The REPLENISH TRIAL: Evaluating TX-001HR (The First Combination 17 β-Estradiol/Natural Progesterone Capsule using SYMBODA™ technology), a new option for the treatment of menopausal symptoms.

Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of TX-001HR.

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INTRODUCTION

- Hormone replacement therapy (HRT) combining estrogens with progestogens is the most consistently effective treatment for menopause symptoms in women with a uterus.[1]
- Recent epidemiological studies suggest the type of estrogen and progestogens (synthetic progestins versus natural progesterone) used in combination HRT may affect a regimen's risk/benefit profile.[2-4]
  - Women using oral conjugated equine estrogens (CEE) had more than twice the risk of venous thromboembolism observed in women using oral estradiol.[2]
  - In women using combination HRT, regimens containing synthetic progestins generally increased the risk of breast cancer to a greater extent than regimens containing natural progesterone.[3,4]
- We anticipate that combining the bio-identical hormones 17β-estradiol and natural progesterone will represent a better alternative for treating menopausal symptoms in women with a uterus.
  - At present, no single drug combining the natural hormones has been approved by the FDA.
  - Although unapproved 17β-estradiol and progesterone combinations are available through compounding pharmacies, their variable purity and potency have led most medical society guidelines for menopause therapy to recommend against their use.[5,6]
- TX-001HR (TherapeuticsMD, Inc, Boca Raton, FL) is a novel oral agent that combines advanced solubilized bio-identical 17β-estradiol with natural progesterone using SYMBODA™ technology, in a gelatin capsule.
- The safety and efficacy of 4 doses of TX-001HR are being investigated in the phase 3 REPLENISH trial, and if TX-001HR is approved, it would become the first FDA approved HRT that combines 17β-estradiol and progesterone.

OBJECTIVES

- Determine mean change in the frequency and severity of moderate to severe vasomotor symptoms (VMS) at weeks 4 and 12.
- Evaluate TX-001HR for endometrial safety based on rate of hyperplasia at 12 months.
- Compare outcomes with 4 different doses to identify the lowest effective dose having acceptable endometrial safety.

STUDY POPULATION

- After screening, investigators will enroll 1750 healthy postmenopausal women (N=1750) with a uterus who are seeking treatment for menopause-related VMS (Table 1).
- A 12-week VMS substudy will include 750 women (150 per treatment arm) who reported ≥7 moderate to severe hot flushes per day, or ≥50 per week, for at least 14 days during screening (Table 1).

STUDY DESIGN

Figure 1. The REPLENISH Trial Design

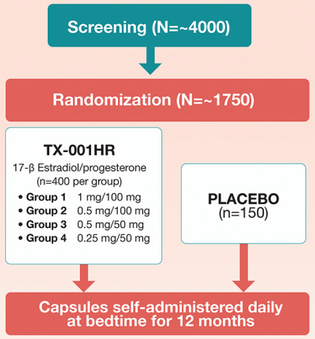

Table 1. Main Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Women aged 40 to 65 years old • Intact uterus • Postmenopausal (serum estradiol, ≤50 pg/mL) • Generally healthy per pre-specified criteria • BMI ≤34 kg/m2 • Use of no more than 2 antihypertensive drugs	• Contraindications to hormone use • Heavy smoker (≥15 cigarettes/day) • Abnormal endometrial biopsy at screening • History of endometrial hyperplasia or of undiagnosed vaginal bleeding • History of melanoma or of breast, uterine, or ovarian cancer • History of clinically significant, relevant physical or mental illnesses

Figure 2. The REPLENISH Trial Timeline

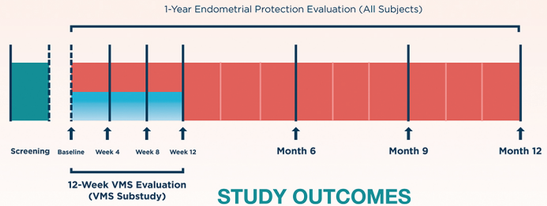

Table 2. Secondary Endpoints

Total Population
• Rates of amenorrhea • Number of days with bleeding and spotting • MENQOL scores • MOS-Sleep scores

STUDY OUTCOMES

- The primary efficacy endpoint consists of 4 co-primary endpoints, the mean changes from baseline in moderate to severe VMS versus placebo for:
  - frequency of VMS at week 4
  - severity of VMS at week 4
  - frequency of VMS at week 12
  - severity of VMS at week 12

SAMPLE SIZE

- Sample size was based on 2 or fewer reports of endometrial hyperplasia, which is the average background rate in the general postmenopausal population.
- Assuming that 20% of participants in each group will be ineligible for primary analyses in the VMS substudy, enrolling 150 women in each treatment group should provide at least 90% power to test the primary VMS hypotheses.

CONCLUSIONS

- The REPLENISH Trial is a phase 3, randomized, placebo-controlled study designed to evaluate the safety and efficacy of a novel oral drug (TX-001HR) that combines the advanced bio-identical 17β-estradiol plus progesterone, solubilized by SYMBODA technology (1 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, or 0.25 mg/50 mg) for the treatment of menopause-related VMS.
- A total of 1750 postmenopausal women with an intact uterus will be randomly assigned to 1 of 4 dosing regimens or placebo for 12 months.
- The 12-week VMS substudy will run concurrently to evaluate the primary efficacy endpoint, which is a reduction in the frequency and severity of moderate to severe hot flushes.
- Data from the 12-month study will be used to evaluate the primary safety endpoint, which is the rate of endometrial hyperplasia.
- If approved, TX-001HR would become the first FDA-approved HRT that combines advanced solubilized bio-identical 17β-estradiol with progesterone via SYMBODA technology in a single dosage form, which the data suggest may represent a better alternative than existing HRT regimens.

References

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