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Review

17β-Estradiol and natural progesterone for menopausal hormone therapy: REPLENISH phase 3 study design of a combination capsule and evidence review

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ABSTRACT

Several formulations combining estrogens and progestins for hormone therapy (HT) have been approved worldwide for the treatment of menopausal symptoms, yet recent data indicate a decline in their use and an increase in compounded bioidentical HT. Up to now, no single product combining natural 17β-estradiol and progesterone has been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). A phase 3 trial (REPLENISH) is underway to study a novel oral formulation of solubilized 17β-estradiol and natural progesterone combined in a single gelatin capsule (TX-001HR; TherapeuticsMD, Inc, Boca Raton, FL) for treating vasomotor symptoms (VMS) in postmenopausal women. The REPLENISH trial evaluates the efficacy and safety of TX-001HR (4 doses) versus placebo for the reduction of moderate to severe VMS frequency and severity at 4 and 12 weeks and evaluates the endometrial safety of the combinations at 1 year. TX-001HR contains hormones that are molecularly identical to endogenous estradiol and progesterone and is intended as an option for women who prefer bioidentical hormones; further, it does not contain peanut oil, a common allergen. The constituents of TX-001HR, in a pharmacokinetic report, showed similar bioavailability and safety compared with reference estradiol tablets and micronized progesterone capsules administered together. Published data suggest a safer profile of estradiol and natural progesterone compared with HT containing conjugated equine estrogens and progestins. This report summarizes the methodology of the REPLENISH trial and reviews the evidence suggesting clinical differences between HT containing progesterone or progestins, and estradiol or conjugated equine estrogens.

Contents

Abbreviations: CBHT, compounded bioidentical hormone therapy; CEE, conjugated equine estrogens; EMA, European Medicines Agency; FDA, Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; HT, hormone therapy; KEEPS, Kronos Early Estrogen Prevention Study; LDL-C, low-density lipoprotein cholesterol; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; PEPI, Postmenopausal Estrogen/Progestin Interventions study; VMS, vasomotor symptoms; WHI, Women's Health Initiative.

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1. Introduction

Several formulations of hormone therapy (HT) containing estrogens and progestins have been approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of menopausal symptoms. The primary indication for HT is the relief of moderate to severe vasomotor symptoms (VMS) [1]. The most effective treatment for hot flushes is HT consisting of estrogens with or without progestogens [2]. However, publication of data showing possible harm in women of a mean age of 63 that were treated for more than 5 years with conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) from the Women's Health Initiative (WHI) in 2002 [3] deterred many women from initiating or continuing prescribed HT [4–7]. An increase in the use of compounded bioidentical hormone therapy (CBHT) [7–9] has occurred in the United States, since this publication, indicating that women appear to be concerned with the hormones contained in FDA-approved HT. Using a combination of cross-sectional Internet survey data, US Census Bureau statistics, and PHAST 2.0 prescription data, a recent US study estimated that CBHT may account for 28% to 68% of all HT prescriptions and may be used by 1 to 2.5 million women aged ≥40 years annually, accounting for $1 to $2 billion in health care spending every year [10].

Women with a uterus take a progestogen with exogenous estrogen to prevent uterine stimulation and possible endometrial cancer [1,11]. Progestogens such as micronized progesterone have been shown to inhibit endometrial hyperplasia related to unopposed estrogen stimulation [12]. Although FDA-approved separate tablet/capsule combinations of estrogen and progesterone monotherapies are available for menopausal symptoms, no single tablet or capsule product combining the natural hormones 17β-estradiol and progesterone has been approved by the FDA. 17β-estradiol and progesterone combinations that do not have regulatory agency approval are available through compounding pharmacies, but have variable purity and potency and lack efficacy and safety data. This has resulted in medical societies [1,8,13] and the FDA [14] cautioning against the use of CBHT.

REPLENISH is a phase 3 trial studying a novel oral formulation of solubilized 17β-estradiol and natural progesterone combined using SYMBODA™ technology in a single gelatin capsule (TX-001HR; TherapeuticsMD, Inc, Boca Raton, FL) for the treatment of VMS in postmenopausal women. TX-001HR capsules contain hormones that are molecularly identical to endogenous estradiol and progesterone, without peanut oil, a common allergen [15]. This formulation is intended to provide a therapeutic option for women who prefer "natural" hormones. Until now, it has been difficult to effectively combine progesterone and estradiol together in a single capsule [15]. One reason may be that effective absorption of oral progesterone is difficult to achieve, although studies have clarified that absorption is influenced by the vehicle used and progesterone particle size [16].

The estradiol and progesterone of the single capsule (TX-001HR) have bioavailability similar to their respective reference estradiol tablets and micronized progesterone capsules administered together, as shown in a preliminary report [15]. This product, if approved, will be the first FDA/EMA-approved HT to combine 17β-estradiol and progesterone in a single oral dosage form and will be the first oral 17β-estradiol/progesterone combination that is available without peanut oil. The purpose of this report is to detail the study methods of the REPLENISH trial of TX-001HR and to review the relevant literature on the benefits of estradiol and progesterone present in this combination capsule.

2. Replenish study

The purpose of the REPLENISH trial is to determine whether different doses of TX-001HR are effective at reducing the frequency and severity of moderate to severe menopause related VMS versus placebo at 4 and 12 weeks, and to evaluate endometrial safety after 12 months of continuous use of this combination.

2.1. Study population

Eligible participants are healthy postmenopausal women ($N = 1750$) with a uterus who are seeking treatment for menopause-related VMS and fulfill additional inclusion and exclusion criteria (Table 1). During the screening period, all women will complete diaries for 14 consecutive days to assess the frequency and severity of VMS. The 12-week VMS substudy will include women who report ≥7 moderate to severe hot flushes per day, or ≥50 per week, for at least 14 days during screening.

2.2. Study design

The REPLENISH trial (NCT01942668; www.clinicaltrials.gov) is a phase 3, prospective, randomized, double-blind, placebo-controlled, parallel-group, 12-month, multicenter trial (80 sites in the United States) evaluating the safety and efficacy of a 17β-estradiol-natural progesterone combination capsule in postmenopausal women. Approximately 4000 women will be screened for study eligibility to enroll 1750 women who meet the inclusion and exclusion criteria (Table 1).

At baseline (week 0), 1750 eligible women will be randomly assigned to self-administer orally at bedtime 1 of 4 doses of TX-001HR (estradiol/progesterone: 1.0 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, or 0.25 mg/50 mg) or placebo for 12 months. Participants in the 12-week VMS substudy ($n = 750$) will be randomized equally within each study site to each active treatment group

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