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*APPLICATION NUMBER:*

**210132Orig1s000**

**CLINICAL REVIEW(S)**

-Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.

Standard NDA 210132

Bijuva™ (estradiol and progesterone) capsules, for oral use

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 210132
Priority or Standard	Standard
Submit Date(s)	December 28, 2017
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PDUFA Goal Date	October 28, 2018
Division/Office	Division of Bone, Reproductive, and Urologic Products/ Office of Drug Evaluation III
Reviewer Name(s)	Theresa H. van der Vlugt, M.D., M.P.H.
Review Completion Date	October 25, 2017
Established/Proper Name	Estradiol and progesterone capsules, for oral use
(Proposed) Trade Name	Bijuva™
Applicant	TherapeuticsMD
Dosage Form(s)	Oral softgel capsule
Applicant Proposed Dosing Regimen(s)	Combined 1 mg estradiol and 100 mg progesterone administered orally daily (b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe vasomotor symptoms in a woman with an intact uterus
Recommendation on Regulatory Action	Approval of the combined 1 mg estradiol and 100 mg progesterone dosage strength is recommended. (b) (4)
Recommended Indication(s)/Population(s) (if applicable)	Postmenopausal women with a uterus

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## Glossary

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AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence interval
CGI	Clinical Global Impression
CMC	Chemistry, Manufacturing and Controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
ECG	electrocardiogram
eCTD	electronic common technical document
EA	Environmental analysis
EE	Efficacy evaluable
ES	Endometrial safety
EOT	End-of-Trial
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MENQOL	Menopause-Specific Quality of Life
MITT	modified intent to treat
MMRM	Mixed Effect Model Repeat Measurement
MOS-Sleep	Medical Outcome Study -Sleep
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality

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OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PR	Progesterone receptor
PRO	patient reported outcome
QC	Quality Control
SAE	serious adverse event
SAP	statistical analysis plan
	(b) (4)
SOC	standard of care
TEAE	treatment emergent adverse event
VMS	Vasomotor symptoms

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## 1. Executive Summary

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### 1.1. Product Introduction

Bijuva™ (estradiol and progesterone) capsules, for oral use is a fixed-dose combination product, subject to CFR 300.5, consisting of 1 mg estradiol and 100 mg micronized progesterone proposed for the treatment of moderate to severe vasomotor symptoms, due to menopause in a woman with a uterus. Bijuva™ capsules are administered orally once per day at bedtime with food. The progesterone component is added to protect the endometrium from unopposed estradiol (the active ingredient with respect to effect on vasomotor symptoms)-induced risk of endometrial hyperplasia and cancer.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

This clinical reviewer concludes that substantial evidence of overall efficacy for Bijuva™ (estradiol and progesterone) capsules 1 mg estradiol and 100 mg progesterone is demonstrated, based on successfully achieving the primary protocol-defined co-primary endpoints of 1) a statistically significant mean change in the frequency of moderate to severe vasomotor symptoms at Week 4; 2) a statistically significant mean change in the frequency of moderate to severe vasomotor symptoms at Week 12; 3) a statistically significant mean change in the severity of moderate to severe vasomotor symptoms at Week 4; and 4) a statistically significant mean change in the severity of moderate to severe vasomotor symptoms at Week 12. In addition, the combined 1 mg estradiol and 100 mg progesterone capsules demonstrated a clinically meaningful difference in the frequency of hot flashes (at least 2 hot flashes above placebo per day, or 14 per week) at Week 5 that is maintained through Week 12. A subgroup analysis by race demonstrated a lack of efficacy in three of the four protocol-defined co-primary endpoints in women who self-identified as Black/African American. The absence of overall efficacy in subgroup race analysis will be included in labeling.

(b) (4)

### 1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Vasomotor symptoms are common during menopause and can negatively impact quality of life for women. A decrease in estrogen at the time of menopause is associated with vasomotor symptoms (hot flashes/hot flushes). Estrogens are the pharmacologic treatment of choice for most postmenopausal women with vasomotor symptoms. The administration of estradiol to postmenopausal women significantly improves vasomotor symptoms. Unopposed estrogen, however, is associated with an increased incidence of endometrial hyperplasia and endometrial cancer in a postmenopausal woman with a uterus. The addition of a progestogen (a synthetic progestin or micronized progesterone) reduces that risk.

Bijuva™ is comprised of estradiol and progesterone in a softgel oral capsule administered continuously to alleviate vasomotor symptom in a woman with a uterus, while protecting the endometrium from unopposed estrogen.

The risks associated with estrogen plus progestogen products are well-defined by large epidemiologic studies, including but not limited to, the Women’s Health Initiative (WHI) substudies (estrogen-alone and estrogen plus progestin substudies), and include increases in the risk of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, invasive breast cancer, and probable dementia. However, the overall absolute risk of severe outcomes is low. Numerous estrogen-alone or estrogen with progestin drug products are approved for the treatment of moderate to severe vasomotor symptoms.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"><li>Menopause is a natural biological process and marks the end of fertility because of permanent ovarian failure.</li><li>Symptoms of menopause, such as vasomotor symptoms (VMS; hot flashes/hot flushes) and VVA symptoms [vaginal dryness, vaginal irritation/itching, and pain with sexual activity (dyspareunia)] can be debilitating with respect to a woman’s ability to accomplish her</li></ul>	<ul style="list-style-type: none"><li>Menopause symptoms, though not life-threatening, constitute a significant public health concern.</li></ul>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>normal activities including sleep. However, menopause is not a life-threatening condition.</p> <ul style="list-style-type: none"> <li>Up to 80% of postmenopausal women will experience vasomotor symptoms.<sup>1</sup></li> <li>In 2000, there were an estimated 45.6 million postmenopausal women in the United States (US). About 40 million of them were older than age 51, the average age of natural menopause in the Western world. By the year 2020, the number of US women older than age 51 is expected to be more than 50 million.<sup>2</sup></li> </ul>	
<p><a href="#">Current Treatment Options</a></p>	<ul style="list-style-type: none"> <li>Current treatment options for an indication for the treatment of moderate to severe vasomotor symptoms include multiple estrogen products, used alone in a woman without a uterus, or in combination with a progestogen (synthetic progestin or micronized progesterone) in a woman with a uterus. These approved products offer a range of dosage strengths and different routes of administration including oral tablets, transdermal systems, topical gels/lotion, and vaginal ring.</li> <li>Estradiol is the active moiety in most of the Agency’s approved estrogen-alone and estrogen plus progestogen products with an indication for the treatment of moderate to severe vasomotor symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>Numerous estrogen-alone or estrogen plus progestogen drug products are approved for the treatment of moderate to severe vasomotor symptoms. Women with a uterus, using estrogen and progestogen products, should be started at the lowest effective dose that relieves their vasomotor symptoms and protects the endometrium from estrogen exposure. Titration of dose to relieve vasomotor symptoms should be undertaken based on treatment goals and risks for the individual woman.</li> </ul>

<sup>1</sup> Centers for Disease Control and Prevention, *Menopause: Women’s Reproductive Health*. Available at <https://www.cdc.gov/reproductivehealth>.

<sup>2</sup> US Census Bureau. Population survey: female population by age, sex, and race and Hispanic origin: March 2002. Available at <https://www.census.gov/population>.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>TX-001HR is the first combination formulation containing estradiol and micronized progesterone being evaluated for the treatment of moderate to severe vasomotor symptoms due to menopause, and protection of the endometrium in a woman with a uterus. Individual single estradiol-alone products are currently approved for a VMS indication. Prometrium® (micronized progesterone, USP) is approved for the protection of the endometrium with associated use of oral 0.625 mg conjugated estrogens in a woman with a uterus.</li> </ul> <p>TX-001HR is peanut oil free and thus can be used in women with peanut allergies.</p> <ul style="list-style-type: none"> <li>TherapeuticsMD developed an oral, fixed-dose combination product (TX-001HR) consisting of a softgel formulation containing solubilized estradiol with micronized progesterone intended to treat moderate to severe VMS while protecting the endometrium from unopposed estradiol.</li> </ul>	<ul style="list-style-type: none"> <li>A woman with a uterus using Bijuva™ can expect a reduction in the frequency and severity of moderate to severe vasomotor symptoms.</li> <li>The applicant’s rationale for the development of TX-001HR is to provide postmenopausal women with a product that is a combination of estradiol and progesterone, thus alleviating the need for non-FDA approved compounded hormone therapy that are not clinically evaluated for bioavailability, safety, or efficacy.</li> <li>TX-001HR is peanut oil free and thus can be used in women who are unable to tolerate currently approved hormone therapy due to peanut allergies.</li> </ul>
<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>Use of FDA approved estradiol plus progesterone therapy leads to a reduction in the frequency and severity of vasomotor symptoms and prevents the risk of endometrial hyperplasia associated with unopposed estrogen use.</li> <li>The most common adverse reactions (incidence ≥ 3%) with Bijuva™ are breast tenderness, headache, pelvic pain, vaginal bleeding, and vaginal discharge.</li> </ul>	<ul style="list-style-type: none"> <li>Risk associate with estrogen plus progestogen use, including this product, are well-defined with increases in the risk of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, invasive breast cancer, and probable dementia. The overall risk of these serious outcomes remains low as defined by the Women’s Health Initiative (WHI) estrogen plus progestin substudy (2002).</li> </ul>

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## 1.4. Patient Experience Data

The following primary clinical outcome assessment data (trial endpoints for phase 3, 52-week Trial TXC12-05), for the 1 mg estradiol/100 mg progesterone capsules (b) (4)

was submitted in the NDA 210132 application received December 28, 2017. These clinical endpoints comply with the Agency's 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", hereafter, referred to as the Agency's 2003 draft Hormone Therapy Guidance for Industry:

- Mean change in frequency of moderate to severe VMS from Baseline to Week 4 in an active treatment group compared with placebo
- Mean change in frequency of moderate to severe VMS from Baseline to Week 12 in an active treatment group compared with placebo
- Mean change in severity of moderate to severe VMS from Baseline to Week 4 in an active treatment group compared with placebo
- Mean change in severity of moderate to severe VMS from Baseline to Week 12 in an active treatment group compared with placebo

No measure of the acceptability of the combination estradiol/progesterone product was conducted during phase 3 Trial TXC12-05.

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

Menopause is a natural biological process and marks the end of fertility because of permanent ovarian failure. Symptoms of menopause, such as vasomotor symptoms (VMS; hot flashes/hot flushes) and vulvar and vaginal atrophy symptoms [VVA; vaginal dryness, vaginal irritation/itching, and dyspareunia (pain with sexual activity)] can be debilitating with respect to a woman's ability to accomplish her normal activities including sleep. However, menopause is not a life-threatening condition. In the US, nearly 40 million women are past the average age of natural menopause (51 years). Although the US Census Bureau year 2000 report does not provide the exact number of women over age 51, it does report the number of women age 55 and older, who can be mostly assumed to be postmenopausal.<sup>2</sup>

During the reproductive years, estradiol in women is produced primarily by the granulosa cells of the ovaries by the aromatization of  $\Delta^4$ -androstenedione (produced in the theca folliculi cells)

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to estrone, followed by conversion of estrone to estradiol by 17 $\beta$ -hydroxysteroid dehydrogenase. Smaller amounts of estradiol are also produced by the adrenal cortex in women. In postmenopausal women, fat cells produce active precursors to estradiol. Estradiol is conjugated in the liver to form estrogen conjugates (estradiol sulfate, estradiol glucuronide) and, as such, is excreted via the kidneys. Some of the water-soluble conjugates are excreted via the bile duct, and partly reabsorbed after hydrolysis from the intestinal tract. This enterohepatic circulation contributes to maintaining estradiol levels.

Progesterone is an endogenous steroid and sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species. Progesterone belongs to a group of steroid hormones called progestogens. It is the major progestogen in the body. Progesterone, like other steroid hormones, is synthesized from pregnenolone, which itself is derived from cholesterol. Approximately 30 mg of progesterone is secreted from the ovaries per day in women, while the adrenal glands produce about 1 mg of progesterone per day. Progesterone binds extensively to plasma proteins (96-99%, primarily to serum albumin (50-54%) and transcortin (43-85%). Progesterone is metabolized primarily by the liver to pregnanediols and pregnanones, which are conjugated in the liver to glucuronide and sulfate metabolites, then excreted in the bile, and may be further metabolized in the intestines. Enzymes that metabolize progesterone are also expressed widely in the brain, skin, and other extrahepatic tissues.

## 2.2. Analysis of Current Treatment Options

FDA has approved numerous hormone therapy products, both estrogen-alone for use in a woman without a uterus, and estrogen plus progestogen products for use in a woman with a uterus, as well as non-hormonal products, for the treatment of moderate to severe vasomotor symptoms. Treatment options for estrogen plus progestogen products are presented in Table 1, Table 2, and Table 3.

Table 1: Estrogen Plus Progestin Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Estrogen Plus Progestin Products	Available Dosage Strengths
Activella® (estradiol [E2] plus norethindrone acetate [NETA])	0.5 mg E2 plus 0.1 mg NETA taken daily or 1 mg E2 plus 0.5 mg NETA taken daily
Angeliq® (drospirenone [DRSP] plus E2)	0.5 mg E2 plus 0.25 mg DRSP or 1 mg E2 plus 0.5 mg DRSP taken daily
femhrt® (ethinyl estradiol [EE] plus NETA)	2.5 mg EE plus 0.5 mg NETA taken daily
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE taken daily for 14 days, then 0.625 mg CE plus 0.5 mg MPA taken daily for days 15-28
Prempro® (CE plus MPA)	0.3 mg or 0.45 mg CE plus 1.5 mg MPA taken daily or 0.625 mg CE plus 2.5 mg or 5.0 mg MPS taken daily
Transdermal Estrogen Plus Progestin Products	Available Dosage Strengths

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ClimaraPro® (E2 plus levonorgestrel)	0.045 mg E2 plus 0.015 mg levonorgestrel; patch applied weekly
CombiPatch® (E2 plus NETA)	Release of 0.05 mg E2 plus 0.14 mg NETA; patch applied twice weekly or 0.05 mg E2 plus 0.25 mg NETA; patch applied twice weekly

Table 2: Estrogen Plus Progestin Agonist/Antagonist Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Tablet or Capsule	Available Dosage Strengths
Duavee® (conjugated estrogens [CE]/bazedoxifene)	0.45 mg CE plus 20 mg bazedoxifene taken daily

Table 3: Progestogen Alone Products Used in Combination with Conjugated Estrogens Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Progestogen Tablet or Capsule	Available Dosage Strengths
Prometrium® (progesterone in peanut oil)	100 mg or 200 mg taken daily for 12 to 14 days of each 28-day cycle
Provera® (medroxyprogesterone acetate [MPA])	2.5 mg, 5 mg or 10 mg taken once daily for 12 days of each 28-day cycle
Various Generics	2.5 mg, 5 mg or 10 mg taken once daily for 12 days of each 28-day cycle

## 3. Regulatory Background

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### 3.1. U.S. Regulatory Actions and Marketing History

Estradiol, the estrogen moiety in combined estradiol and progesterone oral capsules, has been used in women and men for several decades for various indications with numerous routes of administration and dosage strengths. Estradiol is approved for use in postmenopausal women for the treatment of moderate to severe VMS due to menopause, the treatment of moderate to severe vulvar and vaginal atrophy (VVA) symptoms due to menopause, and the prevention of postmenopausal osteoporosis.

Progesterone, the progestogen moiety in combined estradiol and progesterone oral capsules, has been used in postmenopausal women for several decades for the approved indication for the prevention of endometrial hyperplasia in a woman with a uterus exposed to unopposed conjugated estrogens-alone therapy. The progestogen Prometrium® (progesterone, USP), is approved for the prevention of endometrial hyperplasia in a woman with a uterus exposed to

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unopposed conjugated estrogens-alone therapy, and is also indicated for secondary amenorrhea.

Synthetic progestogens, called progestins, are available in a wide variety of formulations and for use in different routes of administration for the treatment of moderate to severe VMS. See Table 1 above.

Currently, there is no fixed-dose combined estradiol plus progesterone product approved in the US or by the European Medicines Agency (EMA) for the treatment of moderate to severe VMS and/or VVA indications.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

TX-001HR is the code name for the combined estradiol plus progesterone oral capsule.

December 30, 2013: TherapeuticsMD request a meeting to discuss their clinical development plan for TX-001HR stating their clinical development plan will be stalled: "...continuing to enroll this pivotal Phase 3 study absent a clearer understanding of the approval requirements is problematic therefore, the purpose of this meeting is for clarification and for TherapeuticsMD to understand the view of the Division on the need to demonstrate the role of progesterone for the efficacy endpoint of vasomotor symptoms associated with menopause in our combined product for women with uterus and gain consensus on a phase 3 program."

February 3, 2014: Preliminary Meeting Comments letter sent to TherapeuticsMD which includes a response to the following question:

*Question 1*: Does the Division agree that data demonstrating the contribution of progesterone to the claimed effect "treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus" is not required for approval of the combination product TX-001HR? If not, please clarify the basis of your disagreement.

FDA Response:

We acknowledge that the progestogen component of your product is needed to protect the endometrium from the proliferative effects of the estrogen component, regardless of whether the progestogen component contributes to a reduction in vasomotor symptoms. You will satisfy the combination rule by showing that your progestogen dose(s) in combination with the to-be-marketed estrogen dose(s) results in an acceptable incidence of endometrial hyperplasia. You do not need to assess efficacy on vasomotor symptoms with a progestogen-alone arm to satisfy the combination drug rule as you will already have support for including progestogen in your product based on endometrial protection.

However, given the significant safety concerns with estrogen plus progestogen therapies, we

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have consistently recommended to all sponsors that these development programs should identify the lowest dose of each component in the combination product that is effective for the treatment of vasomotor symptoms and protection of the endometrium. It is in this context that we recommended that you evaluate whether your progestogen dose(s) contribute to efficacy given that there are available data that support an effect of progestogen on vasomotor symptoms. For example, this information may permit a lowering of the estrogen dose in your combination product while still achieving an effective dose of your combination product on vasomotor symptoms.

**February 4, 2014:** TherapeuticsMD cancels the scheduled February 4, 2014 Type A meeting.

**July 27, 2017:** TherapeuticsMD requests a Type B pre-NDA meeting; meeting scheduled for August 28, 2017.

**August 25, 2017:** Preliminary Meeting Comments letter sent to TherapeuticsMD which includes responses to the following questions:

Chemistry, Manufacturing and Controls (CMC):

*Question 1:* Does the Agency have any comments regarding the proposed drug product specifications?

**FDA Response:**

The tests proposed for inclusion in the drug product specification appear adequate. However, the final determination of the adequacy of the test methods and proposed acceptance criteria will be assessed based on the totality of the information submitted in the NDA.

The selection of the specification time point should be where  $Q = \frac{(b)}{(4)}\%$  dissolution occurs. The final determination on the acceptability of the dissolution method and acceptance criterion is a review issue and will be made during the NDA review based on complete dissolution data (individual, mean +/- SD, mean profile, n=12/batch) from the pivotal clinical trial batches and primary (registration) stability batches.

*Question 2:* Does the Agency agree with the above proposals to: 1) provide 12 months of data from the proposed commercial manufacturer's registration batches; 2) perform regression analysis on those Catalent registration batches to support the proposed commercial shelf life; 3) include summary information for  $(b)(4)$  clinical batches in the NDA, and 4) incorporate the individual  $(b)(4)$  clinical batch data in the NDA by reference to the IND?

**FDA Response:**

No, we do not completely agree. Your proposal to submit 12 months long-term stability data for three registration batches for each product strength manufactured by Catalent, is

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acceptable. Accelerated stability data through 6 months should also be provided for these batches.

Submission of regression analyses to support the proposed commercial shelf life is acceptable. Establishment of the shelf life is a review issue and will be assessed based on the totality of the data provided in the NDA.

Final stability data reports for all clinical batches manufactured at (b) (4) ( ) should be submitted in the NDA. The NDA also should include Certificates of Analyses for all clinical and registration batches manufactured at (b) (4) and Catalent. Include a tabulation identifying the drug product batches used in each clinical trial.

The stability study reports should include the following information:

- The date the test sample was pulled from the stability chamber
- The date on which the sample test was conducted
- The analytical test method used to generate the data (including revision number)

We have the following additional chemistry, manufacturing and controls (CMC) comments:

- Provide a chronological sequence of changes that have been made to all the analytical test methods for determination of assay, related substances, and dissolution.
  - Include all methods used for testing clinical and registration batches of drug product at release and on stability.
  - List the reasons for the change and indicate if the method was validated and/or verified to be suitable for intended purpose.
  - Demonstrate and provide justification to support that any changes in dissolution methods (dissolution methodology and associated analytical methodology) did not impact the quality of the data.
- Provide a list of failures (out-of-specification) that have been observed during release and stability testing of the drug product along with impact assessment and resolution.

*Question3:* Does the Agency agree with our plan for the environmental analysis (EA) claim of categorical exclusion and that no extraordinary circumstances exist?

FDA Response:

No. Agreement at this time is premature. Your application might be eligible for the exclusion under 21 CFR 25.31(a), if the action does not increase use of the active moiety (see definitions on p. 30 of <https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf>). Otherwise, FDA needs the following information before making a determination about the exclusion under §25.31(b): (1) the expected use amounts and associated expected introduction concentrations (EICs), with supporting calculations; (2) a summary of any applicant-internal data on potential for aquatic effects, including those relevant to FDA's 2016 guidance, Environmental

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Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity, taking into account the substance's EIC, mechanism of action, nonclinical and other toxicity data, plasma-based analysis, "read across" analysis, and any other factors related to environmental risk assessment.

*Question 4:* Given the rationale and data provided in Section 5.1.5, does the Agency agree with TherapeuticsMD's approach to selecting the surfactant concentration in the dissolution medium?

FDA Response:

No, we do not agree at this time. We note that you evaluated different concentrations of surfactant. Additionally, evaluate surfactants other than SLS and dissolution media with different pH. Include the data supporting the selection of the type and amount of surfactant in your dissolution method development report. The testing conditions used for each test should be clearly specified.

Your dissolution method should demonstrate discriminating ability. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm 10$ -20% change to the specification-ranges of these variables). The acceptability of the dissolution method and proposed acceptance criterion will be assessed during review of your submitted NDA.

Biopharmaceutics:

*Question 5:* Does the Agency have any further comments on the approach to bridge, as outlined above, for the formulation and manufacturing site changes during the development of TX-001HR?

FDA Response:

Your approach to bridge appears reasonable. Provide, in your NDA submission, details about the formulation and manufacturing process changes during development, and changes in dissolution method used to test these formulations. Our final decision on acceptability of your bridging of formulation revisions and manufacturing site changes will be based on the totality of the data provided in the NDA.

Nonclinical:

*Question 6:* Does the Agency agree that TherapeuticsMD may rely on published literature for estradiol and FDA's finding of safety for Prometrium as the RLD for progesterone, as the complete support for Sections 8 (Use in Specific Populations) and 13 (Nonclinical Toxicology) of the label and the Non-clinical sections of the proposed 505(b)(2) NDA?

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FDA Response:

Yes. Your approach appears acceptable. We also refer you to our response to Question 15 regarding submission of 505(b)(2) applications.

Your proposed labeling must comply with the Pregnancy and Lactation Labeling Rule (PLLR). Nonclinical information from the published literature for estradiol and the labeling for Prometrium will be necessary to inform Sections 8 and 13 of your label under the PLLR. We refer you to PRESCRIBING INFORMATION later in this document for additional details.

Clinical Pharmacology:

*Question 7:* Does the Agency have any comments regarding the proposed food effect protocol TXC17-02?

FDA Response:

We note that you submitted a full protocol for proposed Trial TXC17-02 on August 4, 2017, amended on August 14, 2017. The proposed food effect trial design appears reasonable. At this time, we have not identified any clinical safety concerns.

*Question 8:* Other than the food effect bioavailability study results, does that Agency agree that the results of Study TXC16-01 will fully inform the Clinical Pharmacology section of the proposed label?

FDA Response:

Yes, with qualifications. Your proposal to include the effective half-lives of estradiol and estrone in the labeling of your drug product is acceptable. However, we recommend that you determine the terminal half-lives of estradiol and estrone in your food effect trial (Trial TXC17-02). Whether the results of Trial TXC16-01 are adequate to support the Clinical Pharmacology section of your labeling will be a review issue.

*Question 9:* Does that Agency agree that assessment of estrone sulfate is not required for approval of TX-001HR?

FDA Response:

Yes, we agree.

*Question 10:* Does the Agency agree that the in vivo bioavailability requirement for the 0.5 mg/50 mg strength of TX-001HR may be waived?

FDA Response:

Yes. Considering the linear pharmacokinetics of progesterone and estradiol within the

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proposed dose range and proportional similarity of the different strengths, we agree that the bioavailability requirement for the 0.5 mg/50 mg strength of TX-001HR can be waived, provided that the 0.5 mg/50 mg strength meets in vitro test requirements. Clarify whether the formulation of 0.25 mg/50 mg strength is proportionally similar to that of other strengths.

*Question 11:* Does the Agency agree that the Clinical Pharmacology program described herein, which includes the completed studies and the planned food effect study, is complete, and that no further Clinical Pharmacology studies are needed?

FDA Response:

Yes, pending review of your NDA submission. We have not currently identified a need for further Clinical Pharmacology trials.

Clinical:

*Question 12:* Does the Agency agree that these six studies constitute a complete clinical program, and that no other clinical studies should be needed for filing or approval of the NDA?

FDA Response:

Yes. Completed phase 3, 52-week Trial TXC12-05 appears to be adequately designed and conducted to submit your proposed NDA for filing for the indication of treatment of moderate to severe vasomotor symptoms due to menopause. Approvability will be a review issue.

*Question 13:* Does the Agency agree that Sections 2.7.3 and 2.7.4 may serve as the narratives for the ISE and ISS as described in the FDA guidance, based on the information provided above?

FDA Response:

Yes. We agree that Sections 2.7.3 and 2.7.4 may serve as the narratives for the ISE and ISS.

*Question 14:* Does the Agency agree with the proposed clinical study data standardization plan?

FDA Response:

Yes. We agree with your proposed clinical trial data standardization plan.

Proposed 505(b)(2) NDA:

*Question 15:* Does the Agency agree with the proposed regulatory pathway outlined for the planned 505(b)(2) NDA for TX-001HR?

FDA Response:

Yes. Your proposal to submit a 505(b)(2) application that relies on published literature for estradiol and FDA's finding of safety and effectiveness for Prometrium Capsules as reflected in the information provided in Table 19 of your meeting package "Information Essential for

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Approval by Reliance on Published Literature or a Reference Listed Drug”, appears acceptable. You must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. You also must establish that reliance on studies described in the literature or on other studies is scientifically appropriate. Refer to the 505(b)(2) Regulatory Pathway section below for additional information about submitting a 505(b)(2) NDA.

*Question 16:* Does the Agency agree that the proposed contents of the planned NDA constitute a complete 505(b)(2) new drug application for review?

FDA Response:

The proposed content appears complete for the purpose of submission for filing of your proposed NDA. From a technical standpoint (not content) the proposed documents location for the planned NDA, is acceptable.

August 25, 2017: Pre-NDA meeting, scheduled for August 28, 2017 cancelled by TherapeuticsMD.

December 28, 2017: NDA 210132 submitted to the Agency.

January 31, 2018: Applicant submits a Request for Proprietary Name Review for Bijuva™. The Bijuva™ proprietary name received a conditional acceptance, dated July 24, 2017, under IND 114477. On September 22, 2017, TherapeuticsMD received notification that Bijuva™ was no longer considered acceptable since another product under review had a similar name. TherapeuticsMD believes that the other similar name has since been abandoned and submits the Request for Proprietary Name Review for Bijuva™ to NDA 210132.

March 8, 2018: Filing Communication: No Filing Review Issue Identified letter to applicant stating “We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review.” The user fee goal date is October 28, 2018.

We request that you submit the following information:

1. Trials 351, 352 and 459: Include trial period and trial sequence for each subject in your pharmacokinetic concentration dataset and include trial period, trial sequence, and treatment product (reference or test) for each subject in your pharmacokinetic parameter dataset.
2. Trial TXC16-01: Provide the subject ID for the three subjects who discontinued early. Include CL/F and Vd in your pharmacokinetic parameter dataset.

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3. Trial TXC12-05: Include the drug dose and blood sample collection time (hours post dosing) for each subject in your pharmacokinetic concentration dataset.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Boxed Warning: Change the word “and” to lower case to separate the warnings.
2. Change PATIENT COUNSELING INFORMATION Section of the FPI to “Advise the patient to read the FDA-approved patient labeling (Patient Information)”.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 2, 2018.

March 22, 2018: TherapeuticsMD responds to the Chemistry, Manufacturing, and Controls (CMC) Information Request (IR) from the Office of Pharmaceutical Quality (OPQ), dated March 1, 2018, and provides the following information:

CMC Question 1: Provide a comparison table of in-process controls for each unit operation (i.e., (b) (4)) between phase 3 clinical batches (at (b) (4)), registration batches (at Catalent, exclude (b) (4)), and the proposed commercial batches (at Catalent, exclude (b) (4)) in Section 3.2.P.3.4. Include corresponding in-process test results for phase 3 clinical batches (at (b) (4)) and registration batches (at Catalent) to support your proposed in-process controls for commercial batches (at Catalent).

TherapeuticsMD Response to Question 1:

“A comparison table of in-process controls for each unit operation for 1) phase 3 clinical batches manufactured at (b) (4), 2) registration batches manufactured at Catalent Pharma Solutions LLC, St. Petersburg FL (Catalent), excluding (b) (4) the proposed commercial batches (Catalent) is provided in Section 3.2.P.2.3.5, Table 17. The corresponding in-process test results (ranges) for phase 3 clinical batches (b) (4) and registration batches (Catalent) to support the proposed in-process controls for commercial batches (Catalent) are also provided in Section 3.2.P.2.3.5, Table 17.”

Question 2: Provide a copy of representative executed batch records for phase 3 clinical batches, PN0082-33 (0.5 mg/100 mg strength) and PN0082-34 (1 mg/100 mg strength) at (b) (4) in Section 3.2.R. Provide a summary table of batch yield and reconciliation for major unit operations (i.e., (b) (4)) for phase 3 clinical batches and registration batches at Catalent in Section 3.2.P.2.

TherapeuticsMD Response to Question 2:

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Copies of representative executed batch records for phase 3 clinical batches manufactured by (b) (4) PN0082-33 and PN0082-34, are provided in updated Section 3.2.R. A summary table of batch yield and reconciliation for major unit operations for phase 3 clinical batches at (b) (4) and registration batches at Catalent is provided in Section 3.2.P.2.3.6, Table 18 and Table 19, respectively.

