TX-001HR

Supplemental Replenish Trial Design And Topline Phase 3 Results

December 2016

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Yuvvexy™ (TX-004HR), TX-001HR, TX-005HR, and TX-006HR are investigational drugs and are not approved by the FDA. This non-promotional presentation is intended for investor audiences only.

PDF copies of press releases and financial tables can be viewed and downloaded at our website: www.therapeuticsmd.com/pressreleases.aspx.

Replenish Trial Overview

A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Estradiol in Combination with Progesterone in Postmenopausal Women with an Intact Uterus

Replenish Trial Study Design - Flow Chart

Initial Subject Screening

Frequency and Severity of Hot Flash diary data was assessed during Screening

Randomized Study Participants[1]

12-Week VMS Efficacy Substudy

Study Participants who had ≥ 7 moderate or severe hot flashes per day or ≥ 50 per week during Screening

52-Week Endometrial Safety Study

1. Healthy postmenopausal women aged 40 to 65 years with an intact uterus who were seeking relief from vasomotor symptoms (VMS) and who met all inclusion/exclusion criteria were eligible for 12 months of study treatment.

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Replenish Trial Study Design - Populations

- **Safety Population (n = all dosed study subjects)**
  - **52-Week Endometrial Safety Population**
    - A subset of the total safety population group who had a biopsy at week 52
- **VMS Efficacy Population (n = ~150 per active arm & placebo)**
  - **12-Week VMS Efficacy mITT Population**
    - A subset of the total safety population group who had ≥ 7 moderate or severe hot flashes per day or ≥ 50 per week at baseline, and
    - Took at least one dose of study medication, and
    - Have at least 4 days of evaluable data
  - **All VMS Efficacy mITT Population included in Safety Population**
- **Study Treatment Arms**
  - 17β estradiol 1 mg / progesterone 100 mg
  - 17β estradiol 0.5 mg / progesterone 100 mg
  - 17β estradiol 0.5 mg / progesterone 50 mg
  - 17β estradiol 0.25 mg/ progesterone 50 mg
  - Placebo (VMS Substudy only)

Current FDA Guidance for VMS Drug Products*

- **Co-primary efficacy endpoints (12 week VMS Efficacy Population)**
  - Mean Change from Baseline to Weeks 4 and 12 in the frequency and severity of moderate and severe vasomotor symptoms versus placebo
- **Primary safety endpoint (12 month Endometrial Safety Population)**
  - Incidence rate of endometrial hyperplasia at 12 months (to demonstrate a hyperplasia rate that is ≤ 1% with an upper bound of the one-sided 95% confidence interval for that rate does not exceed 4%)

Study Analysis

- **Clinically meaningful and statistically significant reduction within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment**

Study Considerations

- **Single, 12-month study to demonstrate endometrial protection**

Single Pivotal Phase 3 trial required unless:

- **The drug to be studied is considered a new molecular entity**
- **The drug to be studied poses unique safety concerns**

* 2003 FDA Draft Guidance for Industry Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071643.pdf

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Replenish Trial Co-Primary Efficacy Endpoints: Mean Change in Frequency and Severity of Hot Flashes Per Week Versus Placebo at Weeks 4 and 12, VMS-mITT Population

Estradiol/Progesterone	1 mg/100 mg (n = 141)	0.5 mg/100 mg (n = 149)	0.5 mg/50 mg (n = 147)	0.25 mg/50 mg (n = 154)	Placebo (n = 135)
Frequency					
Week 4 P-value versus placebo	<0.001	0.013	0.141	0.001	-
Week 12 P-value versus placebo	<0.001	<0.001	0.002	<0.001	-
Severity					
Week 4 P-value versus placebo	0.031	0.005	0.401	0.1	-
Week 12 P-value versus placebo	<0.001	<0.001	0.018	0.096	-
Replenish Trial Primary Safety Endpoint: Incidence of Consensus Endometrial Hyperplasia or Malignancy up to 12 months, Endometrial Safety Population[Ŧ]					
Endometrial Hyperplasia	0% (0/280)	0% (0/303)	0% (0/306)	0% (0/274)	0% (0/92)

