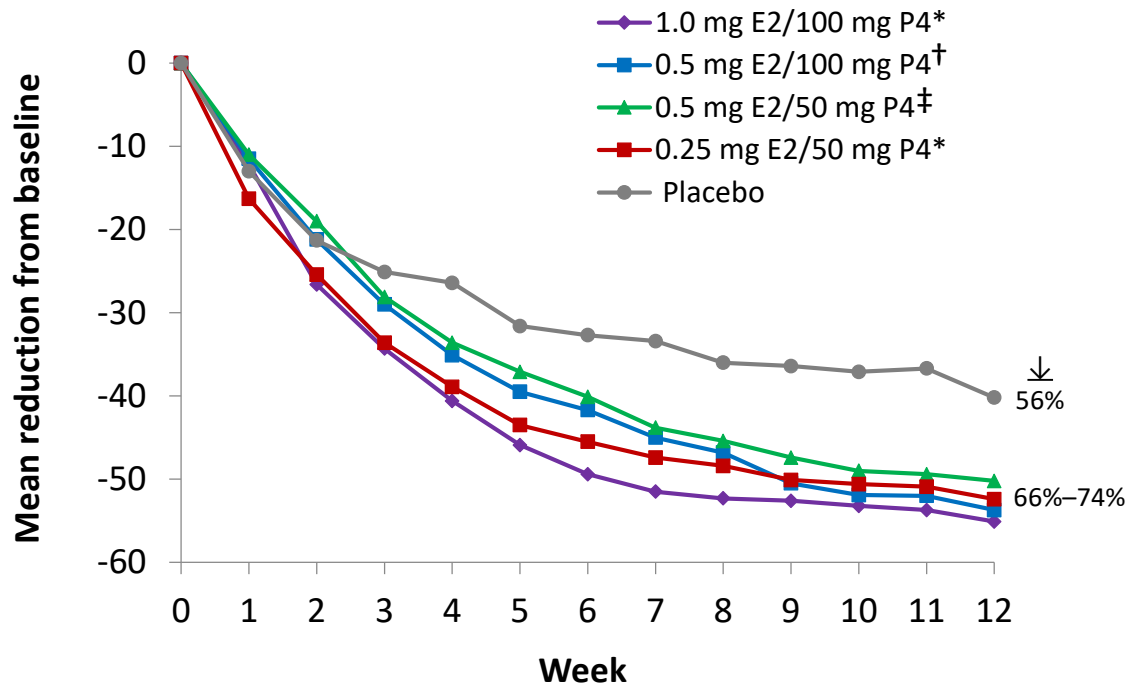
- Did not qualify for VMS substudy
- Randomized 1:1:1:1

Disposition and Demographics

- 89% of women completed the VMS substudy at 12 weeks
- Mean age: 55 years (40–65)
- Mean BMI: 27 kg/m²
- 67% were Caucasian and 31% African-American



Reductions in VMS Frequency



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

↓: Percent reduction from Baseline at 12 weeks

Clinical Meaningfulness Was Assessed Using Two Patient-Reported Outcomes (PRO)

- Clinical Global Impression (CGI)
- Menopause-Specific Quality of Life (MENQOL) Questionnaire

Three steps to determine clinical meaningfulness (Gerlinger Method)^{1,2}

1. Analyze the PROs: CGI and MENQOL / frequency of VMS
2. Correlate reduction in VMS frequency between responders and non-responders (ANCOVA)
3. Compare clinical responders by dose vs placebo

Clinical Global Impression (CGI)

- At weeks 4, 8, and 12, women in the VMS substudy answered the following question