Question 3a: The method lacks sufficient evidence in terms for its discriminating ability toward the critical material attributes (CMAs) and process parameters (CPPs). Therefore, submit the following information/data:



**TherapeuticsMD Response to Question 3a, i:**



**TherapeuticsMD Response to Question 3a, ii:**



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TherapeuticsMD Response to Question 3a, iii:



Question 4: Submit the individual and mean in vitro dissolution profiles (in graphical and tabular form) for all batches tested in phase 1 studies TXC17-02, TXC16-01, (b) (4) PN0082-01 and the mean dissolution profiles for all batches tested in pivotal phase 3 study.

TherapeuticsMD Response to Question 4:

The requested dissolution profiles are provided in Appendix 2.2.

Question 5: Provide a side-by-side table listing all the changes implemented to the formulation tested in phase 3 pivotal batches in comparison to the to-be-marketed drug product.

TherapeuticsMD Response to Question 5:

"The formulations of the Phase 3 pivotal batches (b) (4) and the to-be-marketed product (Catalent) are identical, with the exception of (b) (4)

(b) (4) Table 5 compares the (b) (4) for the Phase 3 formulation (b) (4) to those for the to-be-marketed commercial formulation (Catalent)." The following table is presented in the response to FDA Question 4.

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Function <sup>a</sup>	Phase 3 Pivotal Batches (b) (4)	Proposed Commercial (Catalent)
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N/A = not applicable

March 29, 2018: TherapeuticsMD resubmits labeling in Microsoft Word format with requested labeling changes. The included Clinical Information Amendment addresses Clinical Pharmacology Questions 1, 2, and 3 above as follows:

- Clinical Pharmacology question 1: Trials 351, 352, and 459:
  - The pharmacokinetic (PK) concentration (PC) datasets for Trials 351, 352, and 459 were updated to include trial period and trial sequence for each trial participant.
  - The PK parameter (PP) datasets for Trials 351, 352, and 459 were updated to include trial period, trial sequence, and treatment product (reference or text) for each trial participant.
  - The updated PC and PP datasets are provided in Module 5.
- Clinical Pharmacology Question 2: Trial TXC16-01:
  - Trial participant IDs and reasons for discontinuation for the three participants randomized to receive estradiol 0.5 mg/progesterone 100 mg are noted below (Appendix 16.2, Listing 16.2.1):
    - (b) (6) subject withdrew
    - (b) (6) subject withdrew
    - (b) (6) lost to follow-up
  - The PP dataset was updated to include CL/F and Vd (represented by the controlled terminology “Vz for Dose Int by F”) for estradiol and progesterone, unadjusted and adjusted for baseline, using the below formulas:

Apparent serum clearance after oral administration:

$$\frac{CL}{D_{po}} = \frac{D_{po}}{AUC}$$

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Apparent volume of distribution during terminal phase after oral administration:

$$\frac{V_2}{F} = \frac{D_{po}}{AUC \cdot \lambda_z}$$

The updated ADPP dataset and analysis define.xml are provided in Module 5.

- Clinical Pharmacology Question 3: Trial TXC12-05:
  - The PC dataset was updated to include the dose each subject received, the date and time of the last dose that was taken prior to the blood sample collection, the blood sample collection date and time, and the hours post-dose the sample was collected.
  - The specimen material type (PCSPEC) field in the PC dataset was corrected to indicate that these were serum specimens and not plasma.
  - The updated PC dataset is provided in Module 5.

April 30, 2018: TherapeuticsMD received a Proprietary Name Request, Conditionally Acceptable letter from the Agency indicating, “We have completed our review of the proposed proprietary name, Bijuva, and have concluded that it is conditionally acceptable. If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.”

May 24, 2018: TherapeuticsMD provides the response to the Division of Bone, Reproductive, and Urologic Products (DBRUP) Information Request to provide statistical data, sent via email communication on May 21, 2018:

1. For Trial TXC12-05, provide cumulative distribution function curves for the mean changes from baseline in the frequency and severity of moderate to severe hot flushes at Week 4 and Week 12, respectively
  - by clinical global impression categories (for corresponding Week);
  - by treatment groups.

TherapeuticsMD Response:

Cumulative distribution function curves are provided in Figure 1.1 and Figure 1.2 for the mean change from baseline in the frequency of moderate to severe hot flushes by Clinical Global Impression category at Week 4 and Week 12, respectively, and for severity in Figure 2.1 and Figure 2.2, respectively.

Cumulative distribution function curves for the mean changes from baseline in the frequency of moderate to severe hot flushes by treatment groups for Week 4 and Week

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12 are shown in Figure 3.1 and Figure 3.2, respectively, and for severity in Figure 4.1 and 4.2, respectively

**May 25, 2018:** 120-Day Safety Update received stating, “No studies are ongoing, and no new safety information has become known to TherapeuticsMD since the application was submitted.”

**May 31, 2018:** TherapeuticsMD submits revised draft carton and container labeling in response to May 22, 2018 Agency request.

**June 26, 2018:** TherapeuticsMD submits a Quality Information Amendment in response to a CMC information request dated June 4, 2018. TherapeuticsMD commits to provide additional information “at a later date” to:

- Questions 4d: [REDACTED] (b) (4)
- Question 8: “ [REDACTED] (b) (4)
- Question 12: “Update relevant documents (work flow diagram, description of the process, and MRBs) in Section 3.2.P.3.3 and in-process specification tables in Section 3.2.P.3.4 to reflect the above changes. In addition, provide relevant information regarding all in process test method procedures and method validation or verification, if applicable, in Section 3.2.P.3.4”:
  - TherapeuticsMD will submit the updated MRBs after receiving them from Catalent (expected mid July 2018).
- Question 13a: “ [REDACTED] (b) (4)
  - TherapeuticsMD has requested [REDACTED] (b) (4) and will evaluate the alternative dissolution method/conditions on the drug product formulated with these materials to determine the discriminative capability of the method.
- Question 15a: “Data supporting the manufacturing site change”:

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See a discussion of Product Quality beginning on page 34 of this review.

July 11, 2018: TherapeuticsMD provides the narratives for participants Number (b) (6) and Number (b) (6), requested on July 6, 2018.

July 12, 2018: TherapeuticsMD provides the statistical information and datasets for Trial TXC12-05 subgroup analyses, requested on June 28, 2018. See a discussion of subgroup analyses beginning on page 94 of this review.

July 18, 2018: TherapeuticsMD provides the CMC information, to update master batch records for commercial Catalent, requested on June 4, 2018.

July 30, 2018: Therapeutics MD provides a follow-up to the teleconference with CMC held on July 19, 2018. Per TherapeuticsMD, during the July 19, 2018 teleconference, the Agency indicated that:

- An appropriately discriminative and validated dissolution method (b) (4) must be provided prior to approval.
- The final dissolution procedure must be used to establish a bridge.
- If more time is needed to develop and validate the method, a time extension can be discussed.

TherapeuticsMD agreed to:

- Submit a method development report for the proposed improved dissolution method August 28, 2018 and September 14, 2018, while completing the validation of the method.
- Provide the method validation report on or before September 28, 2018.
- Provide a comparative dissolution report on or before September 28, 2108 for 1 mg estradiol/100 mg progesterone lots manufactured at (b) (4) (phase 3 clinical batch) and Catalent (PK study batches and proposed commercial manufacturer) using the validated method (bridge between sites).
- Revise specifications, if applicable on or before September 28, 2018.
- Submit all experiments performed and information to show that all possibilities have

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been exhausted should the revised method prove to be no more discriminative than current method.

- TherapeuticsMD hopes that “FDA review can occur within the current review cycle without an extension.”

August 6, 2018: TherapeuticsMD responds to Clinical Pharmacology information request, dated July 30, 2018, regarding the large variability in the C<sub>max</sub> and AUC<sub>0-t</sub> of progesterone administered under fed conditions among Trial EPROG-1K-459-12, Trial TXC16-01, and Trial TXC17-02. See the response in Subsection 4.5 Clinical Pharmacology of this review.

August 10, 2018: TherapeuticsMD provides the CMC information, requested on August 7, 2018, for batch analysis data and stability data for the drug product batch (No. PN0082-01 2 mg estradiol/200 mg progesterone product) used in the PK trials.

### 3.3. Foreign Regulatory Actions and Marketing History

Bijuva™, a combination product containing estradiol plus progesterone, is not marketed in the US. However, both estradiol and progesterone are individually approved products.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

Per the application, Trial TXC12-05 was designed, conducted, and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

To ensure compliance with these procedures, and to assess the adequacy of quality control procedures, TherapeuticsMD undertook a good GCP audit program, which focused on trial documentation, investigator sites, and clinical trial reports. These audits were performed by external auditors under the supervision of TherapeuticsMD Quality Assurance and independently of the site monitors. Audit certificates are provided in Appendix 16.1.8 for the following site audits:



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(b) (4)

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No corrective action appears to have resulted from these internal audits. Per the applicant, this audit program helps to provide reassurance that trial conclusions were based on valid procedures for data management and analysis, and that the TherapeuticsMD's clinical trial program was carried out in accordance with GCP guidelines.

See Subsection 13.2 Financial Disclosure, in this review, for information on one (1) subinvestigator with significant equity interest that met the criteria for disclosure at Site # (b) (6) of phase 3 Trial TXC12-05.

The Agency's Office of Scientific Investigation (OSI), Division of Clinical Compliance Evaluation (DCCE) conducted three inspections at the following Trial TXC12-05 clinical sites:

1. Site ID # 127, Scott Redrick, MD, Nature Coast Clinical Research, 6122 W Corporate Oaks Drive, Crystal River, FL 34429 and Suncoast Obstetrics & Gynecology P.A., 582 SE 7<sup>th</sup> Avenue, Crystal River, FL 34429.
2. Site ID # 105, Arthur S. Waldbaum, MD, Downtown Women's Health Care, 1201 E. 17th Avenue, Suite 200, Denver, CO 80209 and Downtown Women's Health Care, 3773 Cherry Creek Drive North, Suite 685, Denver, CO 80209.
3. Site ID # 142, Sandra M. Hurtado, MD, The Woman's Hospital of Texas Clinical Research Center, 7550 Fannin, Suite 146, Houston, TX 77054 and The Woman's Hospital of Texas Clinical Research Center, 7400 Fannin, Suite 1280, Houston, TX 77054.

One alternate site was selected, if needed: Site ID #163, Peter Charles Johnson, MD, Soapstone Center for Clinical Research, 4201 Rainbow Drive, Decatur, GA 30034. OSI did not conduct an inspection at the alternate site.

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On August 23, 2018, OSI/DCCE provided an evaluation of the clinical inspection for Site # 105 (Arthur S. Waldbaum, MD), Site # 127 (Scott Redrick, MD), and Site # 142 (Sandra M. Hurtado, MD). All three sites received a No Action Indicated (NAI) classification.

Site # 105 (Arthur S. Waldbaum, MD): This clinical inspection was conducted between March 26-30, 2018. An audit of the trial records for all randomized women was conducted. No deficiencies or significant errors were noted. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable. Two major protocol deviations were noted during the inspection. Trial participant Number (b) (6) was enrolled with a diagnosis of hyperthyroidism; trial participant Number (b) (6) was enrolled with a history of liver disease. These two protocol deviations are unlikely to have an impact on the efficacy or safety results of Trial TXC12-05.

Site # 127 (Scott Redrick, MD): This clinical inspection was conducted between March 20-23, 2018. An in-depth audit of the trial records for 24 of the 47 randomized women was conducted. No under-reporting of adverse events and no protocol deviations other than those listed in the line listings were observed. The source documentation from the site matched with the line listings provided by the applicant.

Site # 142 (Sandra M. Hurtado, MD): This clinical inspection was conducted between April 24-26, 2018. An audit of the trial records for 74 of 131 subjects that were screened was conducted, including all records for 37 of the 45 women who completed the Trial TXC12-05. The inspection found one (1) case where source data listings did not match those provided to the FDA (participant Number (b) (6), discrepancy in number of severe hot flashes), and one (1) case where the source data could not be verified (participant Number (b) (6), inconsistent use of both tally marks and numbers of hot flashes). The inspection report recommends that data for participant Number (b) (6) not be used in the efficacy analysis because the source data could not be verified against the data listings provided by the applicant. Other than these discrepancies, the source documentation from the site matched with the line listings provided by the sponsor to the FDA. No under-reporting of adverse events and no protocol deviations other than those listed in the line listings were observed.

## 4.2. Product Quality

Estradiol and progesterone softgel gelatin capsules (TX-001HR; oval, light pink on one side and dark pink on the other side) is a fixed-dose combination drug product containing solubilized estradiol, USP, (b) (4) and progesterone, USP, micronized (b) (4)

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Estradiol (b) (4) is a white, crystalline powder, chemically described as Estra-1, 3, 5(10)-triene-3, 17β-diol, h (b) (4). Estradiol (b) (4) has the molecular formula C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>, (b) (4), and is practically insoluble in water, soluble in acetone and ethanol, and slightly soluble in ether and methylene chloride. (b) (4)

Progesterone (CAS 57-83-0) is provided as a white, micronized powder, chemically described as pregn-4-ene-3, 20-dione, with a molecular weight of 314.47. Progesterone has the molecular formula C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>, and is practically insoluble in water, sparingly soluble in acetone and fatty oils, and soluble in ethyl alcohol and dioxane.

Two manufacturing sites have produced batches for the estradiol/progesterone capsule development program: (b) (4), who manufactured the phase 3 clinical batches) and Catalent Pharma Solutions, LLC (Catalent STP, St Petersburg, FL who manufactured batches for the primary pharmacokinetic trials and who will manufacture the commercial product). Slight differences in excipients used in the (b) (4) processes at the two manufacturing sites are noted in Table 4.

Table 4: Excipients

Component	Quality Standard	Source	Function
(b) (4)			
Medium chain mono/di-glycerides (b) (4)	NF		(b) (4)
Lauroyl polyoxyl-32 glycerides (b) (4)	NF		(b) (4)
(b) (4)	(b) (4)		(b) (4)
(b) (4)			(b) (4)
Gelatin, (b) (4)	NF		(b) (4)
Hydrolyzed gelatin	NF <sup>c</sup>		(b) (4)
Glycerin	USP		(b) (4)
(b) (4) Red (b) (4)	In-house		(b) (4)
(b) (4)	(b) (4)		(b) (4)

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Purified water	USP	(b) (4)
(b) (4)		
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
Isopropyl alcohol (b) (4)	USP	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
Medium chain triglycerides (b) (4)	NF	
(b) (4)	(b) (4)	
Propylene glycol <sup>b</sup>	USP	

Source: Adapted from NDA 210132, Submodule 3.2.P.2.1, Components of the Drug Product, Table 1, page 4 of 7.

a Used at Catalent Pharma Solutions LLC, St Petersburg, FL.

b Used at (b) (4)

c Tested to NF

The placebo capsules contained the excipients of TX-001HR without (b) (4) estradiol (b) (4) or progesterone, plus Corn Starch NF as filler that is not present in the active products. Two different sizes of capsules were necessary to accommodate the different doses. The two sizes of placebo capsules contained the excipients in TX-001HR without the (b) (4) estradiol and micronized progesterone.

Per the applicant, the in-process controls and process parameters were nearly identical between the phase 3 (b) (4) and registration batches (Catalent). “A few minor differences in in-process controls have been identified which are not critical parameters. These differences include the following: 1) the test method used to control (b) (4), and 2) the test method used to measure (b) (4) used (b) (4) while Catalent uses (b) (4). Regarding the (b) (4), (b) (4) (phase 3) used (b) (4) as the unit of measurement and a (b) (4), while Catalent uses a (b) (4) with (b) (4) as the unit of measure. Both in-process controls successfully produced capsules that met the appearance acceptance criteria for the

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drug product. The proposed commercial product will be tested according to the Catalent process.”

Clinical Reviewer’s Comments:

The final product formulation was used in phase 3 Trial TXC12-05, and the same formulation is intended as the commercial formulation. Per Chemistry, Manufacturing and Controls (CMC), principles delineated under SUPAC-IR require dissolution profile comparisons to support the commercial manufacturing change to Catalent. However, the original dissolution method report, in the application, was found not adequate as a Quality Control (QC) method especially for the progesterone component.

On March 21, 2018 (received on March 22, 2018), TherapeuticsMD responds to the Agency’s March 1, 2018 Information Request letter regarding the inadequate dissolution method report. See Subsection 3.2 Summary of Presubmission/Submission Regulatory Activity in this review, entry dated March 22, 2018, for the CMC questions and TherapeuticsMD’s responses.

Per CMC, TherapeuticsMD attempted to develop (b) (4). See Subsection 3.2 Summary of Presubmission/Submission Regulatory Activity in this review, entries dated June 26, 2018 and July 30, 2018, for comments/discussions/communications between CMC and TherapeuticsMD regarding dissolution method.

Clinical Reviewer’s Comments:

In an internal email communication, dated August 23, 2018, CMC conveyed the following information to DBRUP:

- The issues regarding 505(b)(2) bridging and the product manufacturing site change ( (b) (4) to Catalent) have been adequately resolved from the CMC/biopharmaceutics perspectives. No further CMC/biopharmaceutics information is needed to support approval of the NDA.
- The Applicant must continue the development of a discriminating dissolution test method for quality control purposes as outlined in the July 30, 2018 amendment. However, it is now clear that dissolution testing with an optimized method could not answer the 505(b)(2) bridging question.
- The site change is supported by other evidence.

On August 24, 2018, CMC informed TherapeuticsMD the following via an email communication:

“Reference is made to your submission, dated 07/30/18, where you outlined the timeline for submitting the data supporting the adequacy/validation of the proposed dissolution method (b) (4). Reference is also made to your submission, dated 6/25/18, where you proposed submitting additional data supporting the adequacy

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and validation of the dissolution methods as a postmarketing commitment (PMC). We have further discussed your proposal internally, and have made the decision to accept your proposal of submitting all data generated as part of method development and validation as a PMC, provided your product receives approval recommendation. Thus, the following method and dissolution acceptance criterion (b) (4) of your drug product will be accepted on an interim basis:

Dissolution Method:

Parameter	Condition
Apparatus	USP 3 – Reciprocating Cylinders
Medium	3% (w/v) SLS in 0.1N HCL
Medium Volume	250 mL
Sample Volume	5-10 mL <sup>a</sup>
Screen Mesh size	40 mesh
Dip rate	30 dpm
Medium Temperature	37 ± 0.5° C
Sampling Time Point	(b) (4) minutes
Specification Time Point	(b) (4) minutes
Filters	Nylon, 0.45µm

<sup>a</sup> Sample volume is 5 mL if collecting for a single active and 10 mL if collecting for both active ingredients.

Recommended Acceptance criterion for both components of the drug product:

*NLT (b) (4) % (Q) dissolves within 15 min.*

Please update the drug product specification table reflecting this recommendation and submit the revised drug product specification table by COB August 28, 2018. Note that a postmarketing commitment proposal will be submitted to you for your review and mutual approval. The PMC will request you to develop and validate a discriminating dissolution test method suitable for the quality control of the drug product, and establish appropriate acceptance criteria.”

Clinical Reviewer’s Comments:

Per the Chemistry, Manufacturing and Controls (CMC) review, dated October 24, 2018 “TherapeuticsMD, Inc.’s 505(b)(2) new drug application for BIJUVA (estradiol and progesterone capsule), is recommended for APPROVAL from the OPQ perspective. Sufficient information and supporting data have been provided in accordance with 21 CFR 314.5 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The revised drug product labeling as submitted on October 24, 2018 is accurate, complete and complies with the requirements under 21 CFR 201. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The claimed categorical exclusion from the requirements to submit environmental assessment based on ‘no increase in use’ is granted.”

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A CMC postmarketing commitment (PMC), to conduct in vitro studies to establish the appropriate dissolution method(s) and acceptance criteria, was signed October 15, 2018. The applicant has agreed to submit the final report by April 12, 2019.

See the CMC Review, dated October 24, 2018.

### 4.3. Clinical Microbiology

The only ingredients in the combined estradiol and progesterone oral capsule considered to have a potential risk for microbial growth are the gelatin and hydrolyzed gelatin. Per the application, (b) (4)

[Redacted text block]

The manufacturing process (b) (4)

[Redacted text block]

The estradiol and progesterone drug product does not contain antimicrobial preservatives. Per the applicant, the estradiol and progesterone drug product has been evaluated per Decision Tree 8 of ICH Guidance Q6A, "Microbial Attributes of Non-Sterile Drug Product." Based on the evaluation of the ingredients and manufacturing process, the applicant has established microbial acceptance criteria based on the USP <1111> for non-sterile dosage forms for oral administration. The microbial tests and acceptance criteria for all strengths of the drug product are provided in the following table.

Table 5: Microbial Tests and Acceptance Criteria for Combined Estradiol and Progesterone Capsules

Microbial Attribute	Test Method	Acceptance Criteria
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Total Aerobic Plate Count	USP<61>		(b) (4)
Total Yeast/Mold	USP<62>		
<i>Escherichia coli</i>			
<i>Salmonella</i>			
<i>Staphylococcus aureus</i>			

Source: Adapted from NDA 210132, Module 3.2.P Drug Product [Product-Dosage Form-Manufacturer], 3.2.P.2 Pharmaceutical Development, 3.2.P.2.5 Microbiological Attributes, Table 1, page 2 of 2.

Clinical Reviewer's Comments:

Per the Clinical Microbiology Review, dated May 25, 2018, "The microbiological quality of drug product is controlled via a suitable testing protocol." "The Microbial Limits specification for "Bijuva" is acceptable from a Product Quality Microbiology perspective." The Clinical Microbiology Reviewer recommends approval from the standpoint of product quality microbiology. See the Clinical Microbiology Review, dated May 25, 2018.

#### 4.4. Nonclinical Pharmacology/Toxicology

In NDA 210132 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, TherapeuticsMD is relying on the well-established safety history of estradiol and progesterone. As discussed with the Agency in the pre-NDA meeting dated August 25, 2017, select literature publications on estradiol and the FDA's previous finding of preclinical safety for Prometrium® (progesterone, USP) are presented to support the nonclinical section of the NDA. Therefore, no nonclinical pharmacology studies were conducted by TherapeuticsMD for their estradiol plus progesterone combination drug product.

Per the application, the acute toxicity of estradiol has been evaluated in rodents and dogs via oral and parenteral administrations. Repeat-dose oral safety studies have been conducted for up to 2 years in rats and dogs. A full battery of reproductive and developmental toxicity studies, including evaluation of fertility, embryo-fetal development, and pre-/postnatal development have been previously conducted. The genotoxicity and carcinogenicity of estradiol are also well-established in the literature.

Published literature for information necessary to inform Section 8 (Use in Special Populations) and Section 13 (Nonclinical Toxicology) of the labeling is provided in the application. In addition, TherapeuticsMD is relying on the FDA's previous finding of nonclinical safety for Prometrium® (NDA 19781) as the basis of support for the nonclinical safety for progesterone of this NDA.

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### Clinical Reviewer's Comments:

This reviewer agrees with the applicant that the safety history of estradiol and progesterone are well-established. The Pharmacology/Toxicology Reviewer recommends approval of TX-001HR for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause in women with a uterus. See the Pharmacology/Toxicology Review, dated September 10, 2018.

## 4.5. Clinical Pharmacology

The primary female sex hormone estradiol is the most potent human estrogen. Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system in addition to secondary sexual characteristics. These hormones exist in a dynamic metabolic equilibrium, with estradiol possessing the greatest affinity at the receptor. The biological effects of estrogens, including estradiol, are based on interaction with ER $\alpha$  and ER $\beta$ , which are ligand-activated transcription factors which alter the synthesis of mRNA from target genes. Approximately 95% to 98% of estradiol is bound loosely to albumin or tightly to sex hormone binding globulin (SHBG).<sup>3</sup>

Estradiol is extensively bound to plasma proteins in blood, including sex hormone-binding globulin (SHBG) and serum albumin. Due to its size and lipophilic nature, estradiol readily distributes past the vascular space and into tissues. In general, estradiol undergoes rapid biotransformation with a half-life of minutes. Estradiol is metabolized by 17 $\beta$ -hydroxysteroid dehydrogenase to estrone, which is in turn converted by 16 $\alpha$ -hydroxylation and 17-keto reduction to estriol, the major urinary metabolite along with a variety of sulfate and glucuronide conjugates. Estrogens also undergo enterohepatic recirculation by the formation of sulfate and glucuronide conjugates in the liver followed by biliary secretion into the intestine, hydrolysis and then reabsorption by the gut.<sup>4</sup>

In postmenopausal women, most endogenous estrogen is produced via conversion of dehydroepiandrosterone secreted by the adrenals to estrone in adipose tissue stroma; therefore, estrone and its sulfate conjugated form are the most abundant circulating estrogens rather than estradiol.

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of

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<sup>3</sup> Kuhl H. Pharmacology of estrogens and progestins: influence of different routes of administration. *Climacteric*. 2005;8 Suppl. 1(March):3-63.

<sup>4</sup> Goodman L, et al. Estrogens and Progestins. In: Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. 10<sup>th</sup> ed. New York: McGraw-Hill; 2001. P. 1597-1634.

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decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. Progesterone administration decreases the circulatory levels of gonadotropins.<sup>5</sup>

Many effects of progesterone are mediated by the progesterone receptor (PR), a member of the nuclear receptor superfamily.<sup>5</sup> Two isoforms, progesterone receptor A (PRA) and progesterone receptor B (PRB,) have been cloned. It has been proposed that PRB is the major mediator of gene transcription activation, whereas PRA provides an inhibitory effect on transcription at PRB as well as the estrogen and glucocorticoid receptor.<sup>6</sup> Progesterone receptor is known to be expressed in uterus, mammary gland, ovary, fallopian tube, and placenta.

Progesterone is approximately 96% to 99% bound to serum proteins, primarily to serum albumin (50% to 54%) and transcortin (43% to 48%). Progesterone is metabolized primarily by the liver, largely to pregnanediols and pregnanones. Pregnanediols and pregnanones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization. Progesterone metabolites are eliminated mainly by the kidneys. Progesterone metabolites, which are excreted in the bile, may undergo enterohepatic recycling or may be excreted in the feces.<sup>5</sup>

### Single-Dose Phase 1 Trials:

Trial EPROG-1K-351-12 compared the bioavailability of oral 2 mg estradiol/200 mg progesterone capsules (Test) to oral 2 mg Estrace® (estradiol USP tablets; hereafter referred to as Estrace) and 200 mg Prometrium® (progesterone, USP; hereafter referred to as Prometrium) (Reference) under fasting conditions in 24 healthy, postmenopausal women. This two-way, cross-over oral bioequivalence trial administered both Test and Reference products to participants (one product per dosing period) with a 14-day washout period between dosing periods. Participants were housed in the clinical facility at least 11 hours before dosing until after the 48-hour postdose blood draw in each period. A single dose of either Test or reference products were administered by a site personnel after participants fasted for at least 10 hours, with the woman in a seated position, with 240 mLs of water. The participant remained seated for an additional 4 hours, given meals at scheduled times, and allowed to move about (no strenuous activity) until they checked out of the facility. A total of 23 blood samples were

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<sup>5</sup> Schumacher M, et al. Genomic and membrane actions of progesterone: implications for reproductive physiology and behavior. *Behav Brain Res.* 1999;105(1):37-52.

<sup>6</sup> Gruber CJ, Huber JC. Differential effects of progestins on the brain. *Maturitas.* 2003 Dec;46(SUPPL. 1):71-75.

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collected (see the NDA for specific collection time points) and used to determine concentrations of progesterone, estradiol, unconjugated estrone, total estrone.

Results of test product (2 mg estradiol/200 mg progesterone) versus reference product (Estrace 2 mg and Prometrium 200 mg) for unconjugated estradiol (baseline-adjusted and baseline-unadjusted), and progesterone (baseline-adjusted and baseline-unadjusted) are presented in Table 6 and Table 7, respectively.

Table 6: Results of Test Product Versus Reference Product for Unconjugated Estradiol (Baseline-Adjusted and Baseline-Unadjusted) in Trial EPOG-1K-351-12

PK Parameter	Geometric Mean <sup>a</sup> Test	Geometric Mean <sup>a</sup> Reference	GM ratio (%)	90% Confidence Interval (%)	Intrasubject CV (%)	Bioequivalent
<b>Unconjugated Estradiol (Baseline-Adjusted)</b>						
C <sub>max</sub> (pg/mL)	95.37	60.22	158.4	116.4 – 215.5	66.67	No
AUC <sub>0-t</sub> (pg.h/mL)	1065	1031	103.3	90.97 - 117.4	25.48	Yes
AUC <sub>0-∞</sub> (pg.h/mL)	1406	1339	105.0	93.16 - 117.4	22.75	Yes
<b>Unconjugated Estradiol (Baseline-Unadjusted)</b>						
C <sub>max</sub> (pg/mL)	98.83	63.27	156.2	115.2 – 211.8	65.84	No
AUC <sub>0-t</sub> (pg.h/mL)	1165	1132	102.9	91.02 – 116.2	24.43	Yes
AUC <sub>0-∞</sub> (pg.h/mL)	1615	1547	104.4	93.58 – 116.4	20.70	Yes

Source: Adapted from NDA 210132, Submodule 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 2, page 14 of 58, and Table 3, page 15 of 58.

<sup>a</sup> Estimate of least square mean used to calculate Geometric Mean (GM).

Abbreviations: Test = test product TX-001HR (estradiol and progesterone) capsules, Reference = reference product ESTRACE (estradiol tablets USP) 2 mg, C<sub>max</sub> = maximum concentration; AUC<sub>0-t</sub> = area under the concentration-time curve to last measurable time point; AUC<sub>0-∞</sub> = area under the concentration-time curve extrapolated to infinity, CV = coefficient of variation.

Table 7: Results of Test Product Versus Reference Product for Progesterone (Baseline-Adjusted and Baseline-Unadjusted) in Trial EPROG-1K-351-12

PK Parameter	Geometric Mean <sup>a</sup> Test	Geometric Mean <sup>a</sup> Reference	GM ratio (%)	90% Confidence Interval (%)	Intrasubject CV (%)	Bioequivalent
<b>Progesterone (Baseline-Adjusted)</b>						
C <sub>max</sub> (ng/mL)	2.28	2.96	76.96	64.56 – 91.75	35.66	No
AUC <sub>0-t</sub> (ng.h/mL)	8.36	10.89	76.78	66.56 – 88.57	28.68	No
AUC <sub>0-∞</sub> (ng.h/mL)	12.77	17.72	72.07	58.41 – 88.92	36.86	No
<b>Progesterone (Baseline-Unadjusted)</b>						
C <sub>max</sub> (ng/mL)	2.28	2.96	76.96	64.56 – 91.75	35.66	No
AUC <sub>0-t</sub> (ng.h/mL)	8.36	10.89	76.78	66.56 – 88.57	28.68	No
AUC <sub>0-∞</sub> (ng.h/mL)	12.77	17.72	72.07	58.41 – 88.92	36.86	No

Source: Adapted from NDA 210132, Submodule 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 4, page 16 of 58, and Table 5, page 16 of 58.

