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-011HR (Estrogen/Progestrone Oral Combination)

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Introduction

Many menopausal women experience vasomotor symptoms (VMS),1,2 which have been reported as bothersome by many.3-5 VMS have been shown to negatively impact quality of life,6 as well as sleep7,8 and work productivity.9

TX-011HR (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 (NCT01942658), TX-011HR significantly reduced the frequency and severity of VMS with no increase in the incidence of endometrial hyperplasia.10

Improved scores of the Menopause-Specific Quality of Life (MENQOL) questionnaire9 and Medical Outcomes Study (MOS-Sleep) scale11 were observed in the TX-001HR arm vs placebo.

Objective

To characterize the relationship between changes in VMS with TX-011HR 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-011HR in menopausal women with an intact uterus. TX-001HR was selected for further development.

Healthy menopausal women (aged 40-65 years; BMI ≤34 kg/m²) with moderate-to-severe VMS were randomized E2/P4 or placebo for the VMS substudy.

Objective

To evaluate various doses of TX-001HR in menopausal women with an intact uterus.

Methods

TX-001HR vs E2/P4

Table 1: Treatments and Randomization

- TX-001HR vs E2/P4
- TX-001HR vs Placebo

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

- 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 flashes 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 constraint of zero at baseline, and freedom at weeks 12, 24, and 36.

A fixed cubic term was used in the growth model for severity to account for some non-linearity in the severity data over time.

Results

Of the 726 women in the MITT VMS population, 591 were in the combined TX-001HR and placebo groups and 135 were in the placebo group; 89% completed the substudy at 12 weeks.

Placebo (daily)

- E2/P4 (daily)
- 1.0 mg/100 mg

Figure 1A-B

Figure 2A-C

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

- Significant changes in the MOS-Sleep total and sleep problem indices were observed in the TX-001HR arms vs placebo.

- Significant changes in the MENQOL total and vasomotor domains were observed across treatment groups.

Conclusions

The REPLENISH trial was a large, phase 3, randomized, controlled trial in which TX-011HR significantly reduced VMS frequency and severity with no endometrial hyperplasia,12 and significantly improved quality of life as measured by the MENQOL questionnaire,6 and most sleep problems as measured by the MOS-Sleep scale.11

Improvements in MENQOL and MOS-Sleep questionnaires with TX-011HR versus placebo appear to be indirect and mediated by improvements in hot flush frequency and severity, as shown in n of the 5 mediation models. Thus, reduction in frequency and severity of VMS with TX-011HR may potentially lead to improvements in quality of life and sleep outcomes.

If approved, TX-011HR 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


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