REPLENISH Trial: Relationship Between Changes in Frequency and Severity of Vasomotor Symptoms and Changes in Quality of Life and Sleep Outcomes in Menopausal Women Treated with TX-001HR (Estrogen/Progesterone Oral Combination)

Sebastian Mirkin, MD[1]; Shelli Graham, PhD[1]; Dennis Revicki, PhD[2]; Randall H Bender, PhD[2]; Ginger Constantine, MD[3]

[1]TherapeuticsMD, Boca Raton, FL; [2]Evidera, Bethesda, MD; [3]EndoRheum Consultants, LLC, Malvern, PA

Introduction

- Many menopausal women experience vasomotor symptoms (VMS),[1-3] which have been reported as bothersome by many[1,3,4]
- VMS have been shown to negatively impact quality of life,[1,5] as well as sleep[1,6] and work productivity[5,7]
- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational 17β-estradiol combined with progesterone (E2/P4) in a single, oral softgel capsule that was developed to treat moderate-to-severe menopausal VMS in women with a uterus
- In the phase 3, REPLENISH trial (NCT01942668), TX-001HR significantly
  - Reduced the frequency and severity of VMS without increasing the incidence of endometrial hyperplasia[8]
  - Improved scores of the Menopause-Specific Quality of Life (MENQOL) questionnaire[9] and Medical Outcomes Study (MOS)-Sleep scale[10]

Objective

- To characterize the relationship between changes in VMS with TX-001HR and changes in the MENQOL questionnaire and MOS-Sleep scale scores in the REPLENISH study

Methods

- REPLENISH was a randomized, double-blind, placebo-controlled, multicenter trial that evaluated various doses of TX-001HR in menopausal women with an intact uterus
- Healthy menopausal women (aged 40-65 years; BMI ≤34 kg/m^2) with ≥7/day or ≥50/week moderate-to-severe hot flushes were randomized E2/P4 or placebo for the VMS substudy, while the remainder were randomized to active E2/P4 only (**Table 1**)
- All women completed daily diaries on the frequency and severity of their hot flushes through week 12, and MENQOL and MOS Sleep questionnaires at baseline, at week 12, and at months 6 and 12
  - The MENQOL questionnaire assesses quality of life over the past month with 29 questions within 4 domains (vasomotor, psychosocial, physical, and sexual)
  - The MOS Sleep questionnaire has 12 items that measure 6 dimensions of sleep over the past 4 weeks; it consists of a sleep problem total score, and sleep problem indices I and II scores

Table 1: Treatments and Randomization

Treatment Groups	Randomization	
E2/P4 (daily) • 1.0 mg/100 mg • 0.5 mg/100 mg • 0.5 mg/50 mg • 0.25 mg/50 mg Placebo (daily)	• VMS Substudy: Women with moderate-to-severe hot flushes • Randomized 1:1:1:1:1 to 1 of 4 E2/P doses or placebo	• Women not qualifying for the VMS substudy • Randomized 1:1:1:1 to 1 of 4 E2/P doses

- Growth models were used to summarize the longitudinal data and provide change estimates with which to examine the relationships between linear changes in frequency and severity of hot flushes over 12 weeks, and changes from baseline in MENQOL (total and VMS domain scores) and MOS-Sleep (total score, sleep problems indices I and II) outcomes at 12 weeks
- A fixed cubic term was used in the growth model for frequency. This term was fixed to a single estimated value across every individual in the sample, and captured the flattening of the curvature in the frequency data over time.
- Similarly, a fixed quadratic term was included in the growth model for severity to account for some non-linearity in the severity data over time
- Growth model fit was evaluated by several fit statistics, including the comparative fit index (CFI; >0.90), root mean square error of approximation (RMSEA; <0.08), and standardized root mean residual (SRMR; <0.10)

Results

- Of the 726 women in the MITT VMS population, 591 were in the combined TX-001HR groups and 135 were in the placebo group; 89% completed the substudy at 12 weeks
- Women in the VMS substudy had a mean age of 55 years (range, 40-65) and mean BMI of 27 kg/m^2; 67% of the women were white and 31% were African American
- All of the 5 linear growth models demonstrated acceptable fit based on CFI, RSMEA, and SRMR criteria (**Table 2**)
- Both frequency and severity changes with treatment over 12 weeks were related to changes in MENQOL total and vasomotor scores from baseline; treatment had a direct effect on the MENQOL vasomotor domain (estimate -0.36; P<0.05), but not on MENQOL total score (**Figure 1A-B**)
- Significant changes in the MOS-Sleep total and sleep problem indices were related to significant changes in hot flush frequency and somewhat by severity (**Figure 2A-C**); no direct effects of treatment were seen on any MOS-Sleep outcome

