TX-001HR is Associated with a Clinically Meaningful Effect on Severity of Moderate to Severe Vasomotor Symptoms in the REPLENISH Trial

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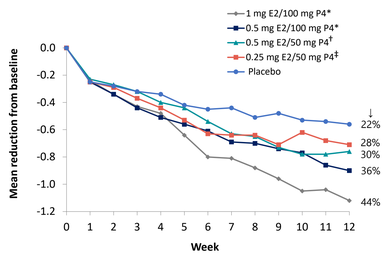
Introduction

- Vasomotor symptoms (VMS) in menopausal women are effectively treated with hormone therapy (HT), which reduces hot flush frequency and severity
- Significant reductions in severity of 0.18 to 1.6 points (on a scale of 0 to 3) from baseline have been reported in some randomized controlled trials;[1-4] however, the clinical relevance of these findings is often unknown
- In the 12-month REPLENISH trial, most doses of TX-001HR (TherapeuticsMD, Boca Raton, FL), an investigational once-daily, oral capsule containing 17β-estradiol (E2) and progesterone (P4), significantly reduced the frequency and severity of moderate to severe VMS in postmenopausal women with a uterus[5]
  - Clinically meaningful differences in VMS frequency reduction of ≥36 at week 4 and ≥39 at week 12 were previously demonstrated[6]
- Compared with placebo, VMS severity (**Figure 1**) was significantly improved with[5]
  - 1 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4 as early as week 3 and maintained to week 12
  - The lower doses 0.5 mg E2/50 mg P4 and 0.25 mg E2/50 mg P4 at most time points after week 6

Figure 1. Reductions in Moderate to Severe VMS Severity in the REPLENISH Trial



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

Objective

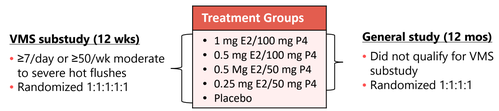
To determine what reduction in VMS severity was meaningful to women (using data from the REPLENISH trial), and the proportion of women with a clinically meaningful response with TX-001HR versus placebo when being treated for moderate to severe VMS

Methods

Study Design

- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated TX-001HR, for the treatment of moderate to severe VMS in menopausal women (age 40-65 years; BMI ≤34 kg/m^2) with a uterus, in a 12-week efficacy substudy[5]
- 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 (reported elsewhere) in the general study (**Figure 2**)[5]

Figure 2. REPLENISH Study Design



- Participants completed a daily VMS diary and recorded the number and severity of hot flushes up to week 12
  - Baseline weekly severity score was calculated by: [(number of moderate hot flushes for 7 days) x 2 + (number of severe hot flushes for 7 days) x 3] / (total number of moderate to severe hot flushes over 7 days)
  - On treatment weekly severity score was calculated by: [(number of mild hot flushes for 7 days) x 1 + (number of moderate hot flushes for 7 days) x 2 + (number of severe hot flushes for 7 days) x 3]/(total number of mild, moderate and severe hot flushes over 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?"

- CGI responses were rated using a 7-point Likert scale (**Table 1**). These responses were then converted to clinically meaningful response ratings to determine clinical meaningfulness

Table 1. Clinically Meaningful Response Ratings

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

- Clinically important differences (CID) and minimal clinically important differences (MCID) for reductions in moderate to severe VMS severity, regardless of treatment, were measured using anchor-based CGI nonparametric discriminant analyses utilizing bootstrapping methods[7,8]
  - 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 (40-65) and a mean BMI of 27 kg/m^2 at baseline (**Table 2**)

