TX-001HR is Associated with a Clinically Meaningful Effect on Vasomotor Symptoms

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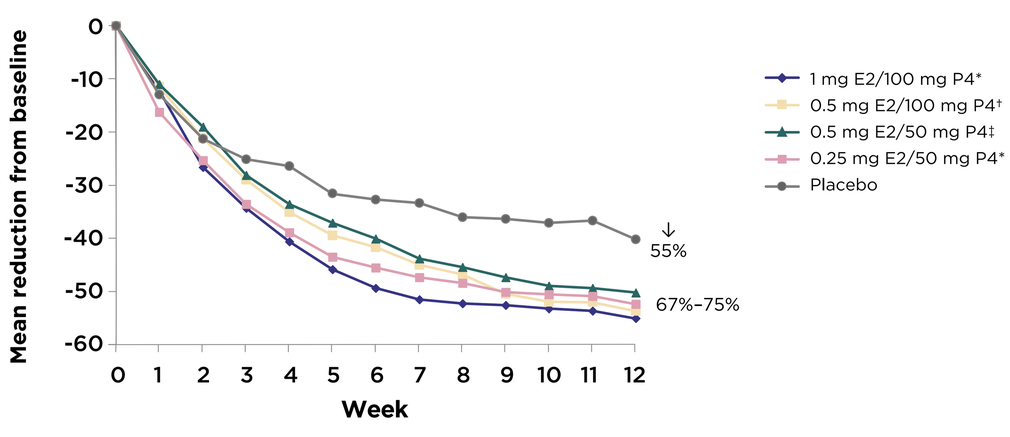
Introduction

- Vasomotor symptoms (VMS) in menopausal women are effectively treated with hormone therapy (HT) reducing hot flush frequency and severity
- Reductions in VMS frequency of 50% to 86% from baseline, or 5.5 to 9.0 hot flushes per day, have been reported in some randomized controlled trials,[1-3] however the clinical relevance of these findings is often unknown[1,4-6]
- The 12-month REPLENISH trial evaluated 4 doses of TX-001HR (TherapeuticsMD, Boca Raton, FL), a once-daily, oral capsule containing 17β-estradiol (E2) and progesterone (P4), for the treatment of moderate-to-severe VMS in menopausal women with a uterus[7]
  - Co-primary efficacy endpoints measured at 4 and 12 weeks demonstrated statistically significant reductions in hot flush frequency with most E2/P4 doses compared with placebo (**Figure 1**)
  - Reductions from baseline in the number of VMS per day equated to 7.2–7.9 for TX-001HR doses and 5.7 with placebo at week 12

Figure 1. Reductions in moderate-to-severe VMS frequency in the REPLENISH trial



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

Objectives

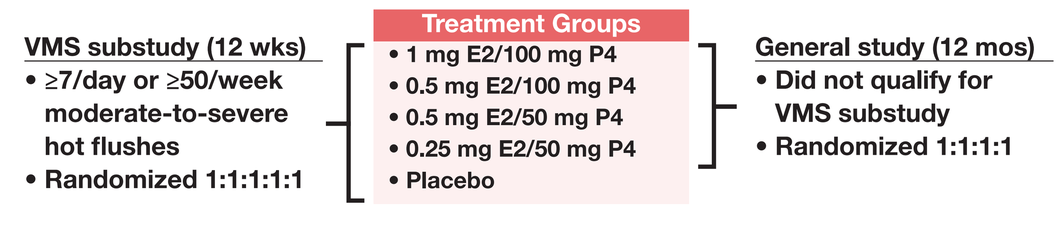
- To determine what reduction in VMS frequency was meaningful to women, using data from the REPLENISH trial (secondary endpoint), and the proportion of women with a clinically important response (meaningfulness) of TX-001HR versus placebo when treating moderate-to-severe VMS in menopausal women