<sup>a</sup> Estimate of least square mean used to calculate Geometric Mean (GM).

Abbreviations: Test = test product TX-001HR (estradiol and progesterone) capsules, Reference = reference product PROMETRIUM (progesterone USP) 200 mg, C<sub>max</sub> = maximum concentration; AUC<sub>0-t</sub> = area under the concentration-time curve to last measurable time point; AUC<sub>0-∞</sub> = area under the concentration-time curve extrapolated to infinity, CV = coefficient of variation.

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Conclusions and Clinical Reviewer's Comments:

In Trial EPROG-1K-351-12, under fasting conditions, 2 mg estradiol/200 mg progesterone AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> for baseline-adjusted and baseline-unadjusted estradiol showed bioequivalence to Estrace 2 mg, but C<sub>max</sub> did not show bioequivalence. The progesterone exposure was lower than Prometrium 200 mg for all primary PK parameters, and did not show bioequivalence in this trial. Small trial population (n=24) and intrasubject coefficient of variation may be contributing factors.

Trial EPROG-1K-352-12 compared the bioavailability of oral 2 mg estradiol/200 mg progesterone capsules to oral 2 mg Estrace and 200 mg Prometrium under high-fat, high-calorie fed conditions in 24 healthy, postmenopausal women utilizing the same trial design as Trial EPROG-1K-351-12.

Results of test product (2 mg estradiol/200 mg progesterone) versus reference product (Estrace and Prometrium) for unconjugated estradiol (baseline-adjusted and baseline-unadjusted), and progesterone (baseline-adjusted and baseline-unadjusted) are presented in the following Table 8 and Table 9, respectively.

Table 8: Results of Test Product Versus Reference Product for Unconjugated Estradiol (Baseline-Adjusted and Baseline-Unadjusted) Under High-Fat Fed Conditions in Trial EPOG-1K-352-12

PK Parameter	Geometric Mean <sup>a</sup> Test	Geometric Mean <sup>a</sup> Reference	GM ratio (%)	90% Confidence Interval (%)	Intrasubject CV (%)	Bioequivalent
Unconjugated Estradiol (Baseline-Adjusted)						
C <sub>max</sub> (pg/mL)	44.99	48.57	92.63	74.60 – 115.0	45.84	No
AUC <sub>0-t</sub> (pg.h/mL)	582.3	826.6	70.44	43.61 – 113.8	124.5	No
AUC <sub>0-∞</sub> (pg.h/mL)	1833	14132	128.0	75.73 - 116.4	112.5	No
Unconjugated Estradiol (Baseline-Unadjusted)						
C <sub>max</sub> (pg/mL)	64.90	62.01	104.7	91.60 – 120.3	28.73	Yes
AUC <sub>0-t</sub> (pg.h/mL)	1447	1482	97.62	92.60 – 115.4	34.67	Yes
AUC <sub>0-∞</sub> (pg.h/mL)	3240	2316	139.9	81.47 – 240.3	128.2	No

Source: Adapted from NDA 210132, Submodule 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 10, page 21 of 58, and Table 11, page 22 of 58.

<sup>a</sup> Estimate of least square mean used to calculate Geometric Mean (GM).

Abbreviations: Test = test product TX-001HR (estradiol and progesterone) capsules, Reference = reference product ESTRACE (estradiol tablets USP) 2 mg, C<sub>max</sub> = maximum concentration; AUC<sub>0-t</sub> = area under the concentration-time curve to last measurable time point; AUC<sub>0-∞</sub> = area under the concentration-time curve extrapolated to infinity, CV = coefficient of variation.

Table 9: Statistical Results of Test Product Versus Reference Product for Progesterone (Baseline-Adjusted and Baseline Unadjusted) Under High-Fat Fed Conditions in Trial EPROG-1K-352-12

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PK Parameter	Geometric Mean <sup>a</sup> Test	Geometric Mean <sup>a</sup> Reference	GM ratio (%)	90% Confidence Interval (%)	Intrasubject CV (%)	Bioequivalent
Progesterone (Baseline-Adjusted)						
C <sub>max</sub> (ng/mL)	47.04	42.99	109.4	73.45 – 163.0	95.29	No
AUC 0-t (ng.h/mL)	107.57	97.81	110.0	82.93 – 145.9	61.91	No
AUC 0-∞ (ng.h/mL)	111.9	111.9	100.0	75.65 – 132.3	57.78	No
Progesterone (Baseline-Unadjusted)						
C <sub>max</sub> (ng/mL)	47.78	44.20	108.1	72.73 – 160.7	94.63	No
AUC 0-t (ng.h/mL)	112.7	109.5	103.0	73.11 – 145.0	78.13	No
AUC 0-∞ (ng.h/mL)	112.5	124.2	90.52	65.41 – 125.3	69.08	No

Source: Adapted from NDA 210132, Submodule 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 12, page 23 of 58, and Table 5, page 16 of 58.

<sup>a</sup> Estimate of least square mean used to calculate Geometric Mean (GM).

Abbreviations: Test = test product TX-001HR (estradiol and progesterone capsules), Reference = reference product PROMETRIUM (progesterone USP) 200 mg, C<sub>max</sub> = maximum concentration; AUC 0-t = area under the concentration-time curve to last measurable time point; AUC 0-∞ = area under the concentration-time curve extrapolated to infinity, CV = coefficient of variation.

### Conclusions and Clinical Reviewer's Comments:

In Trial EPROG-1K-352-12, under fed conditions, 2 mg estradiol/200 mg progesterone was bioequivalent to Estrace 2 mg only for unadjusted estradiol. All the primary PK parameters for progesterone, as well as other parameters for estradiol, did not show bioequivalence. Because of the high degree of variability in Trial EPROG-1K-351-12 and Trial EPROG-1K-352-12, a third, single-dose bioequivalence trial was performed (Trial EPROG-1K-459-12) in healthy, postmenopausal women with the same drug products under high-fat, high-calorie conditions.

Trial EPROG-1K-459-12 was an open-label, balanced, randomized, single-dose, two-treatment, three-period, three-sequence, crossover, partial-replicate, reference-scaled oral bioequivalence trial of combined oral 2 mg estradiol/200 mg progesterone capsules and oral 2 mg Estrace and 200 mg Prometrium capsule in 66 normal healthy, postmenopausal women under fed conditions utilizing the same trial study design as Trials EPROG-1K-351-12 and EPROG-1K-352-12.

Plasma levels of estradiol, progesterone, and unconjugated and total estrone were evaluated under fed conditions. For each period, after an overnight-fast of at least 10 hours, a high-fat, high-calorie breakfast was served 30 minutes prior to administration of investigational products. A total of 24 blood samples were collected during each period at specified time points (see the NDA 210132 application for specific collection time points).

The bioequivalence results for estradiol and progesterone from this trial are presented in the following tables.

Table 10: Point Estimate, 95% Upper Confidence Bound, and Within-Subject SD (Swr) of Test Product Versus Averaged Reference Product for Estradiol and Progesterone

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(Baseline-Adjusted and Baseline-Unadjusted) Under High-Fat Fed Conditions – Trial EPROG-1K-459-12

PK Parameter	N	Point Estimate (%)	95% Upper Confidence Bound	Within Subject SD (Swr)	Bioequivalent
<b>Unconjugated Estradiol (Baseline-Adjusted)</b>					
Cmax (ng/mL)	62	88.24	-0.0310	0.4310	Yes
AUC 0-t (ng.h/mL)	62	93.14	-0.1360	0.7283	Yes
AUC0-∞ (ng.h/mL)	62	92.28	-0.0421	0.4350	Yes
<b>Unconjugated Estradiol (Baseline-Unadjusted)</b>					
Cmax (ng/mL)	53	87.36	0.0037	0.3064	No
<b>Progesterone (Baseline-Adjusted)</b>					
Cmax (ng/mL)	62	115.9	0.0799	0.3881	No
AUC 0-t (ng.h/mL)	62	105.5	-0.1006	0.6305	Yes
AUC0-∞ (ng.h/mL)	62	99.13	-0.1545	0.7398	Yes
<b>Progesterone (Baseline-Unadjusted)</b>					
Cmax (ng/mL)	62	117.57	0.0525	0.4735	No
AUC 0-t (ng.h/mL)	62	107.46	-0.0934	0.6301	Yes
AUC0-∞ (ng.h/mL)	62	101.35	-0.1142	0.6395	Yes

Source: Adapted from NDA 210132, Submodule 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 18, page 28 of 58, Table 19, page 29 of 58, and Table 21, page 31 of 58, and Table 22, page 32 of 58.

Abbreviations: Test = test product TX-001HR (estradiol and progesterone) capsules 2 mg/200 mg, Reference = reference product ESTRACE (estradiol tablets USP) 2 mg and PROMETRIUM (progesterone USP) 200 mg, Cmax = maximum concentration; AUC0-t = area under the concentration-time curve to last measurable time point; AUC0-∞ = area under the concentration-time curve extrapolated to infinity, SD = standard deviation.

Table 11: Test/Averaged Reference Geometric Mean Ratio, 90% Confidence Interval, and Within-Subject Variability (Swr) for Estradiol (Baseline-Unadjusted) Under High-Fat Fed Conditions – Trial EPROG-1K-459-12

PK Parameter	N	Geometric Mean <sup>a</sup> Test	Geometric Mean <sup>a</sup> Reference	GM Ratio %	90% Confidence Interval	Intrasubject SD (Swr)	Bioequivalent
AUC 0-t (ng.h/mL)	53	1255	1430	87.77	81.45 – 94.11	0.1971	Yes
AUC0-∞ (ng.h/mL)	53	1648	1986	82.97	74.66 – 92.20	0.2479	No

Source: Adapted from NDA 210132, Submodule 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 20, page 30 of 58.

a Estimate of least square mean used to calculate Geometric Mean (GM).

Abbreviations: Test = test product TX-001HR (estradiol and progesterone) capsules 2 mg/200 mg, Reference = reference product ESTRACE (estradiol tablets USP) 2 mg, Cmax = maximum concentration; AUC0-t = area under the concentration-time curve to last measurable time point; AUC0-∞ = area under the concentration-time curve extrapolated to infinity, SD = standard deviation.

See the December 28, 2017 NDA 210132 application for PK parameters for estrone in Trials EPROG-1K-351-12, EPROG-1K-352-12, and EPROG-1K-459-12.

Conclusions and Clinical Reviewer's Comments:

In Trial EPROG-1K-459-12, baseline-adjusted and unadjusted AUC0-t and AUC0-∞ met the bioequivalence criteria for all analytes. Baseline-adjusted and unadjusted Cmax for

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estradiol also met the criteria for bioequivalence. However, baseline-adjusted and unadjusted C<sub>max</sub> for progesterone were higher for 2 mg estradiol/200 mg progesterone capsules than for the Prometrium 200 mg with high variability. With the exception of progesterone C<sub>max</sub>, Trial EPROG-1K-459-12 shows that 2 mg estradiol/200 mg progesterone capsules to be bioequivalent to Estrace 2 mg and Prometrium 200 mg in healthy postmenopausal women under fed conditions. These results support the use of Prometrium as a Reference Listed Drug for the purpose of relying on the Agency's findings of safety for progesterone.

This reviewer notes, however, that the product utilized in these three trials differed slightly from the to-be-marketed capsules in formulation (b) (4). Therefore, the Agency recommended (FDA Advice letter dated June 14, 2017 and subsequent clarification email communication dated June 28, 2017) that a bioavailability trial under fasting and fed conditions be conducted with the drug product intended for commercialization.

Trial TXC17-02, a fourth phase 1 trial examined the effect of food on the bioavailability of 1 mg estradiol plus 100 mg progesterone (the highest dose for which market approval is requested), manufactured at the proposed commercial manufacturer (Catalent Pharma Solutions, LLC, St. Petersburg, FL). The following Table 12 and Table 13 summarize the baseline-adjusted and unadjusted PK parameters under fed and fasting condition for estradiol and progesterone, respectively.

Table 12: Summary of Pharmacokinetic Parameters for Estradiol Under Fed and Fasting Conditions – TrialTXC17-02<sup>a</sup>

	Pharmacokinetic Parameter	Fed		Fasted	
		N	Mean (SD)	N	Mean (SD)
Baseline-adjusted	C <sub>max</sub> (pg/mL)	23	29.55 (11.30)	23	74.68 (60.46)
	AUC <sub>0-t</sub> (pg.h/mL)	23	1063 (441.3)	23	1002 (386.2)
	AUC <sub>0-∞</sub> (pg.h/mL)	20	1286 (571.1)	22	1249 (454.5)
	T <sub>max</sub> (h)	23	11.57 (5.846)	23	2.58 (5.006)
	t <sub>1/2</sub> (h)	20	21.77 (6.910)	22	25.49 (15.07)
Baseline-unadjusted	C <sub>max</sub> (pg/mL)	23	32.36 (11.40)	23	78.48 (59.76)
	AUC <sub>0-t</sub> (pg.h/mL)	23	1263 (510.0)	23	1276 (519.9)
	AUC <sub>0-∞</sub> (pg.h/mL)	19	1723 (818.9)	23	1874 (1004)
	T <sub>max</sub> (h)	23	11.57 (5.846)	23	4.58 (5.006)
	t <sub>1/2</sub> (h)	19	28.66 (7.202)	23	47.01 (71.41)

Source: Adapted from NDA 210132, Submodule 2.7.2 Summary of Clinical Pharmacology, Table 14, page 24 of 46. a Trial participant number (b) (6) was excluded from this sensitivity analysis.

Abbreviations: AUC<sub>0-t</sub> = area under the concentration vs time curve for the last non-zero time point, AUC<sub>0-∞</sub> = area under the concentration vs time curve extrapolated to infinity, C<sub>max</sub> = maximum concentration, SD = standard deviation, t<sub>max</sub> = time to maximum concentration, t<sub>1/2</sub> = elimination half-life

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Table 13: Summary of Pharmacokinetic Parameters for Progesterone Under Fed and Fasted Conditions – Trial TXC17-02<sup>a</sup>

	Pharmacokinetic Parameter	Fed		Fasted	
		N	Mean (SD)	N	Mean (SD)
Baseline-adjusted	C <sub>max</sub> (pg/mL)	23	3.60 (5.312)	23	1.82 (3.532)
	AUC <sub>0-t</sub> (pg.h/mL)	23	8.48 (9.39)	23	4.14 (10.8)
	AUC <sub>0-∞</sub> (pg.h/mL)	13	9.80 (12.44)	8	9.71 (15.15)
	T <sub>max</sub> (h)	23	2.48 (1.071)	23	2.64 (1.768)
	t <sub>1/2</sub> (h)	13	3.73 (2.881)	8	7.48 (9.537)
Baseline-unadjusted	C <sub>max</sub> (pg/mL)	23	3.63 (5.315)	23	1.82 (3.532)
	AUC <sub>0-t</sub> (pg.h/mL)	23	8.72 (9.655)	23	7.14 (10.78)
	AUC <sub>0-∞</sub> (pg.h/mL)	13	10.10 (13.24)	8	9.71 (15.15)
	T <sub>max</sub> (h)	23	2.48 (1.071)	23	2.64 (1.768)
	t <sub>1/2</sub> (h)	13	3.99 (3.429)	8	7.48 (9.537)

Source: Adapted from NDA 210132, Submodule 2.7.2 Summary of Clinical Pharmacology, Table 15, page 25 of 46. a Subject (b) (6) was excluded from this sensitivity analysis.

Abbreviations: AUC<sub>0-t</sub> = area under the concentration vs time curve for the last non-zero time point, AUC<sub>0-∞</sub> = area under the concentration vs time curve extrapolated to infinity, C<sub>max</sub> = maximum concentration, SD = standard deviation, t<sub>max</sub> = time to maximum concentration, t<sub>1/2</sub> = elimination half-life.

See the December 28, 2017 NDA 210132 application for PK parameters for estrone in Trial TXC17-02.

Conclusions and Clinical Reviewer's Comments:

Food had no effect on estradiol bioavailability based on specified statistical analyses of the extent of absorption (AUC), but the rate of estradiol absorption was faster under fasting conditions compared to the fed state. However, food increased progesterone absorption following a single dose of TX-001HR.

This reviewer notes that the estradiol C<sub>max</sub> reported in Trial EPROG-1K-459-12, utilizing the 2 mg estradiol/200 mg progesterone capsules (manufactured by Catalent), is dose-proportional to the 1 mg estradiol/200 mg progesterone capsules administered in Trial TXC17-02 under high-fat fed conditions (manufactured by Catalent). AUCs are similar between the two trials.

Multiple-Dose Phase 1 Trials:

A fifth phase 1 trial (Trial TXC16-01), examined the pharmacokinetics of two fixed-doses of estradiol plus progesterone: 1) 1 mg estradiol plus 100 mg progesterone, and 2) 0.5 mg estradiol plus 100 mg progesterone, both manufactured by Catalent. Trial TXC16-01 assessed single-dose and seven daily doses of estradiol plus progesterone at bedtime under moderate-fat, moderate-calorie fed conditions. A total of 37 women (of 40 enrolled women) completed all 7 days of dosing.

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See the following two tables for as summary of single and multiple-dose estradiol and progesterone pharmacokinetic parameters. See the December 28, 2017 NDA 210132 application for PK parameters for estrone in Trial TXC16-01.

Table 14: Summary of Single and Multiple-Dose Estradiol Pharmacokinetic Parameters – Trial TXC16-01

Day	Pharmacokinetic Parameter	Baseline-adjusted				Unadjusted			
		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
1	AUC <sub>t</sub> (pg-h/mL)	20	400.5 (157.9)	20	167.8 (100.0)	20	542.9 (250.0)	20	558.6 (695.3)
	C <sub>max</sub> (pg/mL)	20	31.54 (29.70)	20	13.52 (9.320)	20	37.55 (35.47)	20	33.94 (48.57)
	t <sub>max</sub> (h)	20	10.00 (6.786)	20	11.08 (7.197)	20	10.00 (6.786)	20	11.08 (7.197)
7	AUC <sub>t</sub> (pg-h/mL)	20	772.4 (384.1)	17	386.8 (356.6)	20	910.8 (338.8)	17	698.5 (566.9)
	C <sub>avg</sub> (pg/mL)	19	33.99 (14.53)	17	16.64 (14.50)	20	38.07 (14.17)	17	29.20 (23.70)
	C <sub>max</sub> (pg/mL)	20	42.27 (18.60)	17	23.95 (16.86)	20	48.23 (15.84)	17	37.19 (28.74)
	t <sub>max</sub> (h)	19	4.93 (4.966)	17	5.90 (4.442)	20	5.59 (5.648)	17	5.90 (4.442)
	t <sub>½</sub> (h) <sup>a</sup>	19	26.47 (14.61)	11	28.01 (9.987) <sup>b</sup>	19	21.73 (10.26)	13	27.95 (36.31)

Source: Adapted from NDA 210132, Submodule 2.7.2 Summary of Clinical Pharmacology, Table 17, page 27 of 46.

a Effective t<sub>½</sub> (h) = 24•ln(2)/ ln(accumulation ratio/(accumulation ratio-1)) which was derived for subjects with accumulation ratio >1.

b Results exclude Subjects (b) (6) and (b) (6)

Abbreviations: C<sub>max</sub> = maximum concentration; AUC<sub>t</sub> = area under the concentration-time curve for dosing period; C<sub>avg</sub> = average concentration at steady state, SD = standard deviation, t<sub>max</sub> = time to maximum concentration, t<sub>½</sub> = half-life

Table 15: Summary of Single and Multiple-Dose Progesterone Pharmacokinetic Parameters – Trial TXC16-01

Day	Pharmacokinetic Parameter	Baseline-adjusted		Unadjusted	
		1 mg E2/ 100 mg P	0.5 mg E2/ 100 mg P	1 mg E2/ 100 mg P	0.5 mg E2/ 100 mg P

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		N	Mean (SD)						
1	AUC <sub>T</sub> (ng·h/mL)	20	14.12 (9.928)	20	10.06 (9.409)	20	14.25 (9.900)	20	10.63 (9.466)
	C <sub>max</sub> (ng/mL)	20	6.48 (6.206)	20	3.73 (3.211)	20	6.49 (6.205)	20	3.77 (3.216)
	t <sub>max</sub> (h)	20	2.23 (1.468)	20	2.52 (1.944)	20	2.23 (1.468)	20	2.52 (1.944)
7	AUC <sub>T</sub> (ng·h/mL)	20	18.05 (15.58)	17	12.19 (11.01)	20	18.19 (15.50)	17	12.49 (10.89)
	C <sub>avg</sub> (ng/mL)	20	0.76 (0.645)	17	0.55 (0.446)	20	0.77 (0.642)	17	0.53 (0.448)
	C <sub>max</sub> (ng/mL)	20	11.31 (23.10)	17	4.40 (5.720)	20	11.32 (23.10)	17	4.41 (5.720)
	t <sub>max</sub> (h)	20	2.64 (1.505)	17	2.89 (2.285)	20	2.64 (1.505)	17	2.89 (2.285)
	t <sub>½</sub> (h)	18	9.98 (2.565)	13	8.77 (2.776)	18	10.23 (2.509)	14	9.32 (1.826)

Source: Adapted from NDA 210132, Submodule 2.7.2 Summary of Clinical Pharmacology, Table 18, page 29 of 46.

Abbreviations: C<sub>max</sub> = maximum concentration; AUC<sub>T</sub> = area under the concentration-time curve for dosing period; C<sub>avg</sub> = average concentration at steady state, SD = standard deviation, t<sub>max</sub> = time to maximum concentration, t<sub>½</sub> = half-life

Conclusions and Clinical Reviewer's Comments:

Table 14 shows that mean AUC<sub>T</sub> and C<sub>max</sub> for estradiol were dose-related and were greater by Day 7 than for Day 1 (seen for both baseline-adjusted and unadjusted serum concentrations), demonstrating expected accumulation. For progesterone, mean AUC<sub>T</sub> and C<sub>max</sub> (Table 15) were only moderately higher on Day 7 (progesterone has an approximate elimination half-life of 10 hours) and greater in the 1 mg estradiol/100 mg progesterone group than the 0.5 mg estradiol/100 mg progesterone group (seen for both baseline-adjusted and unadjusted serum concentrations). Per the applicant, the similar pattern between baseline adjusted and unadjusted progesterone “could be an artifact due to high variability and relatively small sample size.”

Table 16 below summarizes the baseline-adjusted, pharmacokinetic parameters at steady state for estradiol, estrone, and progesterone. (b) (4)

Trial TXC16-01 utilized drug product produced by the proposed commercial manufacturer, Catalent.

Table 16: Pharmacokinetic Parameters for Estradiol, Estrone, and Progesterone at Steady State, Baseline Adjusted – Trial TXC16-01

Dosage Strength (estradiol/progesterone)	1 mg Estradiol/100 mg Progesterone		0.5 mg Estradiol/100 mg Progesterone	
	N	Mean (SD)	N	Mean (SD)
Estradiol				
AUC <sub>T</sub> (pg·h/mL)	20	772.4 (384.1)	17	386.8 (356.6)
C <sub>max</sub> (pg/mL)	20	42.27 (18.60)	17	23.95 (16.86)
C <sub>avg</sub> (pg/mL)	19	33.99 (14.53)	17	16.64 (14.50)
t <sub>max</sub> (h)	19	4.93 (4.97)	17	5.90 (4.44)
t <sub>½</sub> (h)	19	26.47 (14.61)	11	28.01 (9.99) <sup>a</sup>
Estrone	N		N	

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AUC <sub>T</sub> (pg·h/mL)	20	4594 (2138)	17	1981 (976.0)
C <sub>max</sub> (pg/mL)	20	238.5 (100.4)	17	108.0 (48.58)
C <sub>avg</sub> (pg/mL)	20	192.1 (89.43)	17	82.81 (40.80)
t <sub>max</sub> (h)	20	5.45 (3.47)	17	8.48 (4.87)
t <sub>1/2</sub> (h)	19	22.37 (7.64)	17	20.46 (5.61)
Progesterone	N		N	
AUC <sub>T</sub> (pg·h/mL)	20	18.05 (15.58)	17	12.19 (11.01)
C <sub>max</sub> (pg/mL)	20	11.31 (23.10)	17	4.40 (5.72)
C <sub>avg</sub> (pg/mL)	20	0.76 (0.65)	17	0.55 (2.29)
t <sub>max</sub> (h)	20	2.64 (1.51)	17	2.89 (2.29)
t <sub>1/2</sub> (h)	18	9.98 (2.57)	13	8.77 (2.78)

Source: Adapted from NDA 210132, Submodule 2.7.2 Summary of Clinical Pharmacology, Table 20, page 31 of 46. a Results exclude trial participants Numbers (b) (6) and (b) (6) with accumulation ratios of 371.7 and 43.86, respectively, and effective t<sub>1/2</sub> of 6174 hours and 721.3 hours, respectively. With trial participants Numbers (b) (6) and (b) (6) included, the mean accumulation ratio is 26.04 and the mean effective t<sub>1/2</sub> is 554.1 hours. Abbreviations: AUC<sub>T</sub> = area under the concentration-time curve for dosing period, C<sub>max</sub> = maximum concentration, SD = standard deviation, t<sub>max</sub> = time to maximum concentration, t<sub>1/2</sub> = half-life

### Conclusions and Clinical Reviewer's Comments:

Trial TXC16-01 administered TX-001HR at bedtime, with food, the same conditions of dosing in phase 3 Trial TXC12-05. Steady-state was reached by Day 7 in baseline-adjusted serum estradiol, estrone, and progesterone concentrations at both dose levels (1 mg estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone).

### Single Time Point Concentrations in Phase 3 Trial TXC12-05:

In phase 3, randomized, double-blind, placebo-controlled Trial TXC12-05, blood was collected from the safety population to assess serum levels of estradiol, estrone, and progesterone at Screening and Visits 2, 4, 5, 6 and 7 (Weeks 4 and 12 and Months 6, 9, and 12, respectively) while serum concentrations of progesterone were assessed at Screening and Visits 4 and 7 (Week 12 and Month 12, respectively). Self-administration of the combined estradiol plus progesterone capsules took place at bedtime on the evening before the blood sample was drawn (8 to 12 hours after dosing). Serum samples were analyzed for estradiol and estrone simultaneously using a validated GC-MS/MS method, and for progesterone using a separate validated LC-MS/MS method.

Table 17 shows a summary of the Baseline-unadjusted mean (SD) concentrations for estradiol, estrone and progesterone for the above specified time points by treatment groups for the safety population in 52-weeks Trial TXC12-05.

Table 17: Baseline-Unadjusted Mean (Standard Deviation) Concentrations for Estradiol, Estrone and Progesterone in Trial TXC12-05

Estradiol Concentration	1 mg E2/ 100 mg P	0.5 mg E2/ 100 mg P	0.5 mg E2/ 50 mg P	0.25 mg E2/ 50 mg P	Placebo
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(pg/ml)	(N=415)	(N=424)	(N=421)	(N=424)	(N=151)
<b>Screening (n)</b>	<b>415</b>	<b>423</b>	<b>421</b>	<b>421</b>	<b>150</b>
Mean (SD)	6.28 (6.62)	6.45 (7.24)	5.75 (6.06)	6.29 (6.25)	5.63 (4.32)
<b>Week 4 (n)</b>	<b>382</b>	<b>394</b>	<b>405</b>	<b>402</b>	<b>130</b>
Mean (SD)	42.49 (36.51)	23.03 (23.91)	24.88 (25.43)	18.50 (33.34)	8.27 (22.50)
<b>Week 12 (n)</b>	<b>352</b>	<b>365</b>	<b>374</b>	<b>371</b>	<b>117</b>
Mean (SD)	44.46 (39.11)	26.52 (27.32)	26.75 (31.05)	16.59 (19.26)	8.54 (23.22)
<b>Month 6 (n)</b>	<b>315</b>	<b>333</b>	<b>338</b>	<b>323</b>	<b>102</b>
Mean (SD)	45.58 (49.03)	24.23 (22.05)	24.16 (16.53)	16.61 (16.96)	5.35 (4.68)
<b>Month 9 (n)</b>	<b>292</b>	<b>318</b>	<b>320</b>	<b>296</b>	<b>95</b>
Mean (SD)	44.46 (35.67)	27.37 (35.27)	24.56 (20.40)	15.06 (13.55)	7.99 (15.18)
<b>Month 12 (n)</b>	<b>282</b>	<b>301</b>	<b>311</b>	<b>280</b>	<b>91</b>
Mean (SD)	42.29 (41.21)	24.60 (26.44)	23.66 (18.65)	15.23 (20.08)	5.73 (7.28)
<b>Estrone Concentration (pg/mL)</b>	<b>1 mg E2/ 100 mg P (N=415)</b>	<b>0.5 mg E2/ 100 mg P (N=424)</b>	<b>0.5 mg E2/ 50 mg P (N=421)</b>	<b>0.25 mg E2/ 50 mg P (N=424)</b>	<b>Placebo (N=151)</b>
<b>Screening (n)</b>	<b>415</b>	<b>422</b>	<b>421</b>	<b>421</b>	<b>150</b>
Mean (SD)	23.32 (12.59)	23.31 (12.05)	22.75 (12.96)	23.60 (11.02)	23.38 (11.15)
<b>Week 4 (n)</b>	<b>382</b>	<b>394</b>	<b>405</b>	<b>402</b>	<b>130</b>
Mean (SD)	213.8 (159.0)	113.6 (72.34)	119.5 (83.79)	69.02 (39.82)	23.78 (18.48)
<b>Week 12 (n)</b>	<b>352</b>	<b>365</b>	<b>373</b>	<b>373</b>	<b>117</b>
Mean (SD)	227.3 (168.1)	127.9 (81.19)	125.6 (94.27)	69.75 (38.20)	25.59 (17.17)
<b>Month 6 (n)</b>	<b>315</b>	<b>334</b>	<b>338</b>	<b>323</b>	<b>103</b>
Mean (SD)	235.03 (176.3)	128.6 (93.07)	128.3 (77.03)	73.43 (43.90)	24.15 (14.13)
<b>Month 9 (n)</b>	<b>293</b>	<b>318</b>	<b>320</b>	<b>296</b>	<b>95</b>
Mean (SD)	241.6 (185.7)	126.1 (88.29)	132.1 (83.54)	72.92 (41.46)	29.84 (44.68)
<b>Month 12 (n)</b>	<b>283</b>	<b>302</b>	<b>311</b>	<b>280</b>	<b>90</b>
Mean (SD)	227.8 (188.1)	119.6 (78.14)	127.6 (93.81)	72.48 (46.48)	28.32 (34.81)
<b>Progesterone Concentration (ng/mL)</b>	<b>1 mg E2/ 100 mg P (N=415)</b>	<b>0.5 mg E2/ 100 mg P (N=424)</b>	<b>0.5 mg E2/ 50 mg P (N=421)</b>	<b>0.25 mg E2/ 50 mg P (N=424)</b>	<b>Placebo (N=151)</b>
<b>Screening (n)</b>	<b>415</b>	<b>422</b>	<b>420</b>	<b>419</b>	<b>150</b>
Mean (SD)	0.056 (0.024)	0.065 (0.150)	0.057 (0.052)	0.056 (0.023)	0.053 (0.011)
<b>Week 12 (n)</b>	<b>351</b>	<b>366</b>	<b>374</b>	<b>373</b>	<b>117</b>
Mean (SD)	0.452 (0.622)	0.548 (1.884)	0.229 (0.619)	0.247 (0.441)	0.057 (0.031)
<b>Month 12 (n)</b>	<b>283</b>	<b>301</b>	<b>311</b>	<b>280</b>	<b>91</b>
Mean (SD)	0.534 (1.375)	0.387 (0.781)	0.181 (0.243)	0.219 (0.678)	0.056 (0.020)

Source: Adapted from NDA 210132, Submodule 2.7.2 Summary of Clinical Pharmacology, Table 21 on page 32 of 46, Table 22 on page 33 of 46, and Table 23 on page 34 of 46.