Table 2. Demographics and Baseline Characteristics of the MITT-VMS Population

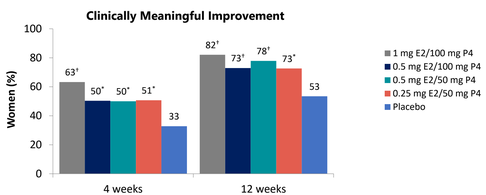
Characteristic	Estradiol/Progesterone				Placebo
	1 mg/ 100mg	0.5 mg/ 100 mg	0.5 mg/ 50 mg	0.25 mg/ 50 mg	
n	141	149	147	154	135
Age, y	54.7 ± 4.8	54.9 ± 4.5	54.8 ± 4.6	54.5 ± 3.8	54.3 ± 4.3
Race, n (%) White African American Other*	 95 (67.4) 45 (31.9) 1 (0.7)	 99 (66.4) 48 (32.2) 2 (1.3)	 99 (67.3) 43 (29.3) 5 (3.4)	 102 (66.2) 48 (31.2) 4 (2.6)	 91 (67.4) 41 (30.4) 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 Weekly severity	 74.4 ± 35.3 2.54 ± 0.32	 72.1 ± 27.8 2.51 ± 0.25	 75.9 ± 28.0 2.50 ± 0.23	 77.0 ± 30.4 2.51 ± 0.26	 72.4 ± 23.3 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 rated their symptoms as "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 by the CGI



*P<0.01; †P<0.001 vs placebo.

- Calculated clinical meaningfulness thresholds were weekly reductions in moderate to severe VMS severity of ≥0.35 points for MCID and ≥0.525 points for CID for week 4 (**Figure 4A**) and reductions of ≥0.225 points for MCID and ≥0.755 points 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

Disclosures

- Dr. Constantine consults for multiple pharmaceutical companies including but not limited to TherapeuticsMD, and has stock options 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; 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 Pharmaceuticals. Dr. Pickar is a consultant for Pfizer, Shionogi, and TherapeuticsMD and has stock options with TherapeuticsMD. Dr Bernick is an employee of TherapeuticsMD with stock/stock options; and is also a Board member. Dr. Mirkin is an employee 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)

Figure 4. Clinical Meaningfulness Analysis at (A) Week 4 and (B) Week 12

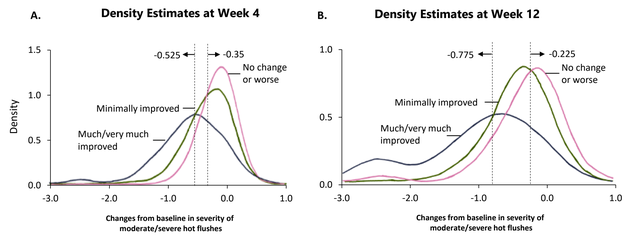
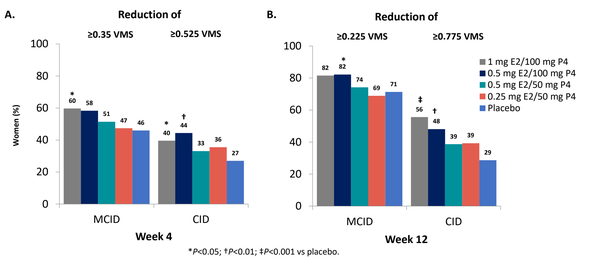


Figure 5. CGI-based CID and MCID Analysis at (A) Week 4 and (B) Week 12



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

Conclusions

- TX-001HR 1 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4 provided clinically meaningful improvements in VMS severity in menopausal women by CGI-based analysis
  - Clinically important differences in VMS severity of ≥0.525 points at week 4 and ≥0.775 points at week 12
- Similar results were observed with the frequency CGI-based analysis, which showed clinically meaningful improvements with all doses with VMS reduction of ≥36 at week 4 and ≥39 at week 12[6]
- A consistency of effect of TX-001HR was apparent as statistically significant and clinically meaningful improvements in the MENQOL questionnaire have also been observed (reported elsewhere)[9]
- One of the limits of this analysis is that the analysis combined all doses together, including lower doses, which showed lower efficacy in reducing VMS frequency and severity; most likely underestimating the strength of effect
- 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 versus placebo at weeks 4 and 12 with most doses[5]
- If approved, TX-001HR would be the first combined, oral E2/P4 softgel capsule that relieves VMS in terms of clinically meaningful reductions in both frequency and severity

References

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