Methods

Study Design

- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated TX-001HR in menopausal women (age 40–65 years; BMI ≤34 kg/m^2) with a uterus[7]
  - 12-week efficacy substudy for the treatment of vasomotor symptoms
  - 1-year endometrial and general safety analyses
- Women with moderate-to-severe hot flushes (≥7/day or ≥50/wk) were randomized to daily E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, 0.25/50 or placebo (VMS substudy, n=726); others were randomized to E2/P4 doses only for endometrial assessment (**Figure 2**)[7]

Figure 2. REPLENISH Study Design



- Participants completed a daily VMS diary and recorded the number and severity of hot flushes up to week 12
  - Weekly hot flush frequency was the total number of moderate and severe hot flushes in the previous 7 days
- Women were included in the modified intent-to-treat (MITT)-VMS population (primary efficacy population) if they were randomized to the VMS substudy, took at least one dose (two capsules) of study medication, had ≥5 days of VMS diary data at baseline, and had ≥4 days of VMS diary data for one on-treatment week

Evaluating Clinical Meaningfulness

- Clinical meaningfulness of treatment was assessed using the Clinical Global Impression (CGI) scale. Participants 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 CGI responses were rated using a 7-point Likert scale (**Table 1**). These responses were then converted to CGI rating responses to determine clinical meaningfulness

Table 1. CGI Ratings

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	

- Clinically important differences (CID) and minimal clinically important differences (MCID) for reductions in moderate-to-severe VMS frequency, regardless of treatment, were measured using anchor-based CGI nonparametric discriminant analyses utilizing bootstrapping methods[8,9]
  - Analyses were performed in the MITT-VMS population
  - Each E2/P4 dose was compared with placebo using the Fisher's Exact test at weeks 4 and 12

Results

Disposition and Demographics

- 766 were enrolled in the VMS substudy and 726 were eligible for the MITT-VMS population
  - 89% of the women completed the 12-week VMS efficacy substudy
- Women in the MITT-VMS population had a mean age of 55 years (range, 40–65) and a mean BMI of 27 kg/m^2 at study entry (**Table 2**)

Table 2. Demographics and baseline characteristics of the MITT-VMS population

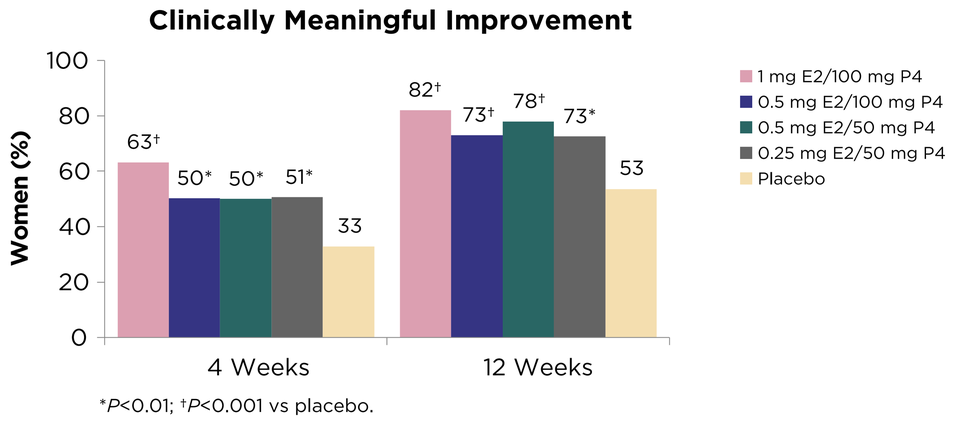
	Estradiol/Progesterone				
Characteristic	**1 mg/100 mg**	**0.5 mg/100 mg**	**0.5 mg/50 mg**	**0.25 mg/50 mg**	**Placebo**
n	141	149	147	154	135
Age, y	54.7 ± 4.8	54.9 ± 4.5	54.8 ± 4.6	54.5 ± 3.8	54.3 ± 4.3
Race, n (%)					
White	95 (67.4)	99 (66.4)	99 (67.3)	102 (66.2)	91 (67.4)
African American	45 (31.9)	48 (32.2)	43 (29.3)	48 (31.2)	41 (30.4)
Other*	1 (0.7)	2 (1.3)	5 (3.4)	4 (2.6)	3 (2.2)
BMI, kg/m^2	26.5 ± 3.9	27.1 ± 4.3	26.6 ± 3.9	26.4 ± 4.0	26.6 ± 3.8
Time since menopause, y	6.1 ± 5.5	6.5 ± 5.4	6.0 ± 4.8	5.2 ± 4.8	5.7 ± 4.9
Bilateral oophorectomy	3 (2.1)	3 (2.0)	1 (0.7)	1 (0.6)	0
Baseline VMS parameters					
Weekly frequency	74.4 ± 35.3	72.1 ± 27.8	75.9 ± 28.0	77.0 ± 30.4	72.4 ± 23.3
Weekly severity	2.54 ± 0.32	2.51 ± 0.25	2.50 ± 0.23	2.51 ± 0.26	2.52 ± 0.25