**Conclusions and Clinical Reviewer’s Comments:**

Table 17 shows that a dose response was observed for serum estradiol concentrations, and levels remained consistent over time for each respective treatment group. Estrone levels, generally, were related in a dose dependent manner to the estradiol dose given, levels remained consistent over time for each respective treatment group. A dose response is also shown for progesterone serum concentrations, and progesterone levels remained consistent over time with each respective treatment group.

A comparison of the mean of the single point determination of estradiol concentrations at Week 4 in phase 3 Trial TXC12-05 as shown above (manufactured by <sup>(b) (4)</sup> with the estradiol Cavg concentration at steady state on Day 7 in phase 1 Trial TXC16-01 shown in Table 16 (manufactured by Catalent) shows that serum estradiol concentrations are

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similar although the supplies for these trials were manufactured at different sites. These data support the equivalence of the two manufacturers of TX-001HR.

On July 30, 2018, Clinical Pharmacology requested that TherapeuticsMD provide a response to the following question, “We note a large variability in the  $C_{max}$  and  $AUC_{0-t}$  of progesterone administered under fed conditions among Trial 459, Trial TXC16-01, and Trial TXC17-02. For example, the  $AUC_{0-t}$  of progesterone (120 ng\*h/mL) observed in Trial 459 was 8-fold and 14-fold higher than that observed in Trial TXC16-01 (14.1 ng\*h/mL) and Trial TXC17-02 (8.5 ng\*h/mL), respectively. Please explain the large inter-trial variability.”

TherapeuticsMD’s response, dated August 6, 2018, highlights the differences in trial design and trial populations, making cross study comparisons difficult:

- Trial 459, conducted in India, provided a high-fat meal that included primarily vegetable oil (medium-chain unsaturated fatty acids), whereas Trial TXC17-02, conducted in the US, provided a high-fat meal that included primarily butter (long-chain fatty-acids). Women in Trial TXC16-01 received a moderate-fat meal.
- Sample size and demographics were different. Women in Trial 459 were, younger, thinner, and had earlier menopause than women in US Trials TXC16-01 and TXC17-02
- 2 mg estradiol and 200 mg progesterone doses were investigated in Trial 459, whereas 1 mg estradiol and 100 mg progesterone doses were investigated in Trials TXC16-01 and TXC17-02.
- Trial 459 showed the higher variability. The plasma progesterone  $C_{max}$  and  $AUC_{0-t}$  in Trial 459 were higher than anticipated.
- The bioanalytical assays utilized differed between the clinical trials.

Conclusions and Clinical Reviewer’s Comments:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology-3 reviewed the information in NDA 210132 and recommends approval of this NDA. Per the Clinical Pharmacology Review, dated September 7, 2018, key review issues with specific recommendations/comments include:

- A dose-dependent increase in estradiol and progesterone plasma concentrations was observed in the primary phase 3 Trial TXC12-05. Consistent concentrations of estradiol and progesterone were maintained over 12 months for each treatment arm, which provided supportive evidence of effectiveness of TX-001HR.
- The to-be-marketed formulation (Catalent 1 mg estradiol/100 mg progesterone) is bridged to the phase 3 trial formulation ( (b) (4) 1 mg estradiol/100 mg progesterone) using in vitro dissolution data and CMC data. No clinical bioequivalence (BE) trial is required. A cross-trial comparison between phase 1 Trial TXC16-01 (Catalent 1 mg estradiol/100 mg progesterone) and phase 3 Trial TXC12-05 ( (b) (4) 1 mg estradiol/100 mg progesterone, sparse PK sampling) did not show a dramatic difference in the plasma concentrations of estradiol or progesterone.

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- A bioequivalence trial using Estrace 2 mg and Prometrium 200 mg as reference drugs and (b) (4) 2 mg estradiol/200 mg progesterone as test drug was conducted. The results of the BE trial showed that the (b) (4) 2 mg estradiol/200 mg progesterone product had similar exposure to progesterone compared to the reference drug Prometrium 200 mg.
- Considering the composition of (b) (4) 2 mg estradiol/200 mg progesterone and Catalent 1 mg estradiol/100 mg progesterone is quantitatively proportional, there is no change in manufacturing process and the proposed highest clinical dose contains only 100 mg progesterone (i.e., half the dose in the BE study), the review team believes that the proposed Catalent 1 mg estradiol/100 mg progesterone product will result in exposure less than or equal to that of Prometrium 200 mg. Therefore, Trial 459 successfully bridged TX-001HR 1 mg estradiol/100 mg progesterone formulation to Prometrium 200 mg for purpose of bridging to the safety findings of Prometrium 200 mg.

This reviewer concurs with the Clinical Pharmacology Review, dated September 7, 2018.

### 4.6. Devices and Companion Diagnostic Issues

There are no device and companion diagnostic tests with the combined estradiol and progesterone oral capsule.

### 4.7. Consumer Study Reviews

No label comprehensive, patient self-selection, or other human factor studies were evaluated during the estradiol and progesterone capsule development program.

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

Table 18: Listing of Clinical Trials

Trial Identifier Type of Trial	Objective(s) of the Trial	Trial Design and Type of Control	Dosage Regimen	Number of Trial Participants	Duration of Treatment
TXC16-01 BA	Describe the single- and seven daily dose PK of oral TX-001HR	Open-label, parallel-group, randomized, trial to assess two fixed-doses of TX- 001HR under fed conditions	TX-001HR: <ul style="list-style-type: none"><li>• 1 mg estradiol and 100 mg progesterone</li><li>• 0.5 mg estradiol and 100 mg</li></ul>	40 enrolled postmenopausal women 40 to 65 years of age  30 completers	Seven daily doses

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			progesterone		
EPROG-1K-351-12 BA/BE	Evaluate the oral comparative BA of TX-001HR combined 2 mg estradiol and 200 mg progesterone capsules versus 2 mg Estrace® (estradiol tablets USP) plus 200 mg Prometrium® (progesterone USP)	Open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose two-way crossover oral BA/BE trial under fasted conditions	TX-001HR: <ul style="list-style-type: none"> <li>• 2 mg oral estradiol and 200 mg progesterone capsules</li> <li>• 2 mg Estrace® oral tablets plus 200 mg oral Prometrium® capsule</li> </ul>	24 enrolled postmenopausal women 40 to 65 years of age  23 completers	Single dose
EPROG-1K-352-12 BA/BE	Evaluate the oral comparative BA of TX-001HR combined 2 mg estradiol and 200 mg progesterone capsules versus 2 mg Estrace® (estradiol tablets USP) plus 200 mg Prometrium® (progesterone USP)	Open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover oral BA/BE trial under high-fat fed conditions	TX-001HR: <ul style="list-style-type: none"> <li>• 2 mg oral estradiol and 200 mg progesterone capsules</li> <li>• 2 mg Estrace® oral tablets plus 200 mg oral Prometrium® capsule</li> </ul>	24 enrolled postmenopausal women 40 to 65 years of age  24 completers	Single dose
EPROG-1K-459-12 BA/BE	Evaluate the oral BE of TX-001HR combined 2 mg estradiol and 200 mg progesterone capsules versus 2 mg Estrace® (estradiol tablets USP) plus 200 mg Prometrium® (progesterone USP)	Open-label, balanced, randomized, single-dose, two-treatment, three-period, three-sequence, reference-replicated, reference-scaled, crossover, oral BA/BE trial under high-fat fed conditions	TX-001HR: <ul style="list-style-type: none"> <li>• 2 mg oral estradiol and 200 mg progesterone capsules</li> <li>• 2 mg Estrace® oral tablets plus 200 mg oral Prometrium® capsule</li> </ul>	66 enrolled postmenopausal women 40 to 65 years of age  62 completers	Single dose
TXC17-02 BA	Assess the effect of food on the BA of TX-001HR	Open-label, balanced, single-dose, two-treatment (fed and fasted), crossover, oral, comparative BA trial	TX-001HR: <ul style="list-style-type: none"> <li>• 1 mg estradiol and 100 mg progesterone capsules</li> </ul>	24 enrolled postmenopausal women 40-65 years of age  24 completers	Single dose
TXC12-05 Efficacy and Safety	VMS subtrial: Determine if TX-001HR given daily is effective at reducing the frequency and	Phase 3, randomized, double-blind, placebo-controlled multicenter trial	Oral TX-001HR: <ul style="list-style-type: none"> <li>• 1 mg estradiol and 100 mg progesterone daily</li> </ul>	VMS subtrial: 766 enrolled postmenopausal women 40 to 65 years of age	52 weeks

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	severity of moderate to severe VMS when compared with placebo at Weeks 4 and 12  Endometrial hyperplasia: Determine if TX-001HR given daily is effective at achieving a ≤ 1% incidence rate of endometrial hyperplasia following 12 months of therapy		<ul style="list-style-type: none"><li>• 0.5 mg estradiol and 100 mg progesterone daily</li><li>• 0.5 mg estradiol and 50 mg progesterone daily</li><li>• 0.25 mg estradiol and 50 mg progesterone daily</li></ul> Oral Placebo daily	726 analyzed  Safety: 1835 enrolled postmenopausal women 40 to 65 years of age  1275 completers	
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Source: Adapted from NDA 210132, Submodule 2.7.6 Synopsis of Individual Studies, Table 1.

Abbreviations: BA – bioavailability; PK – pharmacokinetics; BE – bioequivalence; VMS – vasomotor symptoms.

## 5.2. Review Strategy

The available clinical data in primary 52-week, phase 3, safety and efficacy clinical Trial TXC12-05 (first 12-weeks placebo-controlled) provide the basis for consideration regarding the efficacy of TX-001HR (combined 1.0 mg estradiol plus 100 mg progesterone, (b) (4) oral capsules for the treatment of moderate to severe vasomotor symptoms, due to menopause.

Trial TXC12-05 is the single safety and efficacy trial conducted in support of moderate to severe vasomotor symptoms and, is the single safety trial conducted in support of general and endometrial safety and long-term drug exposure data for this combined estradiol plus progesterone product for use in a postmenopausal woman with a uterus.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. Trial TXC12-05

#### 6.1.1. Study Design

##### Overview:

TherapeuticsMD has developed an oral combination product (TX-001HR) consisting of a softgel formulation containing solubilized estradiol with micronized progesterone intended to treat moderate to severe vasomotor symptoms while protecting the endometrium from unopposed

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estradiol. The product is comprised of active ingredients of estradiol and progesterone that are chemically identical to endogenous estradiol and progesterone in a softgel capsule form. The rationale for the development of TX-001HR, per the applicant, is to provide postmenopausal women with an FDA-approved combination of estradiol and progesterone, and to “alleviate the need for unapproved compounded agents of estradiol and progesterone.”

Postmenopausal women 40 to 65 years of age (at the time of randomization) who qualified per the inclusion and exclusion entry criteria were enrolled in Trial TXC12-05 after they provided written informed consent as described in 21 CFR 50.

A total of 117 clinical sites in the United States screened at least one subject and 111 clinical sites randomized at least one postmenopausal woman into either the vasomotor symptoms (VMS) subtrial (104 sites) or into the non-VMS subtrial (98 sites).

(b) (4) was responsible for processing the central laboratory samples including Papanicolaou (Pap) smears, and endometrial biopsies. (b) (4) was also responsible for the receipt and storage of hormone samples for estradiol, estrone, and progesterone. Hormone levels of estradiol, estrone, and progesterone were analyzed by (b) (4)

Electrocardiograms (ECGs) and mammograms were performed and read locally. The individual clinical site personnel entered the results of these tests directly into the eCRF.

Catalent Pharma Solutions and the (b) (4) were responsible for the packaging, distribution, resupply, storage and destruction of trial medication. Catalent was the primary vendor from approximately July 2013 through August 2014, at which time (b) (4) assumed primary responsibilities through trial completion.

**Trial TXC12-05 Objectives:**

**Vasomotor symptoms:** To determine whether TX-001HR given in a continuous fashion is effective at reducing the frequency and severity of moderate to severe VMS associated with menopause when compared with placebo at Weeks 4 and 12.

**Endometrial hyperplasia:** To determine whether TX-001HR given in a continuous fashion is effective at achieving a ≤ 1% incidence rate of endometrial hyperplasia following 12 months of therapy.

**Trial Design for Phase 3 Trial TXC12-05:**

Trial TXC12-05 was a phase 3, 52-weeks, multi-center (111 clinical sites randomized at least 1 postmenopausal woman), randomized, double-blind, placebo-controlled (first 12 weeks), parallel group trial (1 mg estradiol and 100 mg progesterone, 0.5 mg estradiol and 100 mg progesterone, 0.5 mg estradiol and 50 mg progesterone, 0.25 mg estradiol and 50 mg

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progesterone, and placebo). The trial population consisted of non-hysterectomized postmenopausal women, 40 to 65 years of age, who met the trial entry criteria. During the Screening period, all trial participants were provided with a diary to self-assess the frequency and severity of their VMS. Trial participants who experienced a minimum daily frequency of  $\geq 7$  (or  $\geq 50$  per week) moderate to severe hot flushes participated in the VMS subtrial for the first 12 weeks of treatment (placebo-controlled). The VMS subtrial participants were stratified by treatment arm within the clinical sites, and only VMS subtrial participants had the possibility of being randomized to placebo.

Trial participants who otherwise qualified for the trial except for reporting the required minimum daily frequency of moderate to severe hot flushes were stratified by treatment arm within clinical sites to one of four active treatment arms and received blinded trial medication for 12 months. These participants did not participate in the VMS subtrial.

### Treatments Administered:

Randomized trial participants self-administered orally one of the following four arms of active TX-001HR treatment daily at bedtime with food for 12 months. Two different sizes of capsules were necessary to accommodate the different doses. To maintain the trial blind, the trial had a double-blind, double-dummy treatment. Women randomized to active treatment took a placebo capsule matching the alternate capsule size from their active treatment. Two sizes of placebo capsules that were an identical match to the active medication, but without the estradiol and progesterone, were taken orally by women participating in the VMS subtrial that were randomized to placebo.

- |              |   |
|--------------|---|
| Treatment 1: | Combined 1 mg estradiol/100 mg progesterone [large active; small placebo]   |
| Treatment 2: | Combined 0.5 mg estradiol/100 mg progesterone [large active; small placebo] |
| Treatment 3: | Combined 0.5 mg estradiol/50 mg progesterone [large placebo; small active]  |
| Treatment 4: | Combined 0.25 mg estradiol/50 mg progesterone [large placebo; small active] |
| Treatment 5: | Placebo [large placebo; small placebo]                                      |

All trial participants self-administer orally two capsules daily at bedtime with food for 12 months. Each trial participant was dispensed enough trial medication to last until the next scheduled visit, with allowance for visit windows. The participants were instructed to return the used and unused containers of trial medication in the original packaging to the trial site at Visits 2, 3, 4, 5, 6, and 7. Trial sites verified and documented compliance based on counts of dispensed/returned trial medication and any additional information reported by the participant (for example, lost capsules).

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Following informed consent procedures, trial participants completed initial Screening procedures that included: demographics, medical/gynecological history, concomitant medications, physical examination (including height, weight, and body mass index [BMI] calculation), pregnancy test, vital signs, pelvic and breast examinations, laboratory measurements, 12-lead ECG, Pap smear, mammography, and endometrial biopsy.

Upon completion of the initial Screening procedures, all participants who met eligibility requirements to continue Screening were provided with a hot flush diary that was completed for the remainder of the Screening period. Participants were instructed to complete the diary daily by recording the number and severity of hot flashes in their diaries. A minimum of 14 consecutive days of completed hot flush diary data were required during the baseline assessment at Screening, and the consecutive days must have occurred within the last 14 days prior to Randomization (not counting the day of Randomization). The most recent seven (7) consecutive days of data prior to Randomization was used to determine the baseline number of mild, moderate, or severe hot flashes for each participant.

At Randomization, participants who continued to meet the eligibility criteria with a minimum daily frequency of  $\geq 7$  (or  $\geq 50$  per week) moderate to severe hot flashes in the seven days prior to Randomization (Visit 1) were randomized into the VMS subtrial. All other eligible participants not meeting the VMS subtrial hot flash requirements were randomized into the non-VMS portion of the trial.

All participants (both VMS subtrial and non-VMS subtrial) completed hot flash diaries and bleeding and spotting diaries through Week 12. After Week 12, all participants continued to complete bleeding and spotting diaries until the End-of-Trial (EOT) at Month 12.

Trial participants in the VMS subtrial completed Clinical Global Impression (CGI) questionnaires at Weeks 4, 8, and 12. The Menopause-Specific Quality of Life Questionnaire (MENQOL) and the Medical Outcomes Study-Sleep Questionnaire (MOS - Sleep) were administered at Randomization, Week 12, Month 6, and Month 12.

Vital signs and adverse event (AE) monitoring occurred throughout the trial; laboratory assessments were performed at Week 12, Month 6, Month 9, and Month 12 (or Early Termination).

Trial participants also had blood draws to assess hormone concentration levels at Screening for estradiol, estrone, and progesterone, additional draws at Week 4, Week 12, Month 6, Month 9, and Month 12 (or Early Termination) for estradiol and estrone, and at Week 12 and Month 12 (or Early Termination) for progesterone.

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At Month 12 (or Early Termination), the following assessments were performed: physical examination (including weight), vital signs, pelvic and breast examinations, laboratory measurements, ECG, Pap smear, mammography, and endometrial biopsy.

The total duration of the study was approximately 14.5 months, which included a Screening period of approximately 60 days prior to randomization, approximately 12 months of treatment, and a 15-day follow-up period.

Clinical evaluations were performed at the following time points:

- Screening Period: Days -60 to 0
- Visit 1 (Randomization): Week 0, Day 1
- Visit 2 (Interim): Week 4, Day 28 ( $\pm$  3 days)
- Visit 3 (Interim): Week 8, Day 56 ( $\pm$  3 days)
- Visit 4 (Interim): Week 12, Day 84 ( $\pm$  3 days)
- Visit 5 (Interim): Month 6, Day 180 ( $\pm$  4 days)
- Visit 6 (Interim): Month 9, Day 270 ( $\pm$  4 days)
- Visit 7 (End of Treatment): Month 12, Day 360 ( $\pm$  4 days)
- Telephone Interview approximately 15 days after last dose

### Inclusion Criteria:

For inclusion into the trial, postmenopausal women were required to fulfill all the following criteria:

1. Was a female between the ages of 40 and 65 years (at the time of Randomization) who was willing to participate in the trial, as documented by signing informed consent.
2. Was a postmenopausal woman with an intact uterus and a Screening serum estradiol level of  $\leq$  50 pg/mL. Postmenopausal was defined as:
  - $\geq$  12 months of spontaneous amenorrhea, or
  - at least 6 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level of  $>$  40 mIU/ml, or
  - $\geq$  6 weeks postsurgical bilateral oophorectomy
3. Was seeking treatment or relief for moderate to severe vasomotor symptoms associated with menopause.
4. To participate in the VMS subtrial, a trial participant must have reported  $\geq$  7 moderate to severe hot flushes per day, or  $\geq$  50 per week, at the Baseline assessment during Screening; trial participants whose hot flushes were less frequent were still able to participate as non-VMS subtrial participants.
5. Have a BMI  $\leq$  34 kg/m<sup>2</sup> (BMI values should be rounded to the nearest integer [for example, 34.4 rounds down to 34, while 26.5 rounds up to 27]).
6. Was willing to abstain from using products (other than trial medication) that contained estrogen, progestin, or progesterone throughout trial participation.

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7. Was judged by the investigator as being in otherwise generally good health based on a medical evaluation performed during the Screening period prior to the initial dose of trial medication. The medical evaluation findings must have included:
- a) A normal or non-clinically significant physical examination, including vital signs (sitting blood pressure, heart rate, respiratory rate and temperature). Sitting systolic blood pressure of  $\leq 140$  mm Hg and diastolic blood pressure of  $\leq 90$  mm Hg at Screening. A participant could have been taking up to two antihypertensive medications.
  - b) A normal or non-clinically significant pelvic examination.
  - c) A mammogram that showed no sign of significant disease (may have been performed within previous 6 months prior to initial dose of trial medication). Women must have a breast imaging and reporting and database system (BI-RADS) 1 or 2 to enroll in the trial. An incomplete mammogram result, for example, BI-RADS 0, was not acceptable. The site obtained a copy of the official report for the woman's file, and verified that the mammogram itself was available if needed for additional assessment.
  - d) A normal or non-clinically significant clinical breast examination. An acceptable breast examination was defined as no masses or other findings identified that were suspicious of malignancy.
  - e) A normal Screening Pap smear. Participants with findings of atypical glandular cells (AGC), atypical glandular cells of undetermined significance (AGU)], atypical cells of undetermined significance (ASCUS) with high risk human papillomavirus (HPV) type upon reflex testing, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells of undetermined significance, cannot rule out HSIL (ASC-H)=), dysplastic cells, or malignant cells were excluded from Randomization.
  - f) An acceptable result from an evaluable Screening endometrial biopsy. The endometrial biopsy reports by the two central pathologists at Screening must have each specified one of the following: proliferative endometrium; weakly proliferative endometrium; disordered proliferative pattern; secretory endometrium; endometrial tissue other (including benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc); endometrial tissue insufficient for diagnosis; no endometrium identified; or no tissue identified. At least one pathologist must have identified sufficient tissue to evaluate the biopsy. Additionally, the endometrial biopsy reports by the two central pathologists of Other Findings at Screening must have each specified one of the following: endometrial polyp not present; benign endometrial polyp; or polyp other.
  - g) A normal or non-clinically significant 12-lead ECG.

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The inclusion criteria in Trial TXC12-05 were comprehensive and complete, and considered appropriate for this phase 3 clinical trial at the time of protocol review by DBRUP. For inclusion in VMS trials, we now recommend: 1) postmenopausal women with a body mass index (BMI) between 16 and 38 kg/m<sup>2</sup>, and 2) sitting systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg.

Exclusion Criteria:

Any of the following was regarded as a criterion for exclusion from the trial:

1. Currently hospitalized.
2. A history of thrombosis of deep veins or arteries or a thromboembolic disorder.
3. A history of coronary artery or cerebrovascular disease (for example, myocardial infarction, angina, stroke, transient ischemic attack).
4. A history of a chronic liver or kidney dysfunction/disorder (for example, Hepatitis C or chronic renal failure).
5. A history of a malabsorption disorder (for example, gastric bypass, Crohn's disease).
6. A history of gallbladder dysfunction/disorders (for example, cholangitis, cholecystitis), unless gallbladder had been removed.
7. A history of diabetes, thyroid disease or any other endocrinological disease (participants with diet-controlled diabetes or controlled hypothyroid disease at Screening were not excluded).
8. A history of estrogen-dependent neoplasia; atypical ductal hyperplasia of the breast.
9. A finding of clinically significant uterine fibroids at Screening.
10. Had a uterine ablation.
11. Had a history of undiagnosed vaginal bleeding.
12. Had any history of endometrial hyperplasia, melanoma, or uterine/endometrial, breast or ovarian cancer.
13. Had a history of other malignancy within the last 5 years, with the exception of basal cell (excluded if within 1 year) or non-invasive squamous cell (excluded if within 1 year) carcinoma of the skin
14. Had a history of any other cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychological (for example, bipolar disorder, schizophrenia, major depressive disorder), or musculoskeletal disease or disorder that was clinically significant in the opinion of the investigator.
15. Had any of the following clinical laboratory values at Screening:
  - a) fasting triglyceride of ≥ 300 mg/dL and/or total cholesterol of ≥ 300 mg/dL
  - b) positive laboratory finding for Factor V Leiden mutation
  - c) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of normal
  - d) fasting glucose > 125 mg/dL
16. Was pregnant or had a positive urine pregnancy test.

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17. Had contraindication to estrogen and/or progestin therapy or allergy to the use of estradiol and/or progesterone or any components of the trial medication.
18. Used 15 or more cigarettes per day or currently use any electronic cigarettes.
19. Had a history of drug and/or alcohol abuse within one year of start of trial.
20. Had used, within 28 days prior to the initial dose of trial medication, any medication known to induce or inhibit CYP3A4 enzyme activity that may have affected estrogen and/or progestin drug metabolism.
21. Had used, within 28 days prior to Screening, or planned to use during the trial, any prescription or over the counter (OTC) medication (including herbal products, such as St. John's Wort) that would be expected to alter progesterone or estrogen activity or is being used to treat vasomotor symptoms.
22. Had used estrogen alone or estrogen/progestin, selective estrogen receptor modulator (SERM), testosterone, or estrogen/testosterone for any of the following time periods:
  - a) Vaginal non-systemic hormonal products (rings, creams, gels) within 7 days prior to Screening, or vaginal systemic products (for example, Femring®) within 28 days prior to Screening.
  - b) Transdermal estrogen alone or estrogen/progestin products within 8 weeks prior to Screening,
  - c) Oral estrogen and/or progestin therapy and/or SERM within 8 weeks prior to Screening,
  - d) Progestational implants, estrogen or estrogen/progestational injectable drug therapy within 3 months prior to Screening,
  - e) Estrogen pellet therapy or progestational injectable drug therapy within 6 months prior to Screening,
  - f) Percutaneous estrogen lotions/gels within 8 weeks prior to Screening,
  - g) Oral, topical, vaginal, patch, implantable or injectable androgen therapy within 8 weeks prior to Screening.
23. Had used an intrauterine device within the 12 weeks prior to Screening.
24. For participants in the VMS subtrial only: use of medication that may have affected the outcome of the VMS endpoints within 28 days prior to Screening (for example, selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], aldomet, dopaminergic or antidopaminergic drugs, gabapentin, clonidine, or bellergal).
25. Had any reason which, in the opinion of the investigator, would prevent the woman from safely participating in the trial or complying with protocol requirements.
26. Had a Screening endometrial biopsy sample that was found by both primary pathologists to have endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified (with the approval of the medical monitor, the Screening endometrial biopsy could have been repeated once).
27. Endometrial polyps with atypical nuclei reported by at least one central pathologist.

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28. Had contraindication to any planned study assessments (for example, endometrial biopsy).
29. Had participated in another clinical trial within 30 days prior to Screening, had received an investigational drug within the three months prior to the initial dose of trial medication, or was likely to participate in a clinical trial or receive another investigational medication during the study.
30. Current use of marijuana.

Clinical Reviewer's Comments:

The exclusion criteria in Trial TXC12-05 were comprehensive and complete, and considered appropriate for this phase 3 clinical trial.

Individual Trial Participant Stopping Criteria:

Women were removed from the trial if any of the following circumstances occurred:

- The woman withdrew her consent for any reason.
- The woman's condition worsened to the degree that the investigator felt it was unsafe for the woman to continue in the trial.
- If it was difficult/impossible to obtain laboratory samples.
- If the woman's drug code was unblinded.
- If an AE occurred for which the woman desired to discontinue treatment or the investigator determined that it was in the woman's best interest to be discontinued.
- If there was a significant protocol deviation/violation or a trend in deviations/violations (defined as a deviation/violation that affects the woman's rights, safety, or the integrity of the trial data).
- If a concomitant therapy was reported or required which was likely to interfere with the results of the trial or compromise trial participant safety.
- If the woman was lost to follow-up. The investigator was to document efforts to attempt to reach the participant at least twice by telephone and by a certified follow-up letter before considering that the participant was lost to follow-up.
- If a woman became pregnant. If a pregnancy was reported during trial participation, the pregnancy was to be followed as medically appropriate.
- Administrative reasons.

If a woman was discontinued from the trial for any reason, every attempt was to be made to bring the woman to the clinic and perform the end-of-trial(EOT) procedures. Any outstanding data was captured and the trial medication, diaries and supplies were collected.

If a woman discontinued from the trial at any time due to an adverse event (AE), the reason for discontinuation, the nature of the event and its clinical course were fully documented. The investigator followed the woman until the AE resolved, became clinically insignificant, or was

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stabilized, unless the woman was lost to follow-up. If a woman discontinued or withdrew, she was not replaced.

Primary Efficacy Endpoints (VMS Subtrial):

The following co-primary efficacy endpoints were assessed in the VMS subtrial:

- Mean change in frequency of moderate to severe VMS from Baseline to Week 4 in an active treatment group compared with placebo
- Mean change in frequency of moderate to severe VMS from Baseline to Week 12 in an active treatment group compared with placebo
- Mean change in severity of moderate to severe VMS from Baseline to Week 4 in an active treatment group compared with placebo
- Mean change in severity of moderate to severe VMS from Baseline to Week 12 in an active treatment group compared with placebo

Clinical Reviewer's Comments:

The primary efficacy endpoints in the Trial TXC12-05 VMS subtrial are appropriate, and comply with the Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy symptoms – Recommendations for Clinical Evaluation (hereafter referred to as the Agency's draft 2003 Hormone Therapy Guidance for Industry).<sup>7</sup>

Secondary Endpoints from the VMS Subtrial:

- Mean change in frequency of moderate to severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Mean change in severity of moderate to severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Mean change in frequency of mild, moderate and severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Mean change in severity of mild, moderate and severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Percentage of participants with 50% and, separately, 75% reduction in frequency of moderate to severe VMS from Baseline at each week up to Week 12 in an active treatment group compared with placebo.
- Percentage of participants with 50% and, separately, 75% reduction in frequency of mild, moderate and severe VMS from Baseline at each week up to Week 12 in an active treatment group compared with placebo.