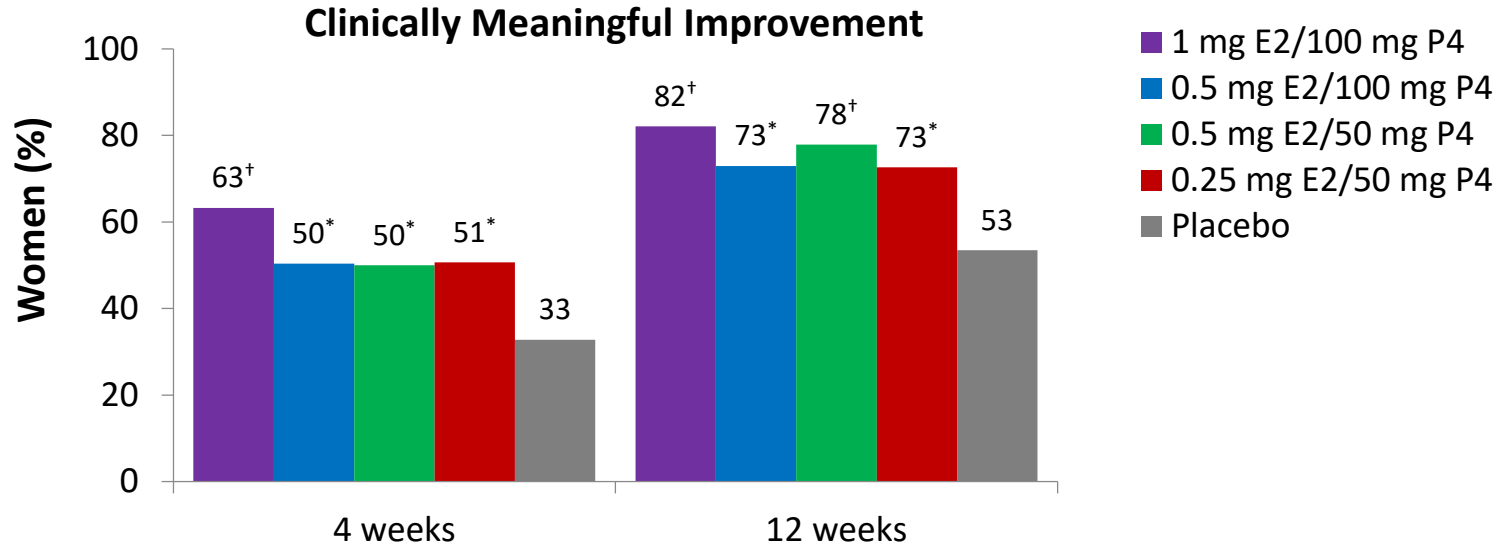
“Rate the total improvement, whether or not in your judgment it is due entirely to drug treatment. Compared to your condition at admission to the study, how much has it changed?”

Potential responses were rated using a 7-point Likert scale

Potential Responses	Score	CGI Ratings Response
Very much improved	1	Clinically meaningful
Much improved	2	
Minimally improved	3	Minimally improved
No change	4	No change or worse
Minimally worse	5	
Much worse	6	
Very much worse	7	

CGI Response

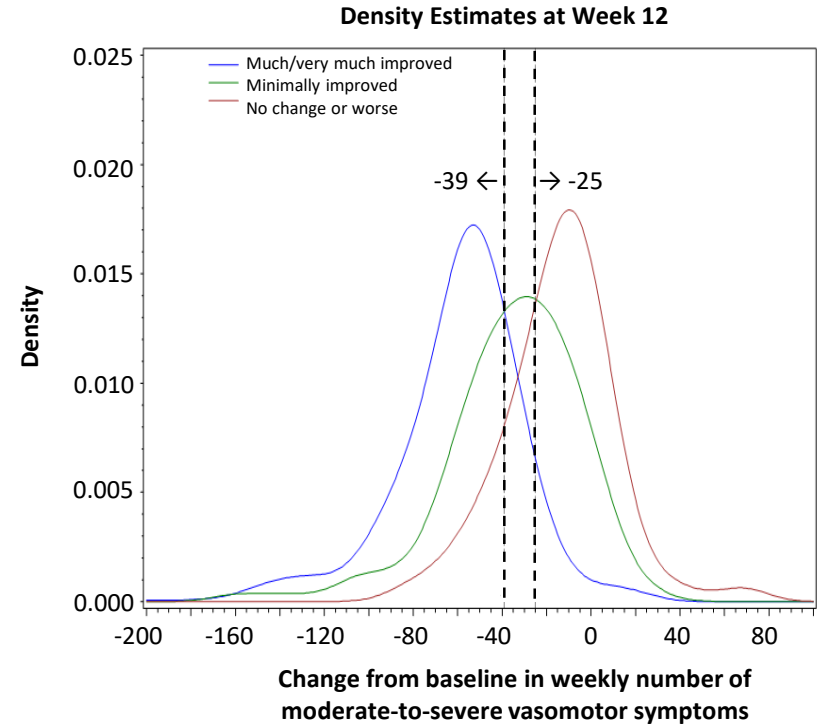
- Significantly more women rated their condition as very much or much improved with TX-001HR versus placebo at weeks 4 and 12