Data presented as mean ± SD, unless stated otherwise.
SD, standard deviation; BMI, body mass index; VMS, vasomotor symptoms.
*Other includes: other (n=10), American Indian or Alaska Native (n=2), Native Hawaiian or Pacific Islander (n=2), and unknown (n=1).

Clinical Global Impression

- Significantly more women responded that they felt their symptoms were either "much improved" or "very much improved" with TX-001HR compared with placebo at weeks 4 and 12 (**Figure 3**)

Figure 3. Proportion of women who rated their condition as very much or much improved (CGI response rate)



P<0.01; †*P*<0.001 vs placebo.

- Calculated clinical meaningfulness thresholds were weekly reductions in moderate-to-severe VMS frequency of ≥15 for MCID and ≥36 for CID for week 4 (**Figure 4A**) and reductions of ≥25 for MCID and ≥39 for CID for week 12 (**Figure 4B**)
- Significantly more clinical responders based on these response thresholds were found with TX-001HR than with placebo at weeks 4 (**Figure 5A**) and 12 (**Figure 5B**) for both MCID and CID

Figure 4. Clinical meaningfulness analysis at (A) week 4 and (B) week 12

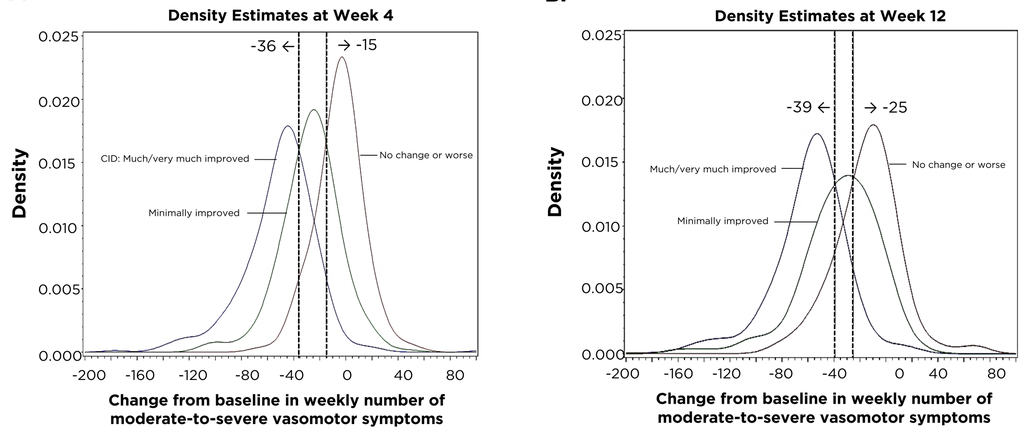
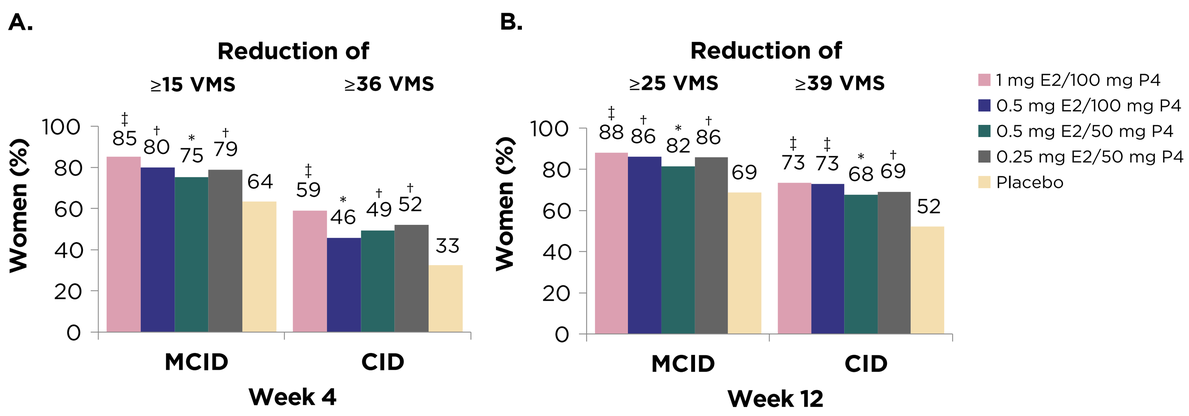