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<sup>7</sup> The Agency's 2003 draft hormone therapy clinical evaluation Guidance for Industry can be viewed at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pdf>

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- Clinical Global Impression (CGI) distribution (number and percentage of participants in VMS substudy only) at Week 4, Week 8, and Week 12, with mean change in the frequency of moderate to severe VMS from Baseline summarized within each CGI category at Weeks 4, 8, and 12 (Gerlinger method). This was utilized to evaluate minimum clinically important changes in VMS frequency that are associated with each CGI category.
- Change from Baseline in Menopause-Specific Quality of Life (MENQOL) evaluation parameter,
- Change from Baseline in Medical Outcome Study - Sleep (MOS – Sleep) evaluation parameters.

### Other Secondary Efficacy Endpoints (Modified Intent-to-Treat):

Other secondary efficacy endpoints include:

- Change from Baseline in MENQOL evaluation parameters
- Change from Baseline in MOS - Sleep evaluation parameters

### Clinical Reviewer's Comments:

On November 7, 2013, in an Advice/Information Request (A/IR) letter, TherapeuticsMD was advised that:

- only data collected on the primary endpoint will be presented in product labeling. Data collected for the proposed secondary endpoints in the vasomotor symptoms (VMS) subtrial will not be used to determine the effectiveness of the drug product for the indications sought, nor will this data appear in product labeling, and
- the findings from secondary endpoints and other endpoints (for example, MENQOL evaluation parameters and MOS-Sleep evaluation parameters) would not be used to support the effectiveness of the drug product to relieve hot flushes and would not appear in labeling.

### Primary Safety Endpoints:

The primary safety endpoint is the incidence of endometrial hyperplasia at 12 months (to demonstrate a hyperplasia proportion that was  $\leq 1\%$  with an upper bound of the one-sided 95 percent confidence interval [CI] for that rate that does not exceed 4%) based on an *a priori* plan which a consensus among two out of three pathologists was the final endometrial pathology diagnosis.

For the primary endpoint, all endometrial biopsies were centrally read by three pathologists. Each pathologist classified the endometrial biopsies into one of the following three categories:

- Category 1: Non-endometrial malignancy/non-hyperplasia includes proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern, secretory endometrium, endometrial tissue (other) [benign, inactive or atrophic

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fragments of endometrial epithelium, glands, stroma, etc], endometrial tissue insufficient for diagnosis, no endometrium identified, no tissue identified, other.

- Category 2: Endometrial hyperplasia includes simple hyperplasia with or without atypia and complex hyperplasia with or without atypia.
- Category 3: Endometrial malignancy.

Clinical Reviewer's Comments:

The Agency's draft 2003 hormone therapy Guidance for Industry recommends that standardized criteria, as provided in Blaustein's pathology text (Pathology of the Female Genital Tract), be used for the diagnosis of endometrial hyperplasia or cancer.<sup>7</sup>

Standardized Histologic Characteristics of the Endometrium under Blaustein's Pathology of the Female Genital Tract is divided into the following individual histologic characteristics:

0. No tissue
1. Tissue insufficient for diagnosis
2. Atrophic
3. Inactive
4. Proliferative
  - a. Weakly proliferative
  - b. Active proliferative
  - c. Disordered proliferative
5. Secretory
  - a. Cystic type
  - b. Progestational type
6. Menstrual type
7. Simple hyperplasia without atypia
8. Simple hyperplasia with atypia
9. Complex hyperplasia without atypia
10. Complex hyperplasia with atypia
11. Carcinoma (specify type)

No grouping of the 11 individual histologic characteristics is recommended.

Secondary Safety Endpoints:

Endometrial biopsies were performed at Screening and at Visit 7 (Month 12)/End-of-Trial by a board-certified gynecologist and the procedure, including instrument used, was documented in the trial participant's source file. Trial participants who discontinued trial participation after receiving ≥ 12 weeks of trial medication were also required to have an endometrial biopsy. Unscheduled endometrial biopsies were performed during the trial, if indicated for medical reasons.

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Biopsy specimens were shipped to a central laboratory ( (b) (4) ) for preparation of slides. To ensure uniformity in interpretation, a chartered Pathology Committee consisting of four independent pathologists (one pathologist was a back-up in the event of illness or unavailability of the other pathologists), who are experts in the field of endometrial pathology, assessed the endometrial biopsy samples in a blinded fashion.

At Screening, endometrial biopsies were read centrally by two pathologists. If at least one pathologist assessed the endometrial biopsy as endometrial hyperplasia, endometrial cancer, or if either pathologist identifies an endometrial polyp with either hyperplasia, glandular atypia of any degree (for example, atypical nuclei) or cancer, the woman was excluded from the trial. Additionally, at least one pathologist had to identify sufficient tissue to evaluate the biopsy for trial eligibility.

With the approval of the medical monitor, the Screening endometrial biopsy may have been repeated once when an initial endometrial biopsy was performed and both primary pathologists reported endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified, and if the woman had met all other protocol-specified eligibility criteria to date.

The Month 12/ End-of-Trial, Early Termination, and on-treatment unscheduled biopsies were centrally read by three pathologists. The End-of-Trial or Early Termination biopsy may have been repeated once if all three of the pathologists reported endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified. End-of-Trial or Early Discontinuation endometrial biopsies that were repeated per protocol must have been performed within 30 days of the final dose of trial medication.

Per the application, the reads of the two primary pathologists were utilized. Consensus was reached when the two primary pathologist readers agreed on any of the above categories. For example, any two subcategories of “Non-endometrial malignancy/non-hyperplasia” were classified as “Category 1: Non-endometrial malignancy/non-hyperplasia”; if the primary pathologists disagreed on the presence of hyperplasia, the result of the third pathologist was utilized and the final decision regarding the presence of hyperplasia was based on the diagnosis of the majority. If all three readings were disparate (each fell into a different category – Category 1, 2, or 3), the final diagnosis was based on the most severe of the three readings. A secondary analysis was performed utilizing the three pathologist reads as described in Section 9.5.4.2.1. If a woman was diagnosed with endometrial hyperplasia at any time during the trial, they were given appropriate treatment (progestogen) at the discretion of the investigator and every attempt to follow-up to resolution was made.

For unscheduled biopsies, the histological diagnosis of endometrial polyp did not require withdrawal, unless hyperplasia or atypical nuclei were present.

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Per the application, a supplemental secondary analysis was performed based on the results from the three pathologists. In this supplemental analysis, the final diagnosis was based on agreement of two of the three pathologists reads. Consensus was reached when two of the three pathologist readers agreed on any of the above categories. For example, any two subcategories of “Non-endometrial malignancy/non-hyperplasia” was classified as “Category 1: Non-endometrial malignancy/non-hyperplasia.” If all three readings were disparate (each fell into a different category – Category 1, 2, or 3), the final diagnosis was based on the most severe of the three readings.

### Clinical Reviewer’s Comments:

This reviewer considers the endometrial biopsy specimen diagnosis of three individual, independent pathologists to be the primary analysis, and not a supplemental secondary analysis. The 2003 draft Hormone Therapy Guidance for Industry recommends concurrent readings by three independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists is accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis.

See Subsection 8.5.1 of this review for a more detailed discussion of the reported endometrial safety findings.

### Other Secondary Endpoints (All Participants):

Other secondary endpoints included:

- Proportion of women with cumulative amenorrhea from Day 1 to Day 364
- No bleeding: percent by cycle and cumulative for consecutive 28-day cycles
- Number of days with bleeding/spotting

### Additional Safety Endpoints:

Overall safety variables included:

- Trial participant incidence of AEs and serious adverse events (SAEs)
- Trial participant incidence of endometrial polyps
- Change from Baseline in:
  - Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis [where applicable])
  - Vital signs
  - Physical examination findings
  - Body weight and BMI

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- Gynecological Examination (pelvic examination, Pap smear, and breast examination)
- Mammogram (BI-RADS)
- 12-lead ECG
- Hormone concentration levels for serum estradiol, estrone, and progesterone

### Statistical Analysis Plan (SAP):

Statistical analysis and programming of tables and listings was conducted by a designee of the sponsor, using SAS® Release 9.2 or higher (SAS Institute Inc, Cary, North Carolina, USA). The statistical analysis plan, version 1 for Trial TXC12-05, was submitted September 21, 2016; version 2 for Trial TXC12-05, was submitted November 15, 2016.

The overall Trial TXC12-05 sample size was based on the target that the combination therapy was effective at achieving a  $\leq 1\%$  incidence rate of endometrial hyperplasia following 12-months of therapy, and that the upper bound of the 95% confidence interval of the estimated incidence rate was  $\leq 4\%$ . The VMS subtrial sample size was based on the expected changes in average weekly frequency and severity of VMS from Baseline to Weeks 4 and 12.

The sample size for the VMS endpoint was based on the change in frequency and severity of hot flashes between the active treatment groups and placebo. All attempts were made to prevent any missing values. Each of the four active treatment groups and the four co-primary outcomes was compared to the placebo group in a hierarchical order to preserve the test level of significance for each comparison at 5% (two-sided). A Mixed Effect Model Repeat Measurement (MMRM) model was used for the final analysis, and a two-group t-test was used to estimate sample size requirements for the VMS subtrial.

### Datasets Analyzed:

- Safety Population - All women who were randomly assigned and had taken at least one capsule of trial medication formed the Safety population. Analysis was based on the actual treatment the women took on trial Day 1. Trial participants who were found to have participated in the trial twice with two separate randomization numbers were included in the AEs and endometrial safety summaries only.
- Endometrial Safety (ES) Population - The analysis population for endometrial safety is the ES population. An ES trial participant is all randomized trial participants who:
  - had taken at least one capsule of trial medication as documented (analysis was based on the actual treatment the trial participant took on trial Day 1);
  - had no major protocol violations (the medical monitor made the final decision on exclusion and the list was provided prior to unblinding);
  - had an acceptable biopsy at Baseline (at least one endometrial biopsy with evaluable tissue and no read of endometrial hyperplasia or cancer, or

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endometrial polyp with either hyperplasia, glandular atypia of any degree (for example, atypical nuclei) or cancer; and

- had an endometrial biopsy at Month 12 (defined as on or after trial Day 326) or had a diagnosis of endometrial hyperplasia prior to Month 12.

Participating women who had an endometrial malignancy were not included in the numerator or denominator of the incidence calculation, per the SAP. Participating women who were found to have participated in the trial twice with two separate randomization numbers were included in the AEs and endometrial safety summaries only.

The incidence rate of endometrial hyperplasia at Month 12 was calculated as follows:

$$I = A / B$$

Where I = incidence rate at Month 12 evaluation

A = all new participants with biopsies positive for endometrial hyperplasia during the study, but post-Baseline

B = all participants with biopsies following Month 11 meeting the criteria specified above, plus all participants with biopsies positive for endometrial hyperplasia by any of the pathologist before Month 11

An upper one-sided 95% confidence limit for the binomial proportion was calculated. In addition, 95% two-sided CIs were calculated for pairwise differences between groups in hyperplasia incidence.

- Modified Intent-to-Treat (MITT) Population - The overall MITT population was comprised of all randomized women who took at least one dose (two capsules, one active and one placebo) of trial medication. Analysis was based on the treatment group to which the woman was randomized. Trial participants who were found to have participated in the trial twice with two separate randomization numbers were excluded.
- MITT- VMS Population - The MITT – VMS population was the primary efficacy population. To be included in the MITT-VMS population, women must have been randomized to the VMS subtrial, had taken at least one dose (two capsules, one active and one placebo) of trial medication, and:
  - 1) had at least five (5) days of VMS diary data for Baseline measurement of frequency and severity of moderate to severe hot flushes; and
  - 2) had at least four (4) days of VMS diary data for one on-treatment week of reporting of frequency and severity of hot flushes following initiation of trial medication.

Analysis was based on the treatment group to which the woman was randomized.

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- Efficacy Evaluable (EE) – VMS - Trial participants were included in the EE-VMS population if they were randomized to the VMS subtrial, had taken at least one dose (two capsules, one active and one placebo) of trial medication, and:
  - 1) had at least seven per day or 50 per week moderate to severe hot flashes at Baseline;
  - 2) had no major protocol violations that could impact the VMS endpoint (the medical monitor made the final decision on exclusion and the list was provided by the sponsor prior to unblinding);
  - 3) had at least four (4) days of VMS diary data for one on-treatment week of reporting of frequency and severity of hot flashes following initiation of trial medication; and
  - 4) had no dispensing error (defined as a participant who initiated the trial with one treatment group but during the first 12-weeks of treatment inadvertently received an incorrect wallet from another randomization code).
- Bleeding Population - Trial participants who took at least one dose (two capsules, one active and one placebo) of trial medication and who had at least one post- Baseline bleeding/spotting diary entry comprised the bleeding population. Women evaluated included the safety population less any women who had no bleeding/spotting diary data. Bleeding data collected for the day on which an endometrial biopsy was performed, and for the six (6) days thereafter, was excluded for both cumulative and non-cumulative summaries. The last available data before the biopsy was performed was carried forward for those days (LOCF). The number of days with bleeding/spotting, as reported on subject diaries, was summarized by cycle and treatment group.

No bleeding was defined as absence of bleeding. Within each treatment group, the percent of women with no bleeding was calculated by cycle and for consecutive cycles and compared between active and placebo treatments.

Cumulative rates for no bleeding was defined as the percentage of women who reported consecutive cycles of no bleeding for a given cycle of time. For example, if a woman had no bleeding from Day 1 to Day 364, then this woman had no bleeding from the 1st to 13th cycle. The number and percentage of woman with no bleeding for each cumulative period was summarized separately for the 1st to 13th cycle, 2nd to 13th cycle, ..., and the 13th cycle.

### Efficacy Analysis:

All efficacy analyses were performed on the MITT-VMS and EE-VMS populations. The primary population was the MITT-VMS population and the secondary population for all efficacy analyses was the more restrictive EE-VMS population.

Four pair-wise comparisons were performed for Week 4 and Week 12 (co-primary) changes

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from Baseline:

- Combined 1 mg estradiol/100 mg progesterone formulation versus placebo
- Combined 0.5 mg estradiol/100 mg progesterone formulation versus placebo
- Combined 0.5 mg estradiol/50 mg progesterone formulation versus placebo
- Combined 0.25 mg estradiol/50 mg progesterone formulation versus placebo

Within each dose level/placebo comparison, there were four co-primary efficacy endpoints. The four co-primary endpoints were each tested at level alpha (0.05, two-tailed).

Within each active dose/placebo comparison, there were four co-primary endpoints:

- Mean change in frequency of moderate to severe VMS from Baseline to Week 4
- Mean change in frequency of moderate to severe VMS from Baseline to Week 12
- Mean change in severity of moderate to severe VMS from Baseline to Week 4
- Mean change in severity of moderate to severe VMS from Baseline to Week 12.

A gatekeeping (hierarchical) testing procedure was followed to account for the multiple comparisons of testing placebo to each of the four active doses of TX-001HR and the multiple testing of the four co-primary endpoints. The testing started by examining the highest dose (combined 1 mg estradiol plus 100 mg progesterone) for the co-primary endpoints. If the four p-values for the co-primaries were significant ( $p \leq 0.05$ ) then the hypothesis testing continued to the next dose (combined 0.5 mg estradiol plus 100 mg progesterone) for each of the co-primary endpoints, as described above. If at any point the hypothesis testing yielded a non-significant result, the testing was stopped. The gatekeeping procedure described was also followed for all secondary efficacy endpoint comparisons of each active treatment group with placebo.

The weekly number of moderate to severe hot flushes for each assessment week (Baseline, and Weeks 1 through Week 12) was derived as:

- Weekly Frequency = total number of moderate and severe hot flushes for the participant's week.

The weekly severity of hot flushes for the change in severity of moderate to severe vasomotor symptoms was derived as:

- Baseline Weekly Severity Score = (number of moderate hot flushes for 7 days) x 2 + (number of severe hot flushes for 7 days) x 3 / total number of moderate to severe hot flushes over 7 days.
- On Treatment Weekly Severity Score = (number of mild hot flushes for 7 days) x 1 + (number of moderate hot flushes for 7 days) x 2 + (number of severe hot flushes for 7 days) x 3 / total number of mild, moderate and severe hot flushes over 7 days).

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The weekly frequency of mild, moderate and severe hot flushes was calculated using the same method as for moderate to severe hot flushes but with the number of mild hot flushes added to the sum. Weekly severity of hot flushes for the change in severity of mild, moderate to severe VMS was derived in the same way as above except in the Baseline calculation, mild hot flushes were included. A weekly severity score of zero (0) was assigned for participants reporting no hot flushes for a given assessment week.

Absolute changes from baseline and respective differences from placebo in frequency and severity of VMS was listed and summarized. Means, SDs, minimum (MIN) and maximum (MAX) are provided for the co-primary efficacy endpoints. A mixed model repeated measure (MMRM) analysis was applied to the 12 weekly change scores. The model included Baseline as covariate, treatment, trial week, and treatment-by-trial week interaction as fixed factors, and participant as the repeated measure unit. Trial week pertained to the 12-individual weekly hot flushes frequency derivations. The variance-covariance matrix of the change scores over time was assumed to be unstructured. If the computation did not converge, the covariance structure was reduced from, in the order of, “unstructured (UN)”, “Toeplitz (TOEP)”, “autoregressive order 1 [AR(1)]” to “compound symmetry (CS)”. Ninety-five percent (95%), two-sided CIs were derived for least square (LS) mean changes from Baseline and respective differences from placebo for each dose and week. The gatekeeping procedure for the primary efficacy endpoints already described was used in the interpretation of P-values and the confidence intervals.

In addition to the principal MMRM analysis of the four co-primary endpoints, a sensitivity evaluation was also conducted using an analysis of covariance (ANCOVA); SAS generalized linear model utilizing last observation carried forward (LOCF). For women who discontinued the trial prior to Week 12 or who had missing data at Weeks 4 or 12, the last observed weekly hot flush frequency or severity value was carried forward to all visits through Week 12. Women who had no post-Baseline data were not included in the ANCOVA consideration (that is, there was no baseline observation carried forward application). The sensitivity evaluation was specifically designed to provide support for the MMRM; the primary MMRM approach was considered to have the most power for statistical inferences and was the principal *a priori* analysis method.

### Analysis of Secondary Efficacy - Frequency and Severity of VMS:

Similar to the continuous co-primary endpoints for Weeks 4 and 12, the same MMRM model was applied to the changes in frequency and severity of mild, moderate and severe vasomotor symptoms for each assessment week up to Week 12. The calculation for frequency and severity of hot flushes remained the same, with the exception that hot flushes of all severities was included.

### Responder Analysis:

Responders were defined as the percent of women with 50% and, separately, 75% reduction

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from Baseline in moderate to severe VMS at Week 12 compared between active and placebo treatments. These proportions were calculated and presented graphically. Simple comparisons of proportions using the Fisher's exact test were made for each active treatment group compared to placebo. The gatekeeping approach for the primary efficacy endpoints previously described was employed for the formulation of inferences concerning each comparison.

### Analysis of Secondary Efficacy:

- CGI: The number and percentage of women for each category of the CGI was summarized at Week 4, Week 8, and Week 12, with mean change in the frequency of moderate to severe VMS from Baseline summarized within each CGI category at Weeks 4, 8, and 12. Trial participants were asked to answer the question "Rate the total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to your condition at administration to the study, how much has it changed using the following scale:
  - Very much improved
  - Much improved
  - Minimally improved
  - No change
  - Minimally worse
  - Much worse
  - Very much worse"

Descriptive analyses were conducted to show the mean changes in frequency of moderate to severe VMS at 12 weeks by different categories of change based on the CGI. The analysis focused on Baseline to Week 12 changes for estimating minimal important differences and responder groups. The minimal important difference was defined based on CGI ratings of 'minimally improved' category, and clinically meaningful responders were defined based on CGI ratings of 'much improved' or 'very much improved' combined. The worsen/no change group was defined as consisting of those women reporting CGI ratings of 'no change' to 'very much worse'. Based on these CGI response groupings, a three-categorical variable was constructed and a nonparametric discriminate analysis was conducted utilizing bootstrapping methods.

- MENQOL: The MENQOL questionnaire assessed changes in quality of life of study subjects over a one-month period. It was self-administered and was measured at Baseline, Week 12, Month 6 and Month 12 during the trial. It is composed of 29 questions distributed across four domains: vasomotor, psychosocial, physical and sexual. Change from Baseline in monthly scores were summarized and described within each treatment group for the MITT-VMS population and the MITT population.
- MOS – Sleep: The MOS - Sleep self-report questionnaire is composed of 12 items that measure six dimensions of sleep over the past four weeks. It was self-administered and was measured at Baseline, Week 12, Month 6, and Month 12 during the trial. Change in

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scores over the past four weeks (total and subscales) were summarized within each treatment group for the MITT-VMS population and MITT populations separately. Most questions were scored with one of six numbers ranging from 1 (all of the time) to 6 (none of the time), indicating the frequency of various aspects of the disease-related sleep disruption over the preceding week. Women also estimated the average amount of sleep per night during the past week.

### Proportion of Subjects in the Safety Population with Cumulative Amenorrhea from Day 1 to Day 364:

Amenorrhea was defined as absence of bleeding or spotting. Within each treatment arm, the portion of women with cumulative amenorrhea from Day 1 to Day 364 was calculated and compared between active and placebo treatments. Cumulative rates of amenorrhea were defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time. For example, if a woman had no bleeding or spotting from Day 1 to Day 364, then this woman had cumulative amenorrhea from the 1st to 13th cycle. The number and percentage of women with amenorrhea for each cumulative period was summarized separately for the 1st to 13th cycle, 2nd cycle to 13th cycle, ..., and the 13<sup>th</sup> cycle.

### Protocol Amendments for Trial TXC12-05:

The original protocol (Version 1.0) was approved on February 18, 2013. Overall, five (5) protocol amendments were submitted (Amendment # 1 dated May 15, 2013, Amendment # 2 dated June 24, 2013, Amendment # 3 dated August 15, 2013, Amendment # 4 dated February 18, 2014, and Amendment # 5 dated June 3, 2014). The Clinical Study Report for Trial TXC12-05 included in the NDA application encompasses Protocol Amendment # 6.

## 6.1.2. Study Results

### Compliance with Good Clinical Practices

The Debarment Certification, dated November 15, 2017, signed by Christine Miller, PharmD, Chief Regulatory and Quality Officer, states “TherapeuticsMD, Inc hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.”

Data management responsibilities and all data were transferred from (b) (4) to (b) (4) in 2014. The data entry system (eCRF) was then managed by (b) (4) based on specifications from TherapeuticsMD. (b) (4) data management platform, (b) (4), was used to integrate the electronic data capture (EDC), data management (DM), Safety reporting, Interactive Web Response System (IWRS), and IP management. TherapeuticsMD, in conjunction with (b) (4) was responsible for coding the concomitant medications using the World Health Organization Drug Dictionary (WHODD) term per the

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March 1, 2014 release, medical history, and adverse events (AEs) using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. (b) (4) was responsible for maintaining records of drug medications received, dispensed, disposed on site, unused and returned.

Treatment Compliance:

The first day that trial medication was administered by the participant was considered Day 1 and all subsequent visits were based on this day. Compliance was determined from the participant's dosing diary. Participants were instructed to use the dosing diary to record all trial medication taken and missed. Each participant must have been at least 80% compliant with trial medication, based on dosing diary over each trial visit interval to be considered compliant. If a woman was less than 80% compliant, the investigator discussed withdrawing the woman with the medical monitor. When a participant's dosing diary was completely missing, the trial medication dispensing/return log was used to determine compliance. The date of Randomization was used as the first dose date. The last dose date was the earlier of the last visit date or the last date that trial medication could have been taken based on the number of capsules dispensed. The difference between the overall dispensed and overall returned was used as the total taken.

Participants were instructed to return completed trial diaries to trial personnel at their visits, which were reviewed with the participant to ensure proper documentation of trial medication dosing and other information recorded on the diary. In addition, trial personnel were responsible for recording the amount of trial medication returned, the amount of trial medication used, and the amount of trial medication unused on a drug accountability log. Discrepancies were documented as protocol deviations.

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Patient Disposition

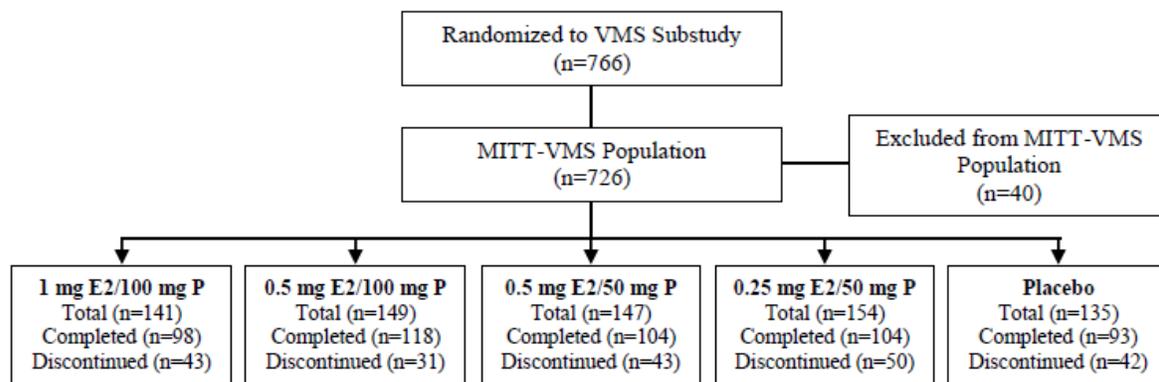
MITT-VMS Population:

The MITT-VMS population was the primary population for the efficacy assessment. Of the 766 postmenopausal women randomized to the VMS subtrial, 726 (94.8%) met the criteria to be included in the MITT-VMS population (see page 71 of this review for criteria). Forty (40) women were excluded for the following reasons:

- no Baseline VMS diary data only (n = 1; 0.1%);
- no Baseline VMS diary data and no post-Baseline VMS diary data (n = 2; 0.3%);
- no post-Baseline VMS diary data (n = 31; 4.0%);
- did not receive trial medication and no post-Baseline VMS diary data (n = 3; 0.4%);
- did not receive trial medication, no post-Baseline VMS diary data; and did not take two or more capsules (n = 2; 0.3%); and
- randomized twice into the study (n = 1; 0.1%)

Figure 2 shows the disposition of postmenopausal women in the MITT-VMS population.

Figure 1: Disposition of Postmenopausal women in the MITT-VMS Population in Trial TXC1-05



Source: Adapted from NDA 210132, Sub-module 5.3.5.1 TXC12-05 Study Report Body, Figure 4: Disposition of Subjects in the MITT-VMS Population, page 74 of 1539.

Definitions: MITT-VMS = modified Intent-to-Treat – vasomotor symptoms; E<sub>2</sub> = estradiol; P = progesterone.

Clinical Reviewer's Comments:

Overall, 71.2% (517 of 726 women in the MITT-VMS population) completed Trial TXC12-05. Discontinuation numbers are similar across treatment groups, with the 0.25 mg estradiol/50 mg progesterone treatment group showing the largest number of discontinuation. The 0.25 mg estradiol/50 mg progesterone treatment group is discussed further in information that follows.

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The most common reasons for discontinuation in the MITT-VMS population were: adverse event (8.5%), lost to follow-up (6.7%), woman withdrew consent (6.7%), protocol deviation (3.7%), lack of efficacy (2.6%), other (0.3%), and investigator/sponsor decision (0.1%). See Table 19.

Table 19: Disposition of the MITT-VMS Population for 52-Week Trial TXC12-05

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)	Total (N=726)
Number of subjects	98 (69.5)	118 (79.2)	104 (70.7)	104 (67.5)	93 (68.9)	517 (71.2)
Number of subjects discontinued, n (%)	43 (30.5)	31 (20.8)	43 (29.3)	50 (32.5)	42 (31.1)	209 (28.8)
Adverse Event	19 (13.5)	5 (3.4)	14 (9.5)	15 (9.7)	9 (6.7)	62 (8.5)
Investigator/ Sponsor Decision	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.1)
Lack of Efficacy	2 (1.4)	0 (0.0)	2 (1.4)	3 (1.9)	12 (8.9)	19 (2.6)
Lost to Follow-up	11 (7.8)	7 (4.7)	10 (6.8)	14 (9.1)	7 (5.2)	49 (6.7)
Protocol Deviation	7 (5.0)	3 (2.0)	4 (2.7)	8 (5.2)	5 (3.7)	27 (3.7)
Subject Withdrew Consent	4 (2.8)	15 (10.1)	11 (7.5)	10 (6.5)	9 (6.7)	49 (6.7)
Other	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.3)

Source: Adapted from NDA 210132, Submodule 5.3.5.1 TXC12-05, Subsection 10.1, Disposition of Subjects, Table 11, page 75 of 1539.

Definitions: MITT-VMS = modified Intent-to-Treat – vasomotor symptoms; E<sub>2</sub> = estradiol; P = progesterone.

Clinical Reviewer's Comments:

As shown in Table 19, adverse events as a reason for discontinuation were highest (14.5%) in the 1 mg estradiol/100 mg progesterone treatment group and lowest (3.4%) in the 0.5 mg estradiol/100 mg progesterone treatment group. These findings are difficult to understand, considering that the two lower dosage strength reported higher discontinuation rates.

EE-VMS Population:

Of the 766 postmenopausal women randomized to the VMS subtrial, 607 (79.2%) women met the EE-VMS criteria (see page 72 of this review) with consistency across all treatment groups. A total of 159 women (20.8%) who were randomized to the VMS subtrial were excluded. Most were excluded due to:

- compliance at Week 12 being < 80% (n = 66; 55.4%);

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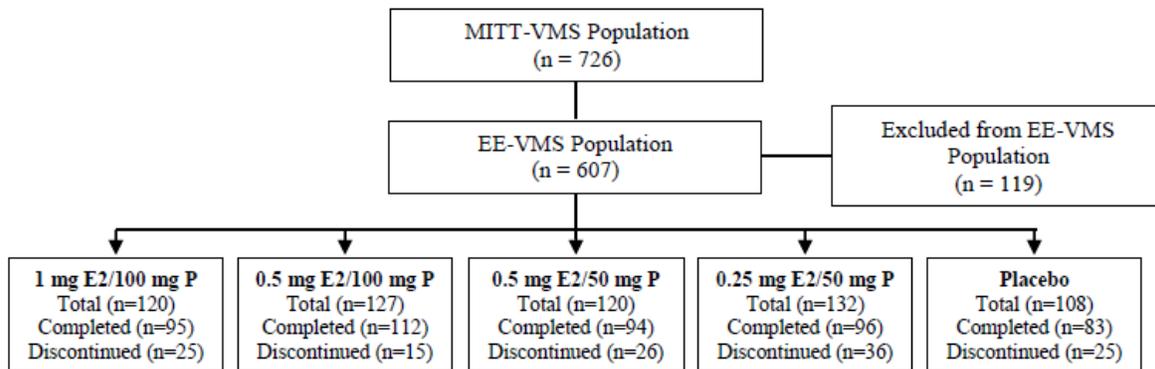
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- participant had received a prohibited medication (n = 31; 4.0%); and
- no post-Baseline VMS diary data and compliance < 80 % (n = 27; 3.5%).