* $P < 0.01$; [†] $P < 0.001$ vs placebo.

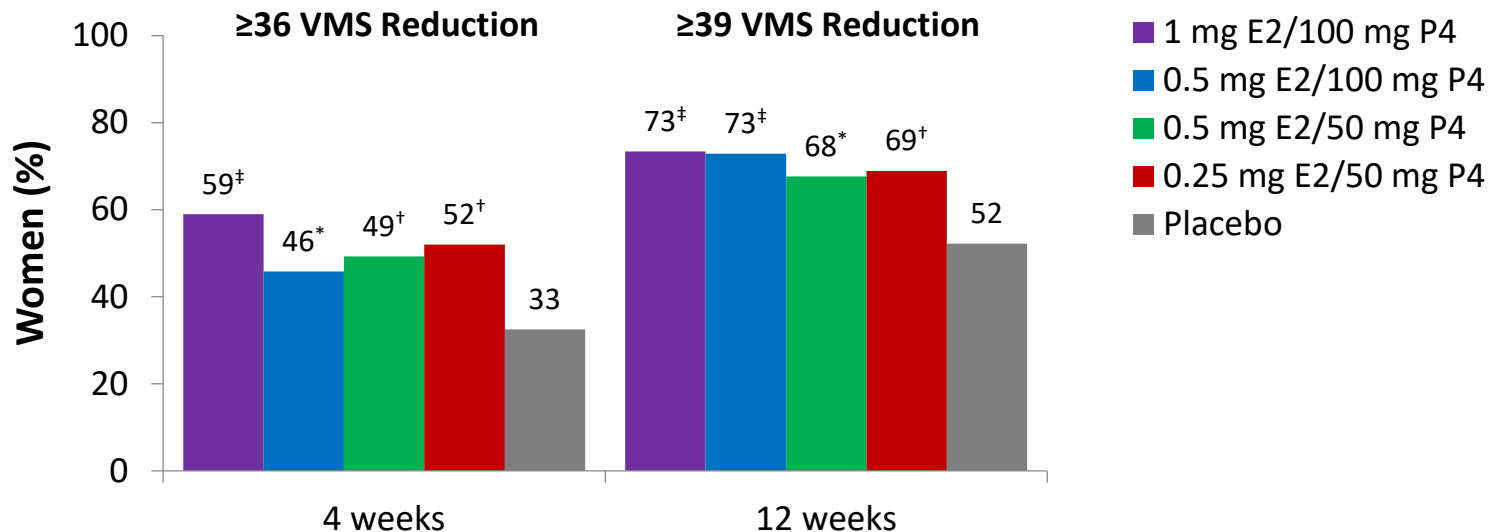
Response Threshold Calculations

- Gerlinger clinical response thresholds were calculated using nonparametric discriminant analyses based on women with a clinically meaningful response by the CGI^{1,2}
- Response thresholds were weekly reductions in frequency of VMS of
 - ≥ 36 at week 4
 - ≥ 39 at week 12



CGI-based Clinical Meaningfulness Analysis

- Significantly more clinical responders were found with TX-001HR than with placebo at weeks 4 and 12



* $P < 0.05$; [†] $P < 0.01$; [‡] $P \leq 0.001$ vs placebo.

