INTRODUCTION

- Hormone replacement therapy (HRT): combining estrogens with progesterone is the most consistently effective treatment for menopausal symptoms in women with a uterus.1
- Recent epidemiological studies suggest that the type of estrogen and progesterone (synthetic progesterone versus natural progesterone) used in combination HRT may affect a woman’s risk/benefit profile.2,3
- Women using oral conjugated estrogen (OHE) had more than twice the risk of venous thromboembolism observed in women using oral estrogen and4
- In women using combination HRT, regimens containing synthetic progesterone generally increased the risk of breast cancer to a greater extent than regimens containing natural progesterone.5
- 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.6
- At present, no single drug combining the natural hormones has been approved by the FDA.7
- Although unapproved 17β-estradiol and progestosterone combinations are available from compounding pharmacies, their variable purity and potencies have led most medical society guidelines for menopause therapy to recommend against their use.8
- 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.9
- 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 rates 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 (No.1750) with a uterus who are seeking treatment for menopause-related VMS (Table 1).
- A 12-week VMS subscale will include 750 women (150 per treatment arm) who reported moderate to severe hot flushes per day, or per week for at least 14 days during screening (Table 1).

STUDY DESIGN

- The REPLENISH TRIAL is a phase 3, randomized, placebo-controlled, multicenter study to evaluate the safety and efficacy of a novel oral drug (TX-001HR) that combines the advanced bio-identical 17β-estradiol plus progesterone, stabilized by SYMBODA technology (1 mg/day of 17β-estradiol, 0.3 mg/day of 17α-progestosterone, or 0.3 mg/day of 17β-progestosterone) 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 subscale 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 using SYMBODA technology in a single-dosage form, which the data suggest may represent a better alternative than existing HRT regimens.

STUDY OUTCOMES

- The primary efficacy endpoint consists of 4 key primary endpoints.
- The mean change 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

TOTAL POPULATION

- Rates of amelioration
- Number of days with bleeding and spotting
- MENS scores
- MOS-Sleep scores

SAMPLE SIZE

- Sample size was based on 2 or more reports of endometrial hyperplasia, which is the primary end-point rate in the general postmenopausal population.
- A minimum of 1200 participants in each group will be eligible for primary analysis in this trial, including 300 women in each treatment arm and a placebo arm at least 80% power to test the primary VMS endpoints.

REFERENCES