See Figure 2.

Figure 2: Disposition of Postmenopausal Women in the EE-VMS Population



Source: Adapted from NDA 210132, Submodule 5.3.5.1 TXC12-05 Study Report Body, Figure 5: Disposition of Subjects in the EE-VMS Population, page 76 of 1539.

Definitions: mITT-VMS = modified Intent-to-Treat – vasomotor symptoms; EE-VMS = Efficacy Evaluable – Vasomotor Symptoms Population; E<sub>2</sub> = estradiol; P = progesterone.

Clinical Reviewer's Comments:

The EE-VMS population is a more restrictive population.

Overall, 79.1% of trial participants completed the 12-month Trial TXC12-05. The most common reasons for discontinuation were: adverse event (5.4%), lost to follow-up (5.4%), woman withdrew consent (5.4%), protocol deviation (2.6%), lack of efficacy (1.8%), and other (0.2%).

Safety Population:

A total of 1845 postmenopausal women were randomly assigned to treatment in phase 3 Trial TXC12-05; 1275 (69.1%) postmenopausal women completed the study. During the applicant's trial data review before database lock and unblinding, it was found that two (2) women were screened and randomized at two separate sites. Trial participant Number (b) (6) and trial participant Number (b) (6) and, separately, trial participant Numbers (b) (6) and (b) (6), were confirmed to be same. For analysis purposes, the first randomization number and treatment group for each woman was utilized (Number (b) (6) and Number (b) (6)). Both women were removed from efficacy analyses and counted once in the Safety population; however, adverse events and endometrial biopsy results (if applicable) collected from the second randomization were included in the full safety profile of the first randomization.

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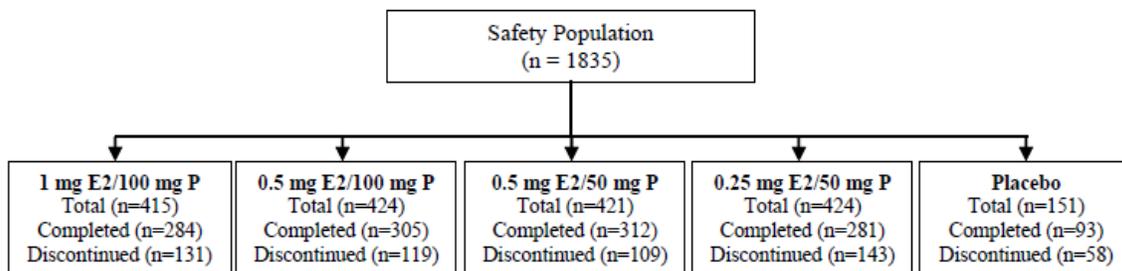
Clinical Reviewer's Comments:

This reviewer concurs with the removal of participants Number (b) (6) and Number (b) (6) from efficacy analyses; and with inclusion of these participants in the Safety population.

Ten (10) of the 1845 randomized women did not take any trial medication, resulting in 1835 randomized women who took at least one dose of trial medication.

The 1835 women who were randomized and took at least one dose of trial medication comprised the Safety population. See Figure 3.

Figure 3: Disposition of Postmenopausal Women in the Safety Population; Trial TXC12-05



Source: Adapted from NDA 210132, Sub-module 5.3.5.1 TXC12-05 Study Report Body, Figure 3: Disposition of Subjects in the Safety Population, page 73 of 1539.

Definitions: E<sub>2</sub> = estradiol; P = progesterone.

Of the 1835 women included in the Safety population, 1275 (69.5%) completed the study and 560 (30.5%) women discontinued prematurely. Overall, the most common reasons for early discontinuations were: AE (8.9%), woman withdrew consent (8.2%), lost to follow-up (7.5%), protocol deviation (3.2%), lack of efficacy (1.9%), investigator/sponsor decision (0.4%), and other (0.3%). See Table 20.

Table 20: Participant Disposition for 52-Week Trial TXC12-05 (Safety Population)

	1 mg E2 / 100 mg P (N=415)	0.5 mg E2 / 100 mg P (N=424)	0.5 mg E2 / 50 mg P (N=421)	0.25 mg E2 / 50 mg P (N=424)	Placebo (N=151)	Total (N=1835)
Number of Subjects	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)	1275 (69.5)
Number of subjects Discontinued, n (%)	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)	560 (30.5)
Adverse Event	46 (11.1)	33 (7.8)	34 (8.1)	41 (9.7)	10 (6.6)	164 (8.9)

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Investigator/ Sponsor Decision	1 (0.2)	3 (0.7)	2 (0.5)	2 (0.5)	0 (0.0)	8 (0.4)
Lack of Efficacy	5 (1.2)	4 (0.9)	4 (1.0)	10 (2.4)	12 (7.9)	35 (1.9)
Lost to Follow-up	27 (6.5)	30 (7.1)	26 (6.2)	38 (9.0)	17 (11.3)	138 (7.5)
Protocol Deviation	15 (3.6)	6 (1.4)	12 (2.9)	20 (4.7)	6 (4.0)	59 (3.2)
Subject Withdrew Consent	36 (8.7)	42 (9.9)	29 (6.9)	31 (7.3)	13 (8.6)	151 (8.2)
Other	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)	0 (0.0)	5 (0.3)

Source: Adapted from NDA 210132, Sub-section 10.1, Disposition of Subjects, Table 10, page 73 of 1539.

Definitions: E<sub>2</sub> = estradiol; P = progesterone.

Clinical Reviewer's Comments:

As shown in Table 20, the placebo treatment group had the highest incidence of lack of efficacy as a reason for discontinuation (7.9%). This is not unexpected. Of the four active treatment groups, the 0.25 mg estradiol/50 mg progesterone had the highest incidence of lack of efficacy as a reason for discontinuation (2.4%) compared to similar incidences (range 0.9% to 1,2 %) in the three higher dosage strength treatment groups. This too is not unexpected. This result offers support for the 0.25 mg estradiol/50 mg progesterone dosage strength as an ineffective dose to relieve moderate to severe VMS in postmenopausal women.

Endometrial Safety (ES) Population:

The ES population was the primary population for assessment of endometrial safety. Of the 1835 postmenopausal women in the Safety population, 1255 participants met the criteria for inclusion into the ES population and 580 subjects were excluded. Six (6) randomized women had insufficient tissue for evaluation on endometrial biopsy at Baseline (no endometrium identified/tissue insufficient for diagnosis for both reads) and 574 participants did not have a post-Baseline biopsy performed on or after trial Day 326 per protocol. See Figure 4.

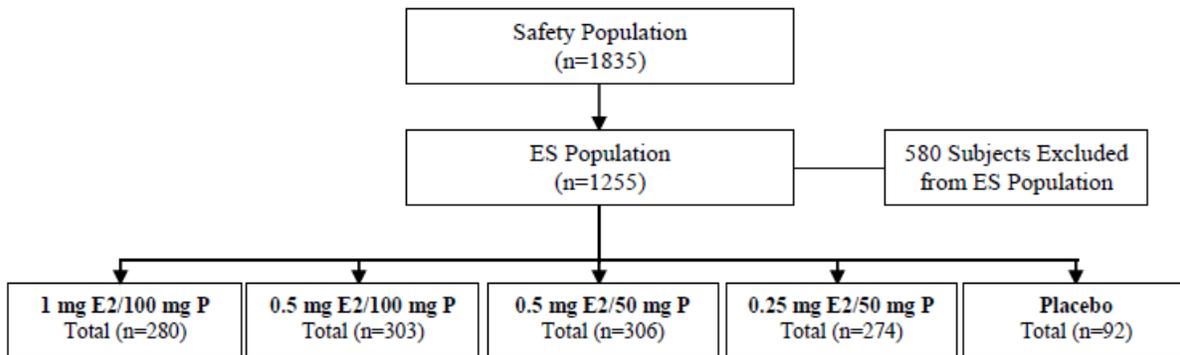
Figure 4: Disposition of Postmenopausal Women with Uteri in Trial TXC12-05

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Source: Adapted from NDA 210132, Sub-module 5.3.5.1 TXC12-05 Study Report Body, Figure 6: Disposition of Subjects in the ES Population, page 76 of 1539.

Definitions: E<sub>2</sub> = estradiol; P = progesterone.

Clinical Reviewer’s Comments:

A total of 580 women with a uterus enrolled in Trial TXC12-05 (32%, 580 of 1835 women in the Safety population) were not evaluated for endometrial safety. Six (6) women were excluded from the ES population because they did not have an evaluable endometrial biopsy at Baseline. Five hundred seventy-four (574) women were excluded from the ES population because they did not have a post-baseline endometrial biopsy performed on or after trial Day 326 (Month 12) per protocol. Valuable safety data was lost for this product as a result.

Protocol Violations/Deviations

Major protocol deviations for phase 3 Trial TXC12-05 are summarized in Table 21.

Table 21: Major Protocol Violations/Deviations in Trial TXC12-05

	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/50 mg P (N=4424)	Placebo (N=151)	Total (N=1835)
Trial participants with at least one major protocol violation/deviation	42 (10.1)	51 (12.0)	56 (13.3)	60 (14.2)	30 (19.9)	239 (13.0)
No readable endometrial biopsy at Screening	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.7)	1 (0.7)	6 (0.3)
Exclusionary blood pressure	0 (0.0)	5 (1.2)	4 (1.0)	4 (0.9)	1 (0.7)	14 (0.4)
Exclusionary mammogram	1 (0.2)	1 (0.2)	2 (0.5)	3 (0.7)	1 (0.7)	8 (0.4)
Exclusionary BMI	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hot flash requirement for VMS sub-trial not met	3 (0.7)	2 (0.5)	4 (1.0)	1 (0.2)	9 (6.0)	19 (1.0)
Dosing discrepancy <sup>a</sup>	1 (0.2)	3 (0.7)	3 (0.7)	5 (1.2)	1 (0.7)	13 (0.7)

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Trial drug overdose	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Low compliance with trial medication	7 (1.7)	4 (0.9)	9 (2.1)	7 (1.7)	1 (0.7)	28 (1.5)
Missed final endometrial biopsy	19 (4.6)	17 (4.0)	19 (4.5)	27 (6.4)	6 (4.0)	88 (4.8)
Missed final Pap smear	3 (0.7)	3 (0.7)	1 (0.2)	5 (1.2)	1 (0.7)	13 (0.7)
Missed final mammogram	12 (2.9)	16 (3.8)	7 (1.7)	10 (2.4)	5 (3.3)	50 (2.7)
Prohibited medication taken	5 (1.2)	9 (2.1)	7 (1.7)	9 (2.1)	11 (7.3)	41 (2.2)

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, 10.2 Protocol Deviations, Table 12, page 77 of 1539.

a Trial participant received treatment from a different group than what she was randomized to.

Abbreviations: E2 = estradiol; P = progesterone; BMI = body mass index; VMS = vasomotor symptoms;

Pap - Papanicolaou Smear

Clinical Reviewer's Comments:

As shown in Table 21, the largest number of protocol violations/deviations were due to missed final endometrial biopsy in Trial TXC12-05 (4.8%, 88 of 1835 women in the safety population). However, a total of 574 trial participants did not have an end-of-trial or early termination endometrial biopsy performed in Trial TXXC12-05, primarily due to refusal to undergo the procedure.

Table of Demographic Characteristics

Demographic characteristics for Trial TXC12-05 are summarized in Table 22.

Table 22: Selected Demographic and Baseline Characteristics for Safety Population in Phase 3 Trial TXC12-05

Demographic Parameters	Placebo Group (N=151)	Treatment Group				Total (N=1835)
		1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/50 mg P (N=424)	
Age (years)						
Mean (SD)	54.5 (4.32)	54.7 (4.37)	54.5(4.52)	54.9 (4.27)	54.4 (4.04)	54.6 (4.31)
Median (years)	54	55	54	55	54	54
Min, Max (years)	40, 65	40, 65	43, 66	41, 65	43, 65	40, 66
Race, n (%)						
White	100 (66.2)	271 (65.3)	281 (66.3)	276 (65.6)	273 (64.4)	1201 (65.4)
Black or African American	46 (30.5)	134 (32.3)	136 (32.1)	133 (31.6)	140 (33.0)	589 (32.1)
Other <sup>a</sup>	5 (3.3)	10 (2.4)	7 (1.6)	12 (2.8)	11 (2.6)	45 (2.4)
Weight (kg)						
Mean (SD)	71.4 (44.48)	72.1 (12.32)	71.7 (13.07)	72.2 (11.79)	72.1 (11.93)	72.0 (12.21)

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Median	71	72	72	72	73	72
Min, Max	45, 98	41, 106	39, 105	41, 110	41, 100	39, 110
BMI (kg/m <sup>2</sup> )						
Mean (SD)	26.63 (3.87)	26.81 (4.12)	26.67 (4.34)	26.74 (3.97)	26.72 (4.00)	26.72 (40.9)
Median	26.6	26.9	27.0	26.6	26.8	26.8
Min, Max	16.0, 34.1	15.2, 34.5	15.2, 34.5	15.5, 34.4	16.9, 34.3	14.0, 34.5

Source: Adapted from NDA 210132, TXC12-05 Study Report Body, Table 13, page 70 of 1539.

a Other includes; Other (n=20), Asian (n=12), American Indian or Alaska Native (n=6), Native Hawaiian or Pacific Islander (n=5), and Unknown (n=2).

Abbreviations: E2 == estradiol; P = progesterone; SD = standard deviation; Min = minimum; Max = maximum, BMI = body mass index.

### Clinical Reviewer's Comments:

Table 22 shows that trial participants demonstrated similar demographic characteristics across treatment groups. The overall mean age of trial participants was 54.6 years and ranged from 40 to 66 years.

Of interest, is the percent of women who self-identified as Black/African American trial participants (32.1%; 589 out of 1835 women in the Safety population). This is an unusually high percentage of such women in a VMS clinical trial, and is a credit to recruitment efforts on the part of the applicant.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The only pertinent Baseline characteristic in phase 3 Trial TXC12-05 MITT-VMS population is the time since last menstrual period. The median years since last menstrual period in the MITT-VMS population was 4.6 years for the 726 postmenopausal women enrolled, with a mean (SD) of 5.9 years (5.10) and a range of 5.2 years (4.75) in the 0.25 mg estradiol/50 mg progesterone treatment group to 6.5 (5.43) in the 0.5 mg estradiol/100 mg progesterone treatment group.

### Clinical Reviewer's Comments:

Overall, postmenopausal women participating in Trial TXC12-05 were recently menopausal.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

### Measurements of Treatment Compliance:

Treatment compliance at Week 12 was defined as the number of capsules taken between trial Day 1 and 84 divided by the number of capsules expected for the respective treatment period (168). The overall compliance was defined as the number of capsules taken between trial Day 1 and 364 divided by the number of capsules expected for the respective treatment period (728). Compliance was calculated for all trial participants regardless of whether the woman completed or discontinued the trial during the respective time periods.

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Treatment compliance, for the co-primary efficacy assessments, was defined as at least 80% of trial drug usage over the 12 weeks of VMS evaluation. Most trial participants (650 or 89.5%) took at least 80% of the expected number of capsules over the 12 weeks in the MITT-VMS population. The mean compliance was 92.5% and ranged from 90.6% (placebo group) to 91.2 to 93.8% for the active treatment groups. By definition, all women in the EE-VMS population were  $\geq 80\%$  compliant at Week 12 (mean compliance rate was 98%).

At Month 12, the overall compliance rate for the Safety population was 76.3%; the compliance for the placebo group (69.3%) was lower than for the treatment groups (75.0% to 79.5%). For the ES population, most women (97.6%) were  $\geq 80\%$  compliant over 12 months and the mean compliance rate was 96.4%.

Clinical Reviewer's Comments:

Relatively good treatment compliance was observed in Trial TXC12-05. Greater compliance in the trial medication treatment groups versus placebo would be anticipated.

Efficacy Results – Primary Endpoint

Four doses of TX-001HR were compared to placebo in phase 3 Trial TXC12-05. Within each dose/placebo comparison, there were four co-primary endpoints: 1) mean change in frequency of moderate to severe VMS from Baseline to Week 4; 2) mean change in frequency of moderate to severe VMS from Baseline to Week 12; 3) mean change in severity of moderate to severe VMS from Baseline to Week 4; and 4) mean change in severity of moderate to severe VMS from Baseline to Week 12. The four co-primary endpoints were each tested at level alpha (0.05, two-tailed). Ninety-five percent (95%), two-sided CIs were derived for least square (LS) mean changes from Baseline and respective differences from placebo for each dose and week.

To account for the multiple comparisons of testing placebo to each of the four active doses of TX-001HR and the multiple testing of the four co-primary endpoints, a gatekeeping (hierarchical) testing procedure was followed. The testing started by examining the highest dose (combined 1 mg estradiol/100 mg progesterone formulation) for the co-primary endpoints. If the four p-values for the co-primaries were significant ( $p \leq 0.05$ ) then the hypothesis testing continued to the next dose (combined 0.5 mg estradiol/100 mg progesterone formulation) for each of the co-primaries, as described above. If at any point the hypothesis testing yielded a non-significant result, the testing was stopped. The gatekeeping procedure for the primary efficacy endpoints already described was used in the interpretation of P values and the confidence intervals. The gatekeeping procedure described was also followed for all secondary efficacy endpoint comparisons of each active treatment group with placebo.

The most recent seven consecutive days of data prior to Randomization was used to determine

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the Baseline frequency and severity of hot flashes for each trial participant. The number of moderate to severe hot flashes from these seven days was also be used to determine eligibility for the VMS subtrial.

The weekly frequency of moderate to severe hot flashes was calculated from the daily diary records using a forward counting process of 7-day intervals beginning with the Baseline date. Diary data extending beyond 12 weeks (84 days) was excluded from this calculation. The weekly number of moderate to severe hot flushes for each assessment week (Baseline, and Weeks 1 through 12) was derived as:

Weekly Frequency = total number of moderate and severe hot flashes for the subject week

The weekly severity of hot flashes for the change in severity of moderate to severe vasomotor symptoms were derived as:

Baseline Weekly Severity Score = (number of moderate hot flashes for 7 days) x 2 + (number of severe hot flashes for 7 days) x 3/total number of moderate to severe hot flashes over 7 days.

**On Treatment Weekly Severity Score** = [(number of mild hot flashes for 7 days) x 1 + (number of moderate hot flashes for 7 days) x 2 + (number of severe hot flashes for 7 days) x 3/total number of mild, moderate and severe hot flashes over 7 days.

A weekly severity score of zero (0) was assigned for subjects reporting no hot flashes for a given assessment week.

A MMRM analysis, pre-specified in the protocol, was applied to the 12 weekly change scores. The model included Baseline as covariate, treatment, trial week, and treatment-by-trial week interaction as fixed factors, and trial participant as the repeated measure unit. Trial week pertained to the 12-individual weekly hot flashes frequency derivations.

A sensitivity evaluation was also conducted using an ANCOVA; SAS generalized linear model utilizing LOCF. For trial participants who discontinued the trial prior to Week 12 or who had missing data at Week 4 or 12, the last observed weekly hot flush frequency or severity value was carried forward to all visits through Week 12. Trial participants who had no post-Baseline data were not included in the analysis. The sensitivity evaluation was specifically designed to provide support for the MMRM; the primary MMRM approach was considered to have the most power for statistical inferences and was the principal *a priori* analysis method.

Baseline Efficacy Values for the MITT-VMS Population:

Table 23 provides the Baseline values for trial participants in the MITT-VMS population for the co-primary efficacy endpoints.

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Table 23: Baseline Values for Co-Primary Endpoints for MITT-VMS Population in Trial TXC12-05

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
Co-Primary Efficacy Endpoints					
Mean (SD) weekly number of moderate to severe VMS	74.4 (35.26)	72.1 (27.76)	75.9 (28.04)	77.0 (30.42)	72.4 (23.26)
Mean (SD) weekly severity score of moderate to severe VMS	2.54 (0.320)	2.51 (0.249)	2.50 (0.231)	2.51 (0.262)	2.52 (0.246)

Source: Adapted from NDA 210132 Clinical Study Report. Table 18, page 84 of 1539.

Abbreviations: MITT-VMS = modified intent to treat – vasomotor symptom; E2 = estradiol; P = progesterone; SD = standard deviation.

Clinical Reviewer's Comments:

Baseline similarities between treatment groups in Trial TXC12-05 are demonstrated in Table 23. The applicant is requesting approval of the 1 mg estradiol/100 mg progesterone (b) (4) for the treatment of moderate to severe vasomotor symptoms, due to menopause.

Weekly Number of Moderate to Severe VMS:

Baseline values, the mean changes from Baseline, and the LS mean change from placebo in the number of weekly moderate and severe VMS at Weeks 4 and 12 for the MITT-VMS population, analyzed by the MMRM method, are shown in Table 24.

Table 24: Change from Baseline and Placebo in the Mean Number of Weekly Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 for the MITT-VMS Population – Mixed Model Repeated Measures (MMRM) Method

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
Week 4 (n)	134	144	142	152	126
Baseline	72.1 (27.80)	72.3 (28.06)	75.2 (27.10)	77.3 (30.51)	72.3 (23.44)
Mean (SD) change from Baseline	-40.6 (30.59)	-35.1 (29.14)	-33.6 (30.64)	-38.9 (31.04)	-26.4 (27.05)
LS Mean (SE) change from placebo	-12.81 (3.30)	-8.07 (3.25)	-4.81 (3.26)	-10.40 (3.22)	---
MMRM P-value vs placebo	<0.001	0.013	0.141	0.001	---
Week 12 (n)	124	129	124	135	115
Baseline	72.2 (25.04)	72.8 (28.96)	75.4 (27.08)	76.5 (29.29)	72.2 (22.66)
Mean (SD) change from Baseline	-55.1 (31.36)	-53.7 (31.93)	-50.2 (31.35)	-52.4 (33.90)	-40.2 (29.79)

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LS Mean (SE) change from placebo	-16.58 (3.44)	-15.07 (3.39)	-10.79 (3.41)	-11.71 (3.36)	---
MMRM P-value vs placebo	<0.001	<0.001	0.002	<0.001	---

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report. Table 19, page 85 of 1539.

Abbreviations: MITT-VMS = modified intent to treat -vasomotor symptom; E2 = estradiol; P = progesterone; SD = standard deviation; LS = least square; SE = standard error; MMRM = mixed model repeated measures.

Clinical Reviewer's Comments:

Per Table 24, all active treatment groups in Trial TXC12-05 demonstrated a statistically significant reduction in the number of moderate to severe vasomotor symptoms at Week 4, except for the 0.5 mg estradiol/50 mg progesterone treatment group (p-value = 0.141). The mean change in moderate to severe VMS from Baseline to Week 4 for the active treatment groups ranged from -40.6 (1 mg estradiol/100 mg progesterone treatment group) to -33.6 (0.5 mg estradiol/50 mg progesterone treatment group) compared to -26.4 for the placebo treatment group. Table 24 also shows that the 0.25 mg estradiol/50 mg progesterone dosage strength performed better than the 0.5 mg estradiol/50 mg progesterone dosage strength. The ratio of estradiol/progesterone may have influenced this result.

By Week 12, all Trial TXC12-05 active treatment groups were statistically significantly different from placebo in reducing the number of moderate to severe VMS ( $p \leq 0.002$ ). The mean change from Baseline to Week 12 for the active treatment groups ranged from -55.1 for the 1 mg estradiol/100 mg progesterone treatment group to -50.2 for the 0.5 mg estradiol/50 mg progesterone treatment group compared with -40.2 for the placebo treatment group.

The Agency recommends that in addition to a statistically significant reduction in the treatment group when compared to placebo, a clinically meaningful threshold of a mean change of 2 moderate to severe vasomotor symptoms per day or 14 per week above placebo must be demonstrated at Week 4 maintained through Week 12.

The LS mean (SE) change from placebo, presented in the application, shows a difference of -12.81 (3.30) moderate to severe VMS at Week 4 for the 1 mg estradiol/100 mg progesterone dosage strength (less the 14 per week), and an LS mean (SE) change of -16.58 (3.44) at Week 12. Table 24 also shows an LS mean (SE) change from placebo of -8.07 (3.25) at Week 4 and -10.79 (3.41) at Week 12 for the 0.5 mg estradiol/100 mg progesterone dosage strength (less than 14 per week at both time points). The two lower dosage strengths (0.50 mg estradiol/50 mg progesterone or 0.25 mg estradiol/50 mg progesterone) also did not meet the 2 above placebo criteria at either time points. The applicant is only requesting approval of the 1 mg estradiol/100 mg progesterone

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The Statistical Reviewer had confirmed these reported findings in the NDA application.

The results of an analysis for the mean number of weekly moderate to severe VMS for each week from selected Week 1 through Week 12 is presented in the application as a secondary endpoint in Trial TXC12-05. The reported results from Week 4 through Week 12 are provided in Table 25.

Table 25: Change in Frequency of Moderate to Severe Vasomotor Symptoms from Baseline to Weeks 4 through 12 for the MITT-VMS Population – MMRM Method

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
Week 4 (n)	134	144	142	152	126
Mean (SD)	-40.6 (30.59)	-35.1 (29.14)	-33.6 (30.64)	-38.9 (31.04)	-26.4 (27.05)
LS Mean (SE) change from placebo	-12.81 (3.30)	-8.07 (3.25)	-4.81 (3.26)	-10.40 (3.22)	---
Week 5 (n)	131	143	139	147	124
Mean (SD)	-45.9 (32.31)	-39.5 (28.53)	-37.1 (30.64)	-43.5 (33.31)	-31.6 (28.96)
LS Mean (SE) change from placebo	-15.59 (3.35)	-9.88 (3.29)	-5.90 (3.31)	-12.05 (3.27)	---
Week 6 (n)	132	143	139	146	123
Mean (SD)	-49.4 (32.76)	-41.7 (29.97)	-40.1 (33.62)	-45.5 (33.14)	-32.7 (28.53)
LS Mean (SE) change from placebo	-17.81 (3.44)	-11.35 (3.39)	-7.82 (3.40)	-12.51 (3.36)	---
Week 7 (n)	130	142	139	147	120
Mean (SD)	-51.5 (31.51)	-45.0 (30.73)	-43.8 (33.20)	-47.7 (32.18)	-33.4 (29.37)
LS Mean (SE) change from placebo	-17.75 (3.41)	-13.29 (3.36)	-10.22 (3.37)	-13.61 (3.33)	---
Week 8 (n)	129	140	137	147	120
Mean (SD)	-52.3 (31.63)	-46.8 (30.64)	-45.4 (32.55)	-48.4 (32.82)	-36.0 (30.66)
LS Mean (SE) change from placebo	-16.63 (3.42)	-12.97 (3.37)	-9.63 (3.38)	-11.97 (3.34)	---
Week 9 (n)	124	137	132	141	119
Mean (SD)	-52.6 (32.57)	-50.5 (31.01)	-47.4 (30.13)	-50.1 (33.92)	-36.4 (29.09)
LS Mean (SE) change from placebo	-17.12 (3.40)	-15.58 (3.40)	-11.05 (3.36)	-13.02 (3.32)	---
Week 10 (n)	126	133	129	140	118
Mean (SD)	-53.2 (32.58)	-51.9 (32.79)	-49.0 (30.24)	-50.6 (33.36)	-37.1 (29.74)
LS Mean (SE) change from placebo	-16.80 (3.45)	-15.66 (3.40)	-11.20 (3.41)	-12.16 (3.37)	---
Week 11 (n)	126	134	129	137	118
Mean (SD)	-53.7 (32.21)	-52.0 (31.24)	-49.4 (30.71)	-50.9 (34.33)	-36.7 (30.32)

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LS Mean (SE) change from placebo	-18.11 (3.47)	-16.45 (3.42)	-12.41 (3.44)	-13.60 (3.39)	---
Week 12 (n)	124	129	124	135	115
Mean (SD)	-55.1 (31.36)	-53.7 (31.93)	-50.2 (31.35)	-52.4 (33.90)	-40.2 (29.79)
LS Mean (SE) change from placebo	-16.58 (3.44)	-15.07 (3.39)	-10.79 (3.41)	-11.71 (3.36)	---

Source: Adapted from NDA 210132, TXc12-05 Clinical Study Report, Table 14.2.2.1, page 613 of 1539.

LS mean difference from placebo derived from the MMRM model with Treatment, Week, Treatment-by-Week interaction as factors, Baseline as covariate, and Subject as repeated measures unit. Difference is estimated from the simple contrast between the least squares means.

Abbreviations: MITT-VMS = modified intent to treat -vasomotor symptom; E2 = estradiol; P = progesterone; SD = standard deviation; LS = least square; SE = standard error; MMRM = mixed model repeated measures.

Clinical Reviewer’s Comments:

It is evident in Table 25, using the application LS mean (SE) change from placebo, that only the 1 mg estradiol/100 mg progesterone dosage strength produces a clinical meaningful difference from placebo in reducing moderate to severe VMS beginning at Week 5 that is maintained through Week 12. The 0.5 mg estradiol/100 mg progesterone dosage strength (b) (4) does not show a LS mean (SE) change from placebo greater than 14 weekly hot flashes until Week 9, which is then maintained through Week 12.

The two lower doses of estradiol/progesterone (0.5 mg estradiol/50 mg progesterone and 0.25 mg estradiol/50 mg progesterone) failed to demonstrated a statistically significant reduction in VMS frequency at Weeks 4 and 12 or a clinically meaningful difference in frequency at either time point. The applicant has not requested approval of these two lower doses of combined estradiol/progesterone.

This reviewer determines that only the 1 mg estradiol/100 mg progesterone dosage strength demonstrates a statistically and clinically meaningful difference in the frequency of moderate to severe vasomotor symptoms at Week 5 (not Week 4) and Week 12. This reviewer supports the approval of the 1 mg estradiol/100 mg progesterone dosage strength at Week 5 and Week 12.

In the NDA application, an ANCOVA LOCF analysis was performed on the MITT-VMS population as a sensitivity analysis. Table 26 shows the ANCOVA LOCF mean number of weekly moderate to severe VMS for Week 4 through Week 12.