MITT = Modified intent to treat

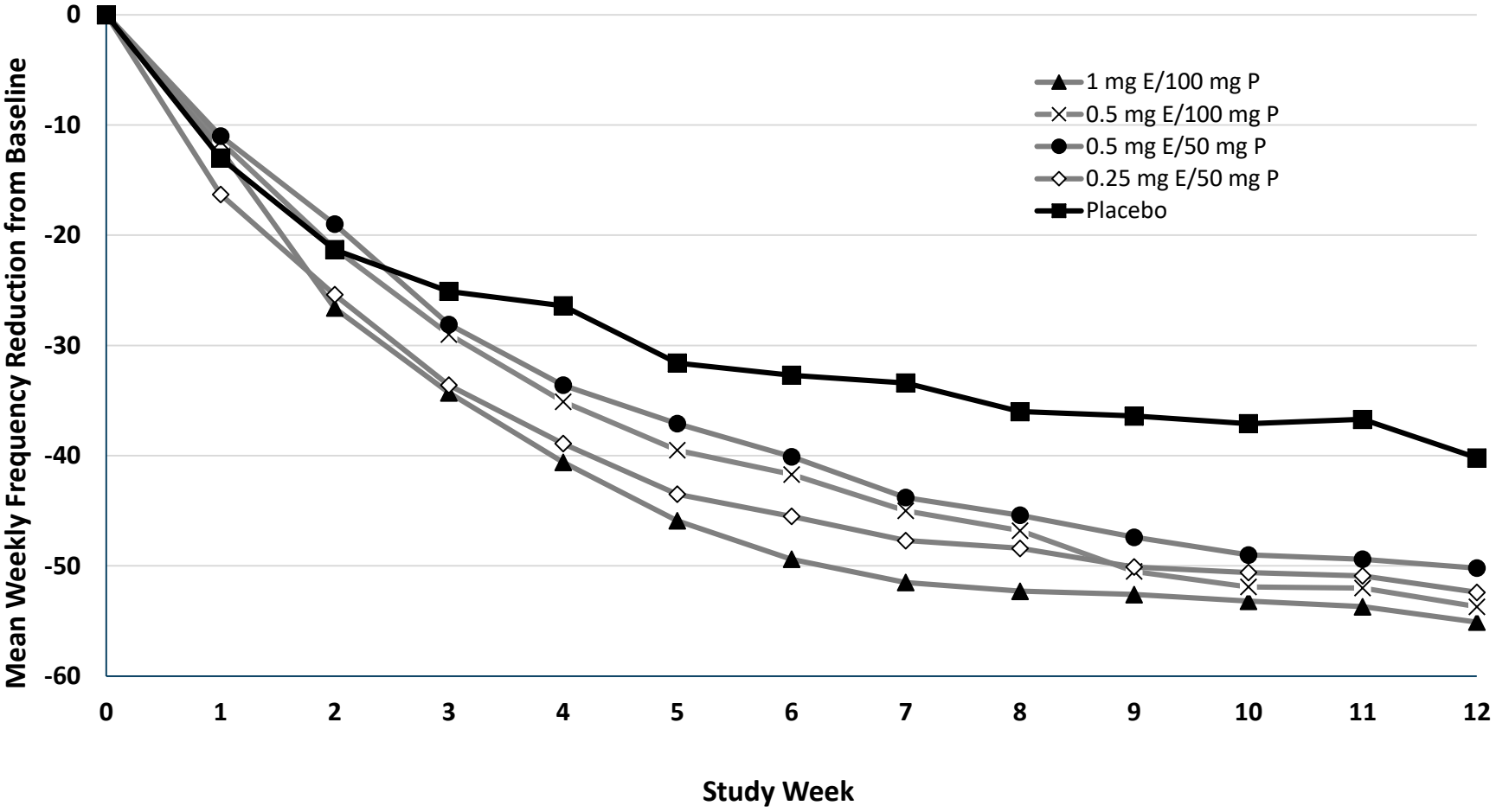
[ŦPer FDA, consensus hyperplasia refers to the concurrence of two of the three pathologists be accepted as the final diagnosis[1]

P-value < 0.05 meets FDA guidance and supports evidence of efficacy

Primary Efficacy Analysis pre-specified with the FDA in the clinical protocol and Statistical Analysis Plan (SAP)

- P-value < 0.05 meets FDA guidance and supports evidence of efficacy

Mean Change from Baseline in Weekly Frequency of Moderate to Severe Hot Flashes for Weeks 1 to 12



Mean Change from Baseline in Weekly Severity of Moderate to Severe Hot Flashes for Weeks 1 to 12