Table 2. Model Fit Statistics for MENQOL and MOS Sleep Scale Growth Models

	MENQOL total	MENQOL VMS	MOS-Sleep total	MOS-Sleep Index I	MOS-Sleep Index II
CFI	0.97	0.97	0.97	0.97	0.97
RMSEA	0.07	0.07	0.07	0.07	0.07
SRMR	0.05	0.08	0.06	0.06	0.06

CFI = comparative fit index; RMSEA = root mean square error of approximation; SRMR = standardized root mean residual.

Figure 1. Relationship of Treatment, Hot Flush Frequency and Severity Changes, and Changes in MENQOL

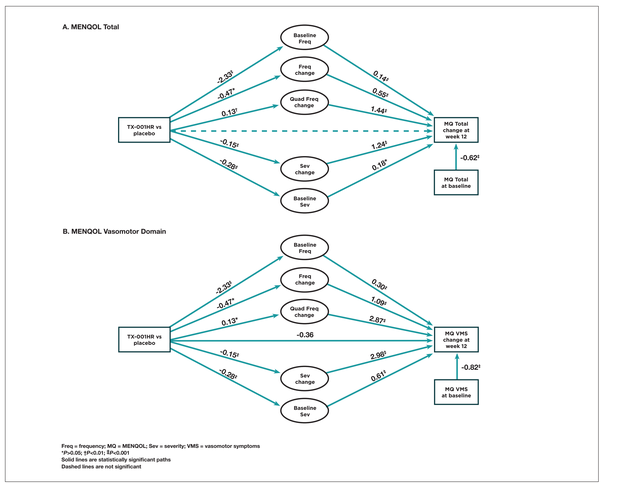
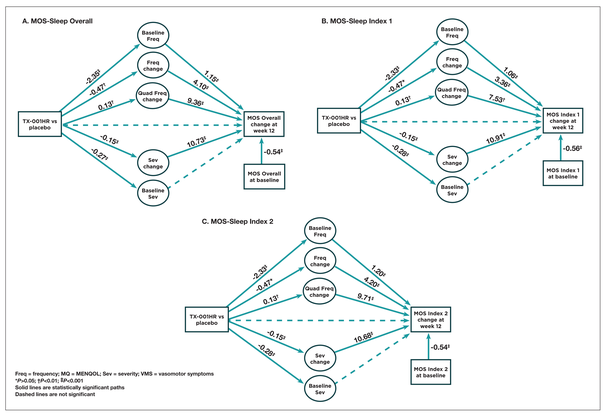


Figure 2. Relationship of Treatment, Hot Flush Frequency and Severity Changes, and Changes in MOS-Sleep Scale



Conclusions

- The REPLENISH trial was a large, phase 3, randomized, controlled trial in which TX-001HR significantly reduced VMS frequency and severity with no endometrial hyperplasia,[8] and significantly improved quality of life as measured by the MENQOL questionnaire,[9] and most sleep problems as measured by the MOS-Sleep scale[10]
- Improvements in MENQOL and MOS-Sleep questionnaires with TX-001HR versus placebo appear to be indirect and mediated by improvements in hot flush frequency and severity, as shown in 4 of the 5 mediation models. Thus, reduction in frequency and severity of VMS with TX-001HR may potentially lead to improvements in quality of life and sleep outcomes.
- If approved, TX-001HR could provide an alternative option for the estimated millions of postmenopausal women with a uterus currently using unregulated and unapproved compounded hormone therapy to treat moderate-to-severe VMS

References

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Disclosures

- SM and SG are employees of TherapeuticsMD (with stock/stock options). GC consults to pharmaceutical companies including but not limited to TherapeuticsMD and has stock options with TherapeuticsMD. DR and RHB are employees of Evidera, which received research funding from TherapeuticsMD.
- TherapeuticsMD sponsored the study and analysis, and supported the medical writing assistance provided by Kathleen Ohleth, PhD, CMPP (Precise Publications, LLC).

Presented at the 2018 ENDO Meeting, March 17-20, 2018 in Chicago, IL