Table 26: Change in Frequency of Moderate to Severe Vasomotor Symptoms from Baseline to Weeks 4 through 12 for the MITT-VMS Population – ANCOVA LOCF

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
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Week 4 (n)	134	144	142	152	126
Mean (SD)	-39.0 (30.99)	-34.4 (28.93)	-32.5 (30.72)	-38.7 (30.89)	-26.6 (27.31)
LS Mean (SE) change from placebo	-11.58 (3.28)	-7.97 (3.23)	-4.51 (3.25)	-10.19 (3.21)	---
Week 5 (n)	131	143	139	147	124
Mean (SD)	-44.3 (32.80)	-38.9 (28.30)	-36.2 (30.50)	-43.1 (32.90)	-29.2 (30.02)
LS Mean (SE) change from placebo	-14.17 (3.28)	-9.92 (3.24)	-5.36 (3.25)	-11.62 (3.22)	---
Week 6 (n)	132	143	139	146	123
Mean (SD)	-47.4 (33.35)	-41.3 (29.82)	-39.9 (33.41)	-44.6 (32.74)	-30.1 (29.62)
LS Mean (SE) change from placebo	-16.27 (3.36)	-11.44 (3.31)	-7.16 (3.33)	-12.13 (3.29)	---
Week 7 (n)	130	142	139	147	120
Mean (SD)	-48.5 (33.48)	-44.5 (30.50)	-42.6 (33.13)	-46.9 (31.92)	-31.0 (30.57)
LS Mean (SE) change from placebo	-16.44 (3.32)	-13.68 (3.28)	-9.69 (3.29)	-13.40 (3.26)	---
Week 8 (n)	129	140	137	147	120
Mean (SD)	-49.6 (32.46)	-46.3 (30.24)	-44.1 (34.35)	-47.5 (32.56)	-33.2 (31.60)
LS Mean (SE) change from placebo	-15.21 (3.32)	-13.27 (3.28)	-8.92 (3.29)	-11.68 (3.26)	---
Week 9 (n)	124	137	132	141	119
Mean (SD)	-50.5 (33.87)	-49.8 (30.39)	-46.1 (32.49)	-49.2 (33.51)	-33.8 (30.98)
LS Mean (SE) change from placebo	-15.50 (3.30)	-16.13 (3.26)	-10.27 (3.27)	-12.74 (3.23)	---
Week 10 (n)	126	133	129	140	118
Mean (SD)	-51.2 (34.00)	-50.7 (31.81)	-47.1 (32.59)	-49.3 (33.25)	-34.7 (31.66)
LS Mean (SE) change from placebo	-15.29 (3.33)	-16.25 (3.29)	-10.40 (3.30)	-11.96 (3.27)	---
Week 11 (n)	126	134	129	137	118
Mean (SD)	52.3 (33.72)	50.9 (30.51)	47.8 (33.09)	50.1 (34.11)	34.1 (31.93)
LS Mean (SE) change from placebo	-17.05 (3.34)	-16.99 (3.30)	-11.59 (3.31)	-13.22 (3.27)	---
Week 12 (n)	124	129	124	135	115
Mean (SD)	-53.4 (32.93)	-52.0 (30.85)	-48.6 (33.25)	-50.7 (34.06)	-36.4 (31.95)
LS Mean (SE) change from placebo	-15.83 (3.32)	-15.84 (3.28)	-10.12 (3.29)	-11.60 (3.26)	---

Source: Adapted from NDA 210132, TXc12-05 Clinical Study Report, Table 14.2.2.1, page 613 of 1539.

Clinical Reviewer's Comment:

The Statistical Reviewer prepared and provided the data shown in Table 26 in an email communication dated September 25, 2018. The ANCOVA LOCF results in Table 26 are similar to those shown in Table 25 for the MMRM analyses for the mean change from placebo in the weekly number of moderate to severe VMS for Week 4 through Week 12.

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Weeks 4, 5, 9, and 12 are summarized below for the 1 mg estradiol/100 mg progesterone dosage strength and the 0.5 mg estradiol/100 mg progesterone dosage strengths (b) (4) :

1 mg/100 mg			0.5 mg/100 mg		
Week 4:	MMRM:	-12.81 (3.30)	MMRM:	-8.07 (3.25)	
	LOCF:	-11.58 (3.28)	LOCF:	-7.97 (3.23)	
Week 5:	MMRM:	-15.59 (3.35)	MMRM:	-9.88 (3.29)	
	LOCF:	-14.17 (3.28)	LOCF:	-9.92 (3.24)	
Week 9:	MMRM:	-17.12 (3.40)	MMRM:	-15.58 (3.40)	
	LOCF:	-15.50 (3.30)	LOCF:	-16.13 (3.26)	
Week 12:	MMRM:	-16.58 (3.44)	MMRM:	-15.07 (3.39)	
	LOCF:	-15.83 (3.32)	LOCF:	-15.84 (3.28)	

The ANCOVA LOCF analysis also supports the approval of the 1 mg estradiol/100 mg progesterone dosage strength at Week 5 and Week 12.

Mean Weekly Severity Score:

Baseline values, mean changes from Baseline, and the LS mean change from placebo in the severity of weekly moderate and severe VMS at Weeks 4 and 12 for the MITT-VMS population are presented in Table 27.

Table 27: Change from Baseline and Placebo in the Mean Weekly Severity Scores of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 for the MITT-VMS Population – MMRM Method

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
Week 4 (n)	134	144	142	152	126
Baseline	2.54 (0.325)	2.51 (0.248)	2.50 (0.230)	2.51 (0.259)	2.52 (0.249)
Mean (SD) change from Baseline	-0.48 (0.547)	-0.51 (0.563)	-0.40 (0.469)	-0.44 (0.514)	-0.34 (0.386)
LS Mean (SE) change from placebo	-0.13 (0.061)	-0.17 (0.060)	-0.05 (0.060)	-0.10 (0.059)	---
MMRM P-value vs placebo	0.031	0.005	0.401	0.100	---
Week 12 (n)	124	129	124	135	115
Baseline	2.55 (0.235)	2.51 (0.248)	2.50 (0.235)	2.50 (0.254)	2.52 (0.245)
Mean (SD) change from Baseline	-1.12 (0.963)	-0.90 (0.783)	-0.76 (0.744)	-0.71 (0.806)	-0.56 (0.603)
LS Mean (SE) change from placebo	-0.57 (0.100)	-0.39 (0.099)	-0.24 (0.100)	-0.16 (0.098)	---
MMRM P-value vs placebo	<0.001	<0.001	0.018	0.096	---

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study report. Table 20, page 87 of 1539.

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Abbreviations: MITT-VMS = modified intent to treat -vasomotor symptom; E2 = estradiol; P = progesterone; SD = standard deviation; LS = least square; SE = standard error; MMRM = mixed model repeated measures.

Clinical Reviewer's Comments:

The mean reduction in severity of moderate to severe VMS was statistically significant for the 1 mg estradiol/100 mg progesterone and the 0.5 mg estradiol/100 mg progesterone dosage strengths at both Weeks 4 and 12. The two lower doses of estradiol/progesterone (0.5 mg estradiol/50 mg progesterone and 0.25 mg estradiol/50 mg progesterone) failed to demonstrate a statistically significant reduction in VMS severity at Week 4, with only the 0.5 mg estradiol/50 mg progesterone treatment group demonstrating a statistically significant difference at Week 12. The inconsistency in performance for the two lower doses in Trial TXC12-05 demonstrates that one or both lower doses are ineffective doses for an indication for the treatment of moderate to severe vasomotor symptoms due to menopause.

The Statistical Reviewer had confirmed these reported findings in the NDA application.

Subgroup Analyses:

Age Subgroup Analysis: < 55 Years and ≥ 55 Years:

Overall, in Trial TXC12-05, Baseline frequency of moderate to severe hot flashes tended to be numerically higher in the < 55 years of age group [ranged from mean (SD) of 71.7 (29.43) to 79.4 (34.60)] than in the ≥ 55 years of age group [ranged from mean (SD) of 70.4 (24.39) to 72.4 (26.21)], consistent with the typical age of onset of VMS (median age among white women from industrialized countries ranges between 50 and 52 years<sup>8</sup>).

In the < 55 years of age group, Trial TXC12-05 reports a statistically significant reduction in hot flash frequency for the 1 mg estradiol/100 mg progesterone treatment group (MMRM p-value versus placebo = 0.007) and the 0.25 mg estradiol/50 mg progesterone treatment group (MMRM p-value versus placebo = 0.005) at Week 4. However, at Week 12, all four treatment groups show a statistically significant reduction in the frequency of hot flashes in the < 55 years of age group. In the ≥ 55 years of age group, similar results are reported, except that only the 1 mg estradiol/100 mg progesterone treatment group was statistically significant at Week 4, while all treatment groups were statistically significant at Week 12.

Likewise, Baseline moderate to severe hot flash severity was numerically higher in the < 55 years of age group [ranged from mean (SD) of 2.50 (0.222) to 2.55 (0.369)] than in the ≥ 55 years of age group [ranged from mean (SD) of 2.48 (0.269) to 2.53 (0.269)].

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<sup>8</sup> Gold EB, The Timing of the Age at which Natural Menopause Occurs. *Obstet Gynecol Clin North Am.* 2011;38(3):425-440.

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In the < 55 years of age group, no treatment group in Trial TXC12-05 shows a statistically significant reduction in hot flash severity at Week 4, and only the 1 mg estradiol/100 mg progesterone dosage strength shows a statistically significant reduction on hot flash severity at Week 12 (MMRM p-value versus placebo = <0.001). For the ≥ 55 years of age group, reported results indicate that, at Week 4, only the 0.5 mg estradiol/100 mg progesterone dosage strength was statistically significant (MMRM p-value versus placebo = 0.004), and that the two higher doses (1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone) were statistically significant in reduction of hot flash severity at Week 12.

**Clinical Reviewer's Comments:**

These inconsistent age subgroup findings are difficult to interpret and do not provide clear evidence of age subgroup effect on the frequency and severity of moderate to severe vasomotor symptoms.

It appears, however, that the 1 mg estradiol/100 mg progesterone dosage strength provides the most consistency in response. This is supportive for this clinical reviewer's recommendation for approval of this dosage strength.

**BMI Subgroup Analyses: < 25 kg/m<sup>2</sup>, ≥ 25 to 30 kg/m<sup>2</sup>, and ≥ 30 kg/m<sup>2</sup>:**

Overall, numerically larger reductions in VMS frequency and severity were observed in the active treatment groups in Trial TXC12-05 compared to placebo. Trial TXC12-05 reports statistical significant difference, as follows, for Weeks 4 and 12 for the 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone, versus the placebo treatment group.

Table 28: Change from Baseline and LS mean Change from Placebo in the Frequency and Severity of Weekly Moderate to Severe VMS at Week 4 and Week 12 by BMI (MITT-VMS Population)

Treatment	Frequency			Severity		
	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	Placebo (N=135)	1 mg E2/ 100 mg P (N=147)	0.5 mg E2/ 100 mg P (N=154)	Placebo (N=135)
<b>BMI &lt; 25 kg/m<sup>2</sup></b>						
<b>Baseline (n)</b>	<b>54</b>	<b>49</b>	<b>46</b>	<b>54</b>	<b>49</b>	<b>46</b>
Mean (SD)	80.4 (45.38)	69.0 (21.44)	73.0 (20.76)	2.53 (0.246)	2.53 (0.270)	2.48 (0.267)
<b>Week 4 (n)</b>	<b>50</b>	<b>46</b>	<b>43</b>	<b>50</b>	<b>46</b>	<b>43</b>
Mean (SD) change from Baseline	-40.9 (30.18)	-30.8 (24.74)	-21.7 (23.88)	-0.51 (0.522)	-0.46 (0.540)	---
LS Mean (SE) change from placebo	-14.16 (5.52)	-7.94 (5.66)	---	-0.22 (0.098)	-0.18 (0.100)	---
MMRM P-value vs placebo	0.011	0.162	---	0.024	0.072	---
<b>Week 12 (n)</b>	<b>48</b>	<b>43</b>	<b>42</b>	<b>48</b>	<b>43</b>	<b>42</b>

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Mean (SD) change from Baseline	-56.8 (30.18)	-47.9 (28.67)	---	-1.08 (0.992)	-0.86 (0.745)	---
LS Mean (SE) change from placebo	-18.78 (6.02)	-14.66 (6.18)	---	-0.61 (0.163)	-0.42 (1.167)	---
MMRM P-value vs placebo	0.002	0.019	---	< 0.001	0.014	---
<b>BMI ≥25 kg/m<sup>2</sup> to &lt; 30 kg/m<sup>2</sup></b>						
<b>Baseline (n)</b>	<b>56</b>	<b>55</b>	<b>61</b>	<b>56</b>	<b>55</b>	<b>61</b>
Mean (SD)	73.5 (23.05)	70.3 (30.29)	70.5 (25.37)	2.61 (0.239)	2.46 (0.253)	2.54 (0.238)
<b>Week 4 (n)</b>	<b>54</b>	<b>53</b>	<b>57</b>	<b>54</b>	<b>53</b>	<b>57</b>
Mean (SD) change from Baseline	-44.1 (33.22)	-33.1 (28.38)	-28.9 (26.54)	-0.53 (0.532)	-0.45 (0.548)	-0.38 (0.415)
LS Mean (SE) change from placebo	-14.71 (5.00)	-4.21 (5.00)	---	-0.15 (0.091)	-0.07 (0.091)	---
MMRM P-value vs placebo	0.004	0.400	---	0.097	0.465	---
<b>Week 12 (n)</b>	<b>49</b>	<b>45</b>	<b>51</b>	<b>49</b>	<b>45</b>	<b>51</b>
Mean (SD) change from Baseline	-54.8 (29.24)	-49 (32.22)	---	-0.21 (0.972)	-0.70 (0.672)	-0.65 (1.705)
LS Mean (SE) change from placebo	-15.79 (5.03)	-8.55 (5.04)	---	-0.61 (0.156)	-0.19 (0.157)	---
MMRM P-value vs placebo	0.002	0.091	---	< 0.001	0.220	---
<b>BMI ≥ 30 kg/m<sup>2</sup></b>						
<b>Baseline (n)</b>	<b>31</b>	<b>45</b>	<b>28</b>	<b>31</b>	<b>45</b>	<b>28</b>
Mean (S)	65.6 (32.30)	77.6 (30.32)	75.7 (22.72)	2.44 (0.498)	2.56 (0.212)	2.55 (0.449)
<b>Week 4 (n)</b>	<b>30</b>	<b>45</b>	<b>26</b>	<b>30</b>	<b>45</b>	<b>26</b>
Mean (SD) change from Baseline	-33.8 (25.77)	-41.8 (33.35)	-28.7 (32.62)	-0.35 (0.606)	-0.64 (0.594)	-0.38 (0.449)
LS Mean (SE) change from placebo	-10.64 (6.90)	-13.12 (6.35)	---	0.00 (0.135)	.027 (0.124)	---
MMRM P-value vs placebo	0.125	0.041	---	0.974	0.033	---
<b>Week 12 (n)</b>	<b>27</b>	<b>41</b>	<b>22</b>	<b>27</b>	<b>41</b>	<b>22</b>
Mean (SD) change from Baseline	-52.7 (36.98)	-63.9 (33.16)	---	-1.02 (0.913)	-1.14 (0.882)	-0.51 (0.536)
LS Mean (SE) change from placebo	-16.39 (7.15)	-23.20 (6.58)	---	-0.47 (0.212)	-0.65 (0.195)	---
MMRM P-value vs placebo	0.023	<0.001)	---	0.029	0.001	---

Source: Adapted from NDA 210132, Clinical Study Report, Table 32, page 107 of 1539; and Table 33, page 109 of 1539.

Abbreviations: LS = least square; MITT-VMS = modified intent to treat – vasomotor symptoms; E2 = estradiol; P = progesterone; SD = standard deviation; MMRM = mixed model repeated measures.

See Table 32 and Table 33 in NDA 210132 Clinical Study Report in the application to see the

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reported results for the 0.5 mg estradiol/50 mg progesterone and 0.25 mg estradiol/50 mg progesterone treatment groups.

Clinical Reviewer's Comments:

No conclusion can be drawn for these inconsistent findings regarding BMI subgroups in phase 3 Trial TXC12-05. Once again, the most consistent positive findings are in the 1 mg estradiol/100 mg treatment group (requested for approval), primarily at Week 12. This is supportive for this clinical reviewer's recommendation for approval of this dose.

Race Subgroup Analyses:

In phase 3 Trial TXC12-05, 65 percent of trial participants were White (1201 of 1835 trial participants), 32.1 percent were women who self-identified as Black or African American (589 of 1835 trial participants), and 2.4 percent were women who self-identified as Other (including Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander) (45 of 1835 trial participants). Baseline, the mean change from Baseline, and the LS mean change from placebo in the number (frequency) and severity of moderate to severe VMS are presented in the application for the White and Black/African American populations. Per the applicant, the Other category is not presented due to the small number of trial participant in this category.

Table 29 shown the change from Baseline and the LS mean change from placebo for the number of moderate to severe VMS at Week 4 and 12 for these two selected race categories.

Table 29: Change from Baseline and LS Mean Change from Placebo in the Frequency of Weekly Moderate to Severe VMS at Week 4 and Week 12 by Race (MITT-VMS Population)

Treatment	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
<b>White</b>					
Baseline (n)	95	99	99	102	91
Mean (SD)	73.8 (27.83)	72.9 (31.04)	75.6 (28.49)	75.6 (31.15)	71.9 (21.73)
Week 4 (n)	90	96	97	102	87
Mean (SD) change from Baseline	-44.0 (28.93)	-37.2 (30.69)	-35.5 (25.95)	-37.3 (31.51)	-24.4 (22.81)
LS Mean (SE) change from placebo	-18.07 (3.74)	-12.35 (3.70)	-9.42 (3.69)	-11.45 (3.66)	---
MMRM P-value vs placebo	<0.001	<0.001	0.011	0.002	---
Week 12 (n)	84	84	88	92	79
Mean (SD) change from Baseline	-59.4 (30.47)	-56.1 (34.63)	-53.5 (28.01)	-50.7 (35.04)	-36.7 (29.66)
LS Mean (SE) change from placebo	-23.98 (3.96)	-20.01 (3.92)	-16.57 (3.90)	-13.35 (3.87)	---
MMRM P-value vs placebo	<0.001	<0.001	<0.001	<0.001	---

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Black or African American					
Baseline (n)	45	48	43	48	41
Mean (SD)	75.4 (47.93)	70.0 (19.56)	77.2 (28.55)	77.6 (28.11)	74.6 (27.01)
Week 4 (n)	43	46	41	46	37
Mean (SD) change from Baseline	-32.5 (32.47)	-30.9 (26.03)	-31.1 (39.69)	-40.5 (30.19)	-32.1 (34.94)
LS Mean (SE) change from placebo	-0.55 (6.60)	1.10 (6.49)	3.73 (6.67)	-6.87 (6.50)	---
MMRM P-value vs placebo	0.933	0.866	0.576	0.292	---
Week 12 (n)	39	43	32	41	34
Mean (SD) change from Baseline	-45.3 (31.56)	-50.1 (26.09)	-42.1 (38.56)	-54.2 (29.53)	-48.8 (29.27)
LS Mean (SE) change from Baseline	0.24 (6.59)	-5.68 (6.46)	1.85 (6.72)	-7.71 (6.50)	---
MMRM P-value vs placebo	0.971	0.380	0.783	0.237	---

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 34, page 111 of 1539.

Abbreviations: MITT-VMS = modified intent-to-treat-vasomotor symptoms; E2 = estradiol; p = progesterone; SD = standard deviation; LS = least square; SE = standard error; MMRM = mixed model repeated measures.

Clinical Reviewer's Comments:

When the data from Trial TXC12-05 is analyzed by race subgroup, participants who self-identified as Black/African American demonstrated no effectiveness in any of the treatment group at Weeks 4 and 12 (no p-value was statistically significant at Week 4 or Week 12 in this race subgroup) for reduction in the number of moderate to severe hot flashes. Per the applicant, the large placebo response (reduction of 48.8 moderate to severe VMS) influenced these reported results.

Table 30 shown the change from Baseline and the LS mean change from placebo for the severity of moderate to severe VMS at Week 4 and 12 for these two selected race categories.

Table 30: Change from Baseline and LS Mean Change from Placebo in the Severity of Weakly Moderate to Severe VMS at Week 4 and Week 12 (MITT-VMS Population)

Treatment	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
<b>White</b>					
Baseline (n)	95	99	99	102	91
Mean (SD)	2.56 (0.255)	2.53 (0.247)	2.48 (0.231)	2.51 (0.257)	2.52 (0.267)
Week 4 (n)	90	96	97	102	87
Mean (SD) change from Baseline	-0.54 (0.537)	-0.53 (0.622)	0.39 (0.472)	-0.41 (0.496)	-0.28 (0.347)
LS Mean (SE) change from placebo	-0.25 (0.075)	-0.25 (0.074)	-0.09 (0.0730)	-0.12 (0.073)	---

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MMRM P-value vs placebo	0.001	<0.001	0.199	0.091	---
Week 12 (n)	84	84	88	92	79
Mean (SD) change from Baseline	-1.13 (0.954)	-0.90 (0.820)	-0.83 (0.767)	-0.68 (0.824)	-0.53 (0.579)
LS Mean (SE) change from placebo	-0.66 (0.125)	-0.43 (0.124)	-0.34 (0.123)	-0.16 (0.122)	---
MMRM P-value vs placebo	<0.001	<0.001	0.005	0.188	---
Black or African American					
Baseline (n)	45	48	43	48	41
Mean (SD)	2.52 (0.427)	2.48 (0.245)	2.54 (0.241)	2.49 (0.267)	2.52 (0.203)
Week 4 (n)	43	46	41	46	37
Mean (SD) change from Baseline	-0.35 (0.546)	-0.49 (0.421)	-0.43 (0.482)	-0.52 (0.560)	-0.51 (0.427)
LS Mean (SE) change from placebo	0.14 (0.103)	-0.01 (0.101)	0.08 (0.104)	-0.05 (0.101)	---
MMRM P-value vs placebo	0.181	0.946	0.428	0.634	---
Week 12 (n)	39	43	32	41	34
Mean (SD) change from Baseline	-1.06 (0.991)	-0.93 (0.716)	-0.83 (0.594)	-0.81 (0.780)	-0.63 (0.656)
LS Mean (SE) change from Baseline	-0.38 (0.171)	-0.36 (0.167)	0.06 (0.176)	-0.22 (0.169)	---
MMRM P-value vs placebo	0.028	0.033	0.747	0.197	---

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 34, page 111 of 1539.

Abbreviations: MITT-VMS = modified intent-to-treat-vasomotor symptoms; E2 = estradiol; p = progesterone; SD = standard deviation; LS = least square; SE = standard error; MMRM = mixed model repeated measures.

Clinical Reviewer's Comments:

Inconsistent results are reported in women who self-identified as Black/African American for the reduction in the severity of moderate to severe VMS. Here, both the 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone dosage strengths show a statistically significant reduction in severity of moderate to severe VMS but only at Week 12 and not at Week 4. The two lower doses in Trial TXC12-05 do not show a statistically significant reduction severity at either timepoint. (b) (4)

On June 20, 2018, the Statistical Reviewer requested the following by-race subgroup analyses because the overall Trial TXC12-05 results demonstrated that the treatment effects for the co-primary efficacy endpoints between participants who self-identified as White and Black or African American are very different, and are driven by the data collected in White trial participants:

- Examine the trial data and identify if there are any possible outliers that have significant impact on the trial efficacy results. If so, conduct sensitivity analyses excluding these outliers.
- Compare the baseline characteristics between racial subgroups of self-identified White and self-identified Black women.

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- Analyze the compliance rate by race for overall trial.
- Conduct detailed analysis by site to see if there are any specific sites that may have caused the difference. For each site:
  - Perform subgroup analysis of the co-primary efficacy endpoints by race.
  - Provide compliance rate by race.

In addition to the requested analysis above, explore any other possible factors that may explain the efficacy difference by race.

On July 11, 2018, the applicant provided a Clinical Information Amendment including the requested specified statistical analyses. The following is a summary of the results of the analyses provided by the applicant:

1. A meaningful site specific analysis could not be performed, due to the small number of women per site in each treatment group. Efficacy for race and site was only evaluated in six (6) sites that enrolled greater than 20 women.
2. In Trial TXC12-05, 31% of the efficacy population was Black/African American.
3. There was a high placebo response in the overall trial that was significantly greater in the Black/African American subgroup than the White subgroup ( $p=0.049$ ).
4. Statistically significantly more Black/African American women were current smokers than White women (34.2% versus 18.9%;  $p<0.0001$ ) for the overall population.
5. White women reported more current alcohol use at a statistically significant greater rate than women who self-identified as Black/African American women (63.2% versus 50.7%;  $p=0.0016$ ).
6. 32.4% of the Black/African American women had a BMI  $\geq 30$  kg/m<sup>2</sup> versus 18.7% of White women.
7. Baseline estradiol concentrations were numerically higher in the Black/African American women than in White women ( $\sim 6.6$  versus 5.5 pg/mL).
8. Numerically more Black/African American women were < 80% compliant with taking trial drug at Week 12 than White women (13.3% versus 8.8%) and were statistically less likely to complete their efficacy diaries.
9. MITT-VMS population was analyzed to identify outliers based on change from Baseline to Weeks 4 and 12 in weekly frequency and severity of moderate to severe VMS. Using the interquartile range (IQR) rule for outliers of 1.5 IQR below the 25<sup>th</sup> percentile or above the 75<sup>th</sup> percentile:
  - 20 and 35 women, respectively were identified as outliers for the change from baseline to Week 4 and Week 12 in the weekly frequency of moderate to severe VMS
  - 19 and 16 women, respectively were identified as outliers for the change from baseline to Week 4 and Week 12 in the weekly severity of moderate to severe VMS

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Using the IQR for outliers of 3.0 IQR below the 25<sup>th</sup> percentile or above the 75<sup>th</sup> percentile:

- 2 and 6 women, respectively were identified as outliers for the change from Baseline to Week 4 and Week 12 in the weekly frequency of moderate to severe VMS
  - 2 women at Week 4 and no women at Week 12 were identified as outliers for the change from Baseline to Week 4 and Week 12 in the weekly severity of moderate to severe VMS
10. While there were numerically greater percentage of outliers in the Black/African American subgroup versus the White subgroup, removal of the outliers did not have a significant impact on the efficacy results shown above in Table 29 and Table 30.
11. There was some efficacy noted in the Black/African American subgroup though certainly different than in the White subgroup. Multivariate analysis suggests the differences are multifactorial (Baseline values of BMI, current smoking and alcohol use, and estradiol concentrations).

Overall, the applicant concludes that the impact of race on efficacy is multifactorial and not dependent on a single covariate:

- there were differences in placebo response rates between White and Black/African American populations,
- there was less than 80% compliance with trial drug and diary completion in the Black/African American subgroup,
- there were differences in reasons for trial discontinuation,
- controlling for confounding factors utilizing multivariate analysis and their interactions with treatment groups (Baseline BMI, smoking, and alcohol use) showed no statistical difference in VMS frequency between race subgroups in Trial TXC12-05
- a statistically significant reduction in weekly severity was observed in the Black/African American subgroup at week 12 for the 1 mg estradiol/100 mg progesterone treatment group.

Clinical Reviewer's Comments:

The July 12, 2018 response provided by the applicant is comprehensive and complete, and fully responds to the Statistical Reviewer's June 20, 2018 information request. The Statistical Reviewer has confirmed these findings. See the Statistical Review, dated September 7, 2018, for additional analyses prepared by the Statistical Reviewer. The Statistical Review concludes the following:

"From a statistical perspective, the data supports the efficacy of 1 mg E2/100 mg P dose for the treatment of moderate to severe vasomotor symptoms associated with menopause. The review team recommends that the lack of efficacy in Black/African

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American population needs to be included in the label, should the Division decide to approve this product.”

Overall, this reviewer supports the approval of the 1 mg estradiol/100 mg progesterone dosage strength based on: 1) the demonstrated statistically and clinically meaningful difference in the frequency of moderate to severe vasomotor symptoms at Week 5 and Week 12, and 2) the demonstrated statistically significant reduction in vasomotor severity at Week 4 and Week 12.

The absence of a statistically significant difference in change from baseline in the frequency and severity of VMS in the sub-population consisting of women who self-identify as Black/African American, should be labeled for this dosage strength. This finding should also be confirmed in trials that are powered to provide efficacy in this sub-population of women seeking treatment of moderate to severe symptoms.

Efficacy Results – Secondary and other relevant endpoints

Responder Analysis:

In Trial TXC12-05, a responder was defined as a trial participant with  $\geq 50\%$  reduction from Baseline in the number of moderate and severe VMS as a secondary endpoint for each week up to Week 12. An analysis of those with  $\geq 75\%$  reduction from Baseline in the number of moderate and severe VMS was also performed as a secondary endpoint for each week up to Week 12. The same analyses were performed for the reduction in the number of mild, moderate, and severe VMS at each week up to Week 12.

The application presents the overall number and percentage of participants with a decrease from Baseline of  $\geq 50\%$  and, separately  $\geq 75\%$  in the mean weekly number of moderate to severe VMS. Table 31 shows the results reported for Week 4 and Week 12.

Table 31: Number (%) of Trial Participants with  $\geq 50\%$  and  $\geq 75\%$  Reduction in Frequency of Moderate to Severe VMS from Baseline to Week 4 and Week 12 (MITT-VMS Population)

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
Week 4 (n)	133	144	142	152	126
$\geq 50\%$ Reduction	82 (61.7)	70 (48.6)	74 (52.1)	81 (53.3)	41 (32.5)
p-value	<0.001	0.009	0.001	<0.001	---
$\geq 75\%$ Reduction	55 (41.4)	34 (23.6)	32 (22.5)	45 (29.6)	15 (11.9)
p-value	<0.001	0.017	0.025	<0.001	---
Week 12 (n)	124	129	124	135	115
$\geq 50\%$ Reduction	98 (79.0)	104 (80.6)	94 (75.8)	99 (73.3)	67 (58.3)
p-value	<0.001	<0.001	0.006	0.015	---

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≥ 75% Reduction	84 (67.7)	75 (58.1)	66 (53.2)	68 (50.4)	37 (32.2)
p-value	<0.001	<0.001	0.001	0.005	---

Source: adapted from NDA 210132, Trial TXC12-05, Table 23, page 93 of 1539.

Abbreviations: VMS = vasomotor symptom; MITT-VMS = modified intent to treat- vasomotor symptom; E2 = estradiol; P = progesterone.