Figure 5. CGI-based CID and MCID analysis at (A) Week 4 and (B) Week 12



P<0.05; †*P*<0.01; ‡*P*<0.001 vs placebo.

Concluding Remarks

- TX-001HR provided clinically meaningful improvements in VMS frequency in menopausal women as determined by CGI
  - Clinically important differences in VMS reduction of ≥36 at week 4 and ≥39 at week 12
- The results of this analysis extend the primary efficacy results of the REPLENISH trial, which showed significant improvements in the frequency and severity of moderate-to-severe VMS with TX-001HR (1 mg E2/100 mg P4, 0.5 mg E2/100 mg P4) versus placebo at weeks 4 and 12[7]
- A consistency of effect of TX-001HR was also observed with statistically significant and clinically meaningful improvements in the MENQOL questionnaire (reported elsewhere)[10]
- If approved, TX-001HR may provide E2/P4 as a new oral option, in a single, oral capsule, to treat moderate-to-severe VMS in menopausal women with a uterus who prefer using E2/P4 (similar to those hormones naturally occurring in women)

Disclosures

• Dr. Constantine consults to multiple pharmaceutical companies including but not limited to TherapeuticsMD, and has stock options from TherapeuticsMD. Dr. Revicki is an employee of Evidera, which is a consultant for TherapeuticsMD. Dr. Kagan is a consultant to Allergan, AMAG, Pfizer, P&G, Duchesnay, Cooper Surgical; Speakers Bureau for Pfizer, Valeant, and AMAG; and has received research grants and support paid to Sutter Health from TherapeuticsMD. Dr. Simon has served (within the past year, or current) as a consultant/advisor to AbbVie, Allergan Plc, AMAG, Ascend Therapeutics, Azure Biotech, Millendo Therapeutics, Nuelle, Radius Health, Regeneron, Roivant Sciences, Sanofi SA, Sebela, Sermonix, Shionogi, Symbiotec Pharmalab, TherapeuticsMD, and Valeant; and has received (within the past year, or current) grant/research support from AbbVie, Allergan Plc, Agile Therapeutics, Bayer Healthcare, New England Research Institute, ObsEva SA, Palatin Technologies, Symbio Research, and TherapeuticsMD; has also served (within the past year, or current) on the speaker's bureaus of Novo Nordisk, Shionogi, and Valeant; and is a stockholder (direct purchase) in Sermonix. Dr. Graham and Dr. Mirkin are employees of TherapeuticsMD with stock/stock options.
• TherapeuticsMD sponsored the study, and provided support for the medical writing assistance of Dominique Verlaan, PhD, CMPP (Precise Publications, LLC).

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