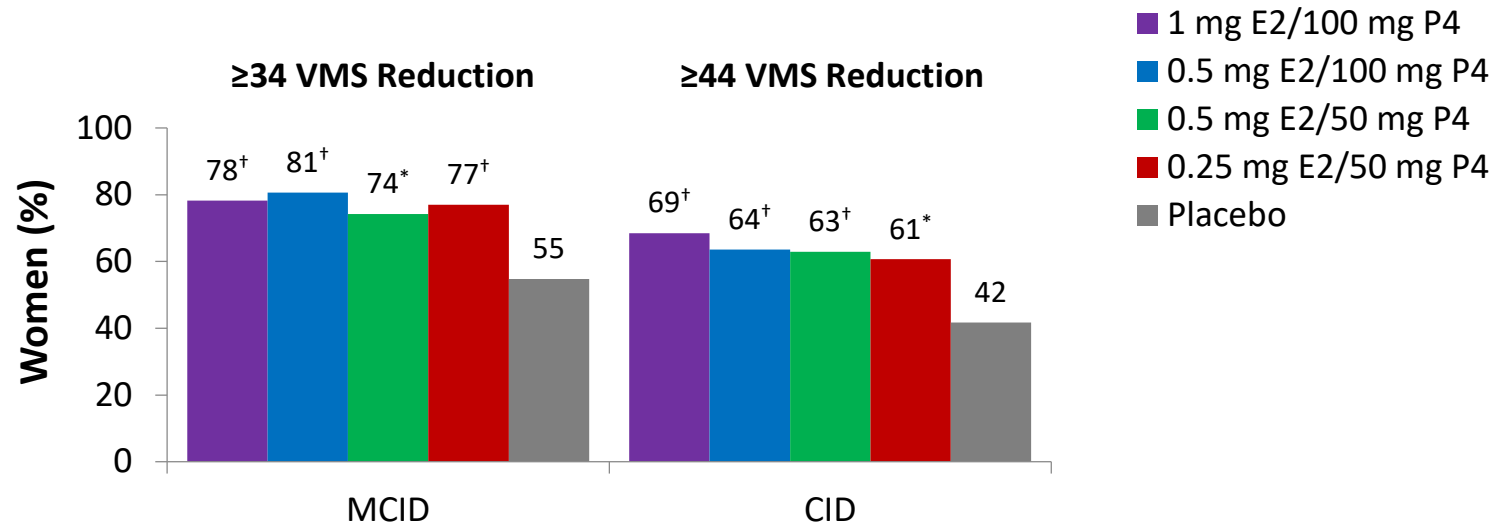
Responders defined as a reduction in frequency of moderate-to-severe VMS from baseline of ≥ 36 at week 4 and ≥ 39 at week 12.

MENQOL Questionnaire

- Questionnaire consists of 29 items (symptoms), and were rated using a 7-item Likert scale ranging from “Not at all bothered” to “Extremely bothered”
 - Items are grouped into 4 domains: vasomotor (3 items), psychosocial (7 items), physical (16 items) and sexual (3 items)
- Subjects were administered the MENQOL questionnaire at baseline, week 12 and months 6 and 12

MENQOL-based Clinical Meaningfulness Analysis

- Significantly more MENQOL-responders had MCID and CID with TX-001HR than with placebo at week 12



* $P < 0.01$; $^{\dagger}P \leq 0.001$ vs placebo.

CID: clinically important difference; MCID: minimal clinically important difference.

MENQOL-responders defined as a reduction in frequency of moderate-to-severe VMS from baseline of ≥ 34 for MCID and ≥ 44 for CID at week 12.

Conclusions

- Clinically meaningful changes in the frequency of VMS can be determined
 - TX-001HR was associated with clinical meaningful improvements in VMS frequency in the REPLENISH trial using the Gerlinger method
 - Was confirmed with two separate PROs showing more responders with TX-001HR than placebo
 - By CGI: VMS reduction of ≥ 36 at week 4 and ≥ 39 at week 12
 - By MENQOL: VMS reduction of ≥ 34 for MCID and ≥ 44 for CID at week 12
- Clinically meaningful improvements were observed despite a high placebo response
- TX-001HR, if approved, may provide a new oral option, as a single E2/P4 capsule to treat moderate-to-severe vasomotor symptoms in menopausal women with an intact uterus, including those women taking unapproved compounded BHT