Clinical Reviewer's Comments:

Per Table 31, the applicant concludes that a statistically significant difference between all treatment groups compared to placebo was observed at Weeks 4 and 12 indicating that each of the treatment groups were successful at reducing the number of moderate to severe VMS based on the protocol definition of a responder. The applicant was previously informed (A/IR letter to the IND dated November 7, 2013) that secondary endpoint analyses (such as this responder analysis) would not be used to determine the effectiveness of TX-001HR for the indication sought, and would not appear in product labeling.

Response to Clinical Global Impression (CGI) for MITT-VMS Population:

In the CGI, the trial participant answered the question: "Rate the total improvement, whether or not in your judgment it is due entirely to drug treatment. Compared to your condition at admission to the study, how much has it changed?" Potential responses included:

- very much improved,
- much improved,
- minimally improved,
- no change,
- minimally worse,
- much worse, or
- very much worse.

Table 32 displays the overall number and percent of participants for each possible response to the CGI at Weeks 4 and 12. In the application, the results of the top two responses for improvement (very much improved and much improved) and no change or worsening (minimally worse, much worse, or very much worse) were combined for each group and the active treatment groups were compared to placebo.

Table 32: Clinical Global Impression for Weeks 4 and 12 in Trial TXC12-05 (MITT-VMS Population)

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	0.5 mg E2/ 50 mg P (N=147)	0.25 mg E2/ 50 mg P (N=154)	Placebo (N=135)
Week 4 (n)	136	141	144	148	125
Very much improved/ much improved	86 (63.2)	71 (50.4)	72 (50.0)	75 (50.7)	41 (32.8)

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Minimally improved	37 (27.2)	49 (34.8)	49 (34.0)	51 (34.5)	49 (39.2)
No change or worsening	13 (9.6)	21 (14.9)	23 (16.0)	22 (14.9)	35 (28.0)
p-value	<0.001	0.005	0.007	0.004	---
Week 12 (n)	123	133	131	139	116
Very much improved/ much improved	101 (82.1)	97 (72.9)	102 (77.9)	101 (72.7)	62 (53.4)
Minimally improved	17 (13.8)	29 (21.8)	22 (16.8)	24 (17.3)	26 (22.4)
No change or worsening	5 (4.1)	22 (16.8)	7 (5.3)	14 (10.1)	28 (24.1)
p-value	<0.001	<0.001	<0.001	0.002	---

Source: adapted from NDA 210132, Trial TXc12-05 Clinical Study Report, Table 24, page 95 of 1539.

Abbreviations: MITT-VMS = modified intent to treat – vasomotor symptoms. E2 = estradiol; P = progesterone.

Clinical Reviewer’s Comments:

At Week 4, the percentage of participants who reported “very much improved and much improved” for the active treatment groups ranged from 50.0 to 63.2% compared to 32.8% for placebo. At Week 12, the percentage of participants reporting “very much improved and much improved” for the active treatment groups ranged from 71.7 to 82.1% compared to 53.4% for placebo. Across the active treatment groups, the highest percentage of “improved” was in the 1 mg estradiol/100 mg progesterone treatment group. All treatment groups, including the placebo treatment group, increased from Week 4 to Week 12 in the “very much improved and much improved” category. This patient reported outcome (PRO) is considered to be exploratory.

Applicant-Identified Clinical Meaningfulness Analysis:

Per the application, the threshold for reporting a meaningful decrease in weekly moderate to severe VMS was based on the “best discrimination between women who reported ‘minimally improved’ and those women who reported ‘much or very much improved’ on the CGI analysis. Based on this nonparametric discriminant analysis, the applicant calculates that this was a decrease of 36 VMS at Week 4 and a decrease of 39 VMS at Week 12. Therefore, the applicant determined that the responder definition (a “clinically” meaningful analysis) should be based on criteria of a decrease of 36 moderate to severe VMS at Week 4 and 39 moderate to severe VMS at Week 12.

The number and percentage of women who were responders, based on the above definition, were statistically significantly different from placebo for all active treatment groups. See Table 33.

Table 33: Number of Trial TXC12-05 Participants with  $\geq 36$  and  $\geq 39$  Reduction in Frequency of Moderate to Severe VMS from Baseline to Week 4 and Week 12 (MITT-VMS Population)

	1 mg E2/ 100 mg P	0.5 mg E2/ 100 mg P	0.5 mg E2/ 50 mg P	0.25 mg E2/ 50 mg P	Placebo
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	(N=141)	(N=149)	(N=147)	(N=154)	(N=135)
Week 4 (n)	134	144	142	152	126
≥ 36 VMS Reduction	79 (59.0)	66 (45.8)	70 (49.3)	79 (52.0)	41 (32.5)
p-value	<0.001	0.034	0.006	0.002	---
Week 12 (n)	124	129	124	135	115
≥ 39 VMS Reduction	91 (73.4)	94 (72.9)	84 (67.7)	93 (68.9)	60 (52.2)
p-value	<0.001	<0.001	0.017	0.009	---

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 25, page 96 of 1539.

Abbreviations: VMS = vasomotor symptoms; E2 = estradiol; P = progesterone.

Clinical Reviewer's Comments:

The applicant's assessment of "clinically meaningful difference" in the number of moderate to severe vasomotor symptoms in Trial TXC12-05 is not in compliance with the Agency's definition of "clinically meaningful difference" provided in an Advice/Information Request (A/IR) letter to IND 114477, dated November 7, 2013:

"We advise you that efficacy of your product will be established when study results show, at both Weeks 4 and 12, that your product demonstrates, a statistically significant reduction of frequency from baseline vs. placebo and a clinically meaningful difference in the reduction of frequency from baseline vs. placebo of at least 2 per day or 14 per week and a statistically significant reduction in severity from baseline vs. placebo."

The applicant's analysis for a "clinically meaningful difference" was not agreed-to by the Agency, and we consider it to be exploratory. See page 89 of this review for further discussion of the reported "clinically meaningful difference" for each treatment group in phase 3 Trial TXC12-05.

This reviewer determines that only the 1 mg estradiol/100 mg progesterone treatment group demonstrated a clinically meaningful difference in moderate to severe VMS over placebo at Weeks 5 and 12.

Menopause-Specific Quality of Life Questionnaire (MENQOL) Vasomotor Domain:

The MENQOL questionnaire was completed at Week 12, Week 26 (Month 6), and Week 52 (Month 12). This self-administered questionnaire assesses the impact of four (4) domains of menopausal symptoms: vasomotor, psychosocial, physical, and sexual. Items pertaining to a specific symptom are rated as present or not present, and if present, how bothersome on a zero (not bothersome) to six (extremely bothersome) scale.

At Week 12, all active treatment groups showed a statistically significant improvement in the MENQOL total score compared to the placebo treatment group. The total MENQOL scores for 1 mg estradiol/100 mg progesterone, 0.5 mg estradiol/100 mg progesterone, and the 0.5 mg

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estradiol/50 mg progesterone treatment groups were also statistically significantly improved over placebo at Weeks 26 and 52. Statistically significant improvements in the vasomotor domain were observed at Week 12 and continued through Weeks 26 and 52 for all treatment groups compared to the placebo treatment group. There were, generally, no statistical differences noted between treatment groups for the psychosocial, physical, and sexual MENQOL domains.

Clinical Reviewer's Comments:

In the overall MITT-VMS population in Trial TXC12-05, statistically significant improvements in the MENQOL vasomotor domain were observed for all active treatment groups compared to placebo at Weeks 12, 26, and 52. However, when analyzed by race, statistically significant improvements were observed for all doses and at all time points in the White population in the MENQOL Vasomotor Domain. No significant differences were noted in the Black or African American population except for the 0.5 mg estradiol/100 mg progesterone and 0.25 mg estradiol/50 mg progesterone treatment groups at Week 12.

TherapeuticsMD was advised on November 7, 2013, under IND 114477, that the findings from secondary endpoints and other endpoints (for example, MENQOL evaluation parameters and MOS-Sleep evaluation parameters) would not be used to support the effectiveness of the drug product to relieve hot flushes and would not appear in labeling.

Medical Outcomes Study Sleep Scale (MOS-Sleep) for MITT-VMS Population:

The MOS-Sleep questionnaire was completed at Week 12, Week 26 (Month 6), and Week 52 (Month 12). Individual scale scores (sleep disturbance, snoring, sleep short of breath or headache, sleep adequacy, sleep somnolence, sleep problems) as well as sleep quality and optimal sleep assessment (based on average number of hour of sleep night in previous 4 weeks) were assessed. Per the application, statistically significant improvements in the MOS Total Sleep Scores for the MITT population at Week 12 were demonstrated ( $p < 0.05$ ), for all active estradiol/progesterone treatment groups in Trial TXC12-05, except for the 0.25 mg estradiol/50 mg progesterone treatment group. By Weeks 26 and 52, statistically significant improvements were demonstrated for all active estradiol/progesterone treatment groups compared to placebo ( $p < 0.01$ ).

Clinical Reviewer's Comments:

TherapeuticsMD was advised on November 7, 2013, under IND 114477, that the findings from secondary endpoints and other endpoints (for example, MENQOL evaluation parameters and MOS-Sleep evaluation parameters) would not be used to support the effectiveness of the drug product to relieve hot flushes and would not appear in labeling.

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## Dose/Dose Response

The results reported in phase 3 Trial TXC12-05 are inconsistent across treatment groups. While the 1 mg estradiol/100 mg progesterone dosage strength produced the most consistent results, the three additional dosage strengths produced inconsistent dose-response results even though approximate dose proportionality was observed for estradiol, estrone, and progesterone. See Subsection 4.5 Clinical Pharmacology in this review for serum concentration of estradiol and estrone (assessed at Screening, Weeks 4 and 12, Months 6, 9, and 12) and for serum progesterone (assessed at Screening, Week 12, and Month 12).

## Durability of Response

A 12-week, placebo-controlled, clinical Trial TXC12-05 was conducted to demonstrate effectiveness of combined estradiol/progesterone drug product for the indication of the treatment of moderate to severe vasomotor symptoms, due to menopause.

## Persistence of Effect

No data is available in the NDA application to determine the effect of the combined estradiol/progesterone oral product over time after treatment is stopped or withheld.

## Additional Analyses Conducted on the Individual Trial

The applicant and the Statistical Reviewer performed additional Race subgroup analyses of data from phase3 Trial TXC12-05.

### Clinical Reviewer's Summary of Efficacy Findings:

Phase 3 Trial TXC12-05 (first 12-weeks placebo-controlled) provides substantial evidence of overall efficacy for the combined 1 mg estradiol and 100 mg progesterone dosage strength. This dose successfully achieved the primary protocol-defined co-primary endpoints of 1) a statistically significant mean change in the frequency of moderate to severe vasomotor symptoms at Week 4; 2) a statistically significant mean change in the frequency of moderate to severe vasomotor symptoms at Week 12; 3) a statistically significant mean change in the severity of moderate to severe vasomotor symptoms at Week 4; and 4) a statistically significant mean change in the severity of moderate to severe vasomotor symptoms at Week 12. In addition, the combined 1 mg estradiol and 100 mg progesterone dose demonstrated a clinically meaningful difference in the frequency of hot flashes (at least 2 hot flashes above placebo per day, or 14 per week) at Week 5 [weekly least square mean difference (SE) from placebo of -15.59 (3.35)], but not at Week 4 [weekly least square mean difference (SE) from placebo of -12.81 (3.30)] that is maintained through Week 12 [weekly least square mean difference (SE) from placebo of -16.58 (3.44)]. The Week 5 delay is acceptable to this reviewer. If approved,

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this will be the first combined estradiol and progesterone product approved for the treatment of moderate to severe vasomotor symptoms due to menopause.



A subgroup analysis by race demonstrated a lack of efficacy in three of the four protocol-defined co-primary endpoints in women who self-identified as Black/African American. The absence of overall efficacy in subgroup race analysis will be included in labeling.

## 7. Integrated Review of Effectiveness

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### 7.1. Assessment of Efficacy Across Trials

Single phase 3 Trial TXC12-05 was conducted to support efficacy (see Subsection 6.1.2 Trial Results in this review). Therefore, a discussion of integrated review of efficacy, is not applicable.

#### 7.1.1. Primary Endpoints

Not applicable.

#### 7.1.2. Secondary and Other Endpoints

Not applicable.

#### 7.1.3. Subpopulations

Not applicable.

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### 7.1.4. Dose and Dose-Response

Not applicable.

### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

Overall, the combined 1 mg estradiol/100 mg progesterone capsule effectiveness and safety was demonstrated in 52-week Trial TXC12-05 (efficacy demonstrated in the placebo-controlled initial 12 weeks of Trial TXC12-05). Trial TXC12-05 randomized 65.4% of trial participants (1201 of 1835 total women randomized and treated) who self-identified as White, 32.1% of trial participants (589 of 1835 total women) who self-identified as Black/African American, and 2.4% of trial participants (45 of 1835 total women) who self-identified as Other. Subgroup analysis demonstrated, however, a lack of effectiveness for three of the four agreed upon VMS co-primary endpoints in women who self-identified as Black/African American (reductions in the number of hot flashes were not statistically significant at Weeks 4 and 12; reduction in the severity of hot flashes was statistically significant at Week 12, but was not statistically significant at Week 4) following treatment with 1 mg estradiol/100 mg progesterone capsule in Trial TXC12-05 conducted to support the indication for the treatment of moderate to severe vasomotor symptoms due to menopause. This reviewer recommends that the absence of effectiveness in women who self-identified as Black/African American should be addressed in labeling.

### 7.2.2. Other Relevant Benefits

TX-001HR is peanut oil free and thus can be used in non-hysterectomized postmenopausal women who are unable to tolerate currently approved hormone therapy for VMS due to peanut allergies.

## 7.3. Integrated Assessment of Effectiveness

Not applicable.

# 8. Review of Safety

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## 8.1. Safety Review Approach

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The primary safety endpoint in phase 3 Trial TXC12-05 was the incidence of endometrial hyperplasia at 12 months (to demonstrate a hyperplasia proportion that was  $\leq 1\%$  with an upper bound of the one-sided 95% CI for that rate that does not exceed 4%) based on an *a priori* plan in which a consensus among two out of three pathologists was the final endometrial pathology diagnosis. Trial participants who had an endometrial malignancy were not included in the numerator or denominator of the incidence calculation.

Clinical Reviewer's Comments:

This reviewer does not agree with the protocol exclusion of trial participants with an endometrial cancer from the numerator or denominator of the hyperplasia or cancer incidence calculation.

For the primary safety endpoint, all endometrial biopsy specimens were read by three pathologists. Each pathologist classified the endometrial biopsy into one of the following three categories:

- Category 1: Non-endometrial malignancy/non-hyperplasia - includes proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern, secretory endometrium, endometrial tissue (other) [for example, benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc], endometrial tissue insufficient for diagnosis, no endometrium identified, no tissue identified, other.
- Category 2: Endometrial hyperplasia includes simple hyperplasia with or without atypia and complex hyperplasia with or without atypia.
- Category 3: Endometrial malignancy.

Clinical Reviewer's Comments:

The Agency's draft 2003 Hormone Therapy Guidance for Industry recommends that standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract) be used for the diagnosis of endometrial hyperplasia or cancer.<sup>9</sup> See Subsection 8.5.1 Endometrium in this review for additional information.

In the NDA application, however, the applicant's presents the final reported histological findings of the three independent pathologists as a category rather than reporting the individual histologic characteristics of the endometrium reported by each of the three independent pathologists for each trial participant with a uterus who had an endometrial biopsy at end-of-treatment/early termination. However, the application contains a copy of each endometrial biopsy report generated by each of the three

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<sup>9</sup> The standardized criteria for histologic evaluation, and the Agency's 2003 draft clinical evaluation guidance can be viewed at

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pdf>

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pathologists for each trial participant with a uterus.

The applicant's Category 2 and 3 classifications, shown above, comply with the Agency's 2003 Hormone Therapy Guidance for Industry. Category 2: hyperplasia includes simple hyperplasia with or without atypia and complex hyperplasia with or without atypia (Blaustein's histologic characteristics numbers 7, 8, 9, and 10). Category 3: malignancy includes carcinoma (Blaustein's histologic characteristics number 11).

The applicant's Category 1 classification does not fully comply with the Agency's draft 2003 Hormone Therapy Guidance for Industry, however. Category 1 classification does not clearly identify the presence of menstrual type endometrium which is included in "endometrial tissue "other" [that is, benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc."].

The reads of the two primary pathologists, designated by the applicant *a priori*, were utilized. Consensus was reached when the two primary pathologist readers agreed on any of the above categories.

Endometrial biopsies were performed at Screening and at Visit 7 (Month 12)/End-of-Treatment. Trial participants who discontinued trial participation after receiving  $\geq 12$  weeks of trial medication were also required to have an endometrial biopsy. Unscheduled endometrial biopsies were performed during the trial, if indicated for medical reasons, such as vaginal bleeding.

The primary analysis population for endometrial safety was the ES population as previously defined (see page 70 of this review). Analyses were also conducted for the overall Safety population for those women with a Screening and a post-Baseline endometrial biopsy.

Per the application, a supplemental secondary analysis was performed based on the results from the three pathologists. In this supplemental analysis, the final diagnosis was based on agreement of two of the three pathologists reads. Consensus was reached when two of the three pathologist readers agreed on any of the above categories. If all three readings were disparate (if each reading gave a different category – Category 1, 2, or 3), the final diagnosis was based on the most severe of the three readings.

Clinical Reviewer's Comments:

This reviewer views the endometrial histologic classification determined by the three independent pathologists as the primary endometrial analysis, not as a supplemental secondary analysis. The applicant was informed of this during multiple occasions during clinical development.

## 8.2. Review of the Safety Database

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### 8.2.1. Overall Exposure

Study drug exposure was based on the dose administration per the participant's diary.

Duration of exposure was defined as last dose date minus first dose date + 1.

Overall trial drug exposure was calculated as the total number of capsules taken divided by two (2) to account for the double-dummy dosing design.

Study drug compliance was calculated for those women with dosing diary data. Compliance was calculated as the total number of capsules taken per the diary divided by the total number of capsules expected to be taken.

- At Week 12 using the participant's diary from Day 1 through Day 84 (total expected = 168), and
- At Week 52 using the participant's diary from Day 1 through Day 364 (total expected = 728).

The proportion of women in each treatment group having at least 80% overall compliance was summarized. In addition, women with < 80% calculated compliance at Week 12 was excluded from the EE population.

Of the 1835 trial participants receiving trial medication, 1275 (69.5%) completed the 12-month trial. A total of 560 (30.5%) participants discontinued prior to completion. A summary of treatment exposure is shown in Table 34 by treatment group.

Table 34: Summary of Treatment Exposure (Safety Population)

Treatment	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)
Duration of Treatment (days)					
Mean (SD)	281.19 (126.45)	291.12 (121.89)	297.05 (115.91)	281.99 (120.07)	258.56 (138.27)
Median	357.0	357.0	358.0	356.0	356.0
Min, Max	1.0, 392.0	1.0, 405.0	1.0, 390.0	1.0, 398.0	1.0, 378.0
Duration of Treatment, N (%)					
< 4 Weeks	22 (5.3)	17 (4.0)	14 (3.3)	10 (2.4)	8 (5.3)
≥ 4 Weeks	393 (94.7)	407 (96.0)	407 (96.7)	414 (97.6)	143 (94.7)
≥ 8 Weeks	372 (89.6)	387 (91.3)	390 (92.6)	390 (92.0)	131 (86.8)
≥ 12 Weeks	349 (84.1)	364 (85.8)	369 (87.6)	369 (87.0)	121 (80.1)
≥ 6 Months	318 (76.6)	331 (78.1)	340 (80.8)	321 (75.7)	104 (68.9)
≥ 9 Months	295 (71.1)	318 (75.0)	318 (75.5)	294 (69.3)	97 (64.2)
≥ 326 Days (Month 12)	283 (68.2)	308 (72.6)	313 (74.3)	282 (66.5)	94 (62.3)

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 40. Page 123 of 1539.

Abbreviations: E2 = Estradiol; P = Progesterone. SD = standard deviation.

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Clinical Reviewer's Comments:

Overall, approximately 86% of women in the active treatment groups (1451 of 1684 women randomized to active treatment), and 80% (121 of 151 randomized to the placebo treatment group) had a treatment duration of  $\geq 12$  weeks. Likewise, approximately 70% of women in the active treatment groups (1196 of 1684 women randomized to active treatment), and 62% of women in the placebo treatment group (94 of 151 women randomized to the placebo treatment group) had a treatment duration of  $\geq 326$  days. An adequate number of women were exposed to trial medication in phase 3 Trial TXC12-05.

8.2.2. Relevant characteristics of the safety population:

See Table 22 in this review for the relevant characteristics of the Safety population in phase 3, 52-week Trial TXC12-05.

8.2.3. Adequacy of the safety database:

The 1835 women who were randomized and took at least one capsule of trial medication comprised the Safety population. One trial participant (Number (b) (6)) who was randomized to the 1 mg estradiol/100 mg progesterone treatment group was unintentionally given the wrong dose at randomization (she received 0.5 mg estradiol /100 mg progesterone for 8 days before the error was noticed). She was discontinued from the trial after 22 days due to this error.

The disposition for the Safety population is summarized in Table 35.

Table 35: Disposition of Trial Participants in 52-Week Trial TXC12-05 – Safety Population

	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)	Total (N=1835)
Number of women completed, n (%)	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)	1275 (69.5)
Number of women discontinued, n (%)	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)	560 (30.5)
Adverse events, n (%)	46 (11.1)	33 (7.8)	34 (8.1)	41 (9.7)	10 (6.6)	164 (8.9)
Investigator/sponsor decision	1 (0.2)	3 (0.7)	2 (0.5)	2 (0.5)	0 (0.0)	8 (0.4)
Lack of efficacy, n (%)	5 (1.2)	4 (0.9)	4 (1.0)	10 (2.4)	12 (7.9)	35 (1.9)
Lost to follow-up	27 (6.5)	30 (7.1)	26 (6.2)	38 (9.0)	17 (11.3)	138 (7.5)
Protocol Deviation	15 (3.6)	6 (1.4)	12 (2.9)	20 (4.7)	6 (4.0)	59 (3.2)
Women withdrew consent	36 (8.7)	42 (9.9)	29 (6.9)	31 (7.3)	13 (8.6)	151 (8.2)
Other	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)	0 (0.0)	5 (0.3)

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Source: Adapted from NDA 210132, Submodule 5.3.5.1, TXC12-05 Study Report Body, Table 10, page 73 of 1539.

Abbreviations: E2 = estradiol; P = progesterone

### Clinical Reviewer's Comments:

In this reviewer's experience, a 30.5% participant's discontinuance rate is high for a VMS clinical trial. However, in Trial TXC12-05, the placebo treatment group had the largest percent of women discontinuing the clinical trial (38.4% versus 29.8% in the combined active treatment groups), influenced by 11.3% of placebo treated women lost to follow-up (17 of 151 women randomized to the placebo treatment group).

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall, the NDA application is well organized, allowing ease of finding information. The applicant responded within the requested time frame when the following additional information was requested:

- CMC request for information dated March 1, 2018; applicant response dated March 21, 2018.
- No Filing Review Issues Identified letter dated March 8, 2018; applicant response dated March 29, 2018.
- Statistical information request dated May 21, 2018; applicant response dated May 24, 2018.
- CMC request for information dated June 4, 2018; applicant responded June 26, 2018 (Part A) and July 18, 2018 (Part B).
- Statistical information request dated June 28, 2018; applicant response dated July 12, 2018.
- Clinical information requested on July 6, 2018; applicant response dated July 11, 2018.
- Clinical Pharmacology information requested July 30, 2018; applicant response dated August 6, 2018.
- CMC information requested on August 7, 2018; applicant response dated August 10, 2018.
- CMC information requested on August 24, 2019; applicant response dated August 24, 2018
- Statistical information requested on October 3, 2018; applicant response dated October 5, 2018.

### 8.3.2. Categorization of Adverse Events

Adverse events (AEs) were coded to standard preferred term (PT) and summarized by system organ class (SOC) as defined in MedDRA, Version 18.0. An AE was defined as any untoward

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medical occurrence in trial participant administered trial medication, including placebo, and which does not necessarily have a causal relationship with treatment.

All AEs that occurred during the trial (starting from signed informed consent) were collected on the AE case report form. Non-serious AEs were collected through 15 days after the last dose of trial medication. Serious adverse events (SAEs) were collected through 30 days after the last dose of trial medication, unless considered possibly or probably related to study medication. These were followed-up until resolution or until the condition was stable. The death of any participant during the trial or within 30 days after the last dose of trial medication, regardless of the cause, was reported to the applicant within 24 hours of the investigator or the trial site becoming aware of the occurrence. For each AE, the investigator evaluated and reported the onset date, resolution date, intensity, causality, action taken, serious outcome (if applicable), and whether it caused the woman to discontinue the trial. AE intensity was assessed as mild, moderate or severe. AE causality was assessed by the site investigator as not related, possibly related, probably related, or definitely related.

Women with AEs that were ongoing at trial completion or trial withdrawal were followed until the AE resolved, became clinically insignificant, or was stabilized, unless the woman was lost to follow-up, or another course of action was approved by the medical monitor.

A participant that had the same treatment-emergent adverse event (TEAE) more than once was counted once for each PT and once within each SOC. A participant with multiple TEAEs within the same SOC/PT was counted using the worst severity and strongest relationship in the by-severity and relationship summary tables.

Clinical Reviewer's Comments:

The categorization of adverse events in Trial TXC12-05 was complete and acceptable.

8.3.3. Routine Clinical Tests

A complete physical examination was conducted at Screening and Month 12/End-of-Trial or Early Termination. The woman's height was measured at Screening only and body weight was measured at Screening, Week 12, Month 6, and Month 12/End-of-Trial or Early Termination. BMI was calculated at Screening. Vital signs (body temperature, heart rate [HR], respiration rate [RR], and sitting blood pressure [BP]) was measured after the woman had been sitting for  $\geq 10$  minutes. Vital signs were collected at all visits.

A standard 12-lead ECG was obtained at Screening and Month 12/End-of-Trial or Early Termination and read locally. The investigator was responsible for reviewing the interpretation of the ECG and for retaining hard copies.

Blood samples for blood chemistry, hematology, coagulation tests, and hormone levels were

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collected and sent to a central laboratory. Chemistry, hematology, coagulation, and urinalysis assessments were performed at Screening, Week 12, Month 6, Month 9, and Month 12 (or Early Termination). Clinical laboratory assessments included:

- Chemistry: Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), iron, albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, alkaline phosphatase, serum creatinine, calcium, phosphate, uric acid, total bilirubin, glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) (fasting a minimum of 8 hours).
- Hematology: Complete blood count (CBC) including white blood cell (WBC) count and differential, red blood cell (RBC) count, hemoglobin, hematocrit and platelet count.
- Coagulation Tests: Prothrombin time, activated partial thromboplastin time (APTT), fibrinogen, Protein C (Factor XIV) and Protein S, antithrombin III, Factor V Leiden (Screening only)
- Hormone Levels:
  - At Screening: FSH (not required for subjects with  $\geq 12$  months of spontaneous amenorrhea or bilateral oophorectomy), estradiol levels (required to be  $\leq 50$  pg/mL for inclusion), and thyroid-stimulating hormone (TSH) were collected. If TSH was abnormal as per lab range, reflex testing of free triiodothyronine (T3) and free thyroxine (T4) was performed.
  - Serum samples were collected for analysis of concentrations of: estradiol and estrone at Screening, Week 4, Week 12, Month 6, Month 9, and Month 12 or Early Termination and progesterone at Screening and at Week 12, and Month 12 or Early Termination.
- Urinalysis: Appearance, specific gravity, protein, pH.
- Urine Pregnancy Test.

Trial participants were required to have a pelvic examination performed during Screening and at Visits 5 (Month 6) and 7 (Month 12/End-of-Trial) or Early Termination. For a woman with an intact cervix, a Pap smear was performed during Screening, regardless of any recent prior assessment, and at Month 12/End-of-Trial or Early Termination (not required if the woman had Pap < 5 months prior to early discontinuation).

Trial participants with a uterus had an endometrial biopsy performed at Screening and at Visit 7 (Month 12)/End-of-Trial. Trial participants who discontinued trial participation after receiving  $\geq 12$  weeks of trial medication were required to have an endometrial biopsy. Unscheduled endometrial biopsies were performed during the trial, if indicated for medical reasons, such as vaginal bleeding.

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Phase 3 Trial TXC12-05 had adequate routine clinical testing to evaluate adverse outcomes arising from the use of combined estradiol and progesterone in healthy postmenopausal women for the treatment of moderate to severe VMS.

## 8.4. Safety Results

### 8.4.1. Deaths

One death occurred during Trial TXC12-05. Participant Number (b) (6), a White female 49 years of age with a BMI of 32 kg/m<sup>2</sup> developed cough and chest congestion on trial Day 37. She reported having worsening hoarseness of voice for past 6 months, and was given prednisone and clarithromycin. Concomitant medications used included acetaminophen-hydrocodone 325 mg, cardizem 180 mg, omeprazole. She was a former smoker (30 pack years; quit smoking in 2013) with a medical history including Schatzki's Ring and inflammation around her vocal cords, intermittent laryngitis, dysphagia, and gastroesophageal reflux disease. She was randomized to the 0.5 mg estradiol/50 mg progesterone treatment group.

An x-ray performed by her primary care physician on trial Day 58 showed a large central left hilar obstructing tumor mass extending into the mediastinum and surrounding the left main pulmonary artery with concerns for a large pericardial effusion and possible pericardial tamponade. She was sent to the emergency room on trial Day 60 for a computed tomography (CT) scan.

A transthoracic echocardiogram was performed and revealed large circumferential pericardial effusion without convincing evidence for hemodynamic compromise and a thick non-mobile echodense material layered on the visceral pericardium. A chest CT scan revealed a new moderately large pericardial effusion as well as a left hilar mass measuring 7.8 x 4.8 x 4.7 cm. On correlation with the CT findings, a persistent mass with associated opacities on the left with effusion and cardiomegaly with pericardial fluid were seen. She underwent pericardial window and left Chamberlain procedures as well as xiphoidectomy; 600 cc of bloody fluid was aspirated from the lumpy-feeling textured pericardium. During the Chamberlain procedure, a portion of a mass was removed and intraoperative frozen section demonstrated non-small cell lung cancer (Non-Small Cell Lung Cancer Stage IV). A post-operative chest x-ray was done on trial Day 61 with findings of mass-like density in the left perihilar region and opacity in the left lower lobe persisting. There was no improvement and no change when compared to the x-ray done prior to surgery. Her right lung remained clear. An ultrasound-guided left thoracentesis was performed on trial Day 63 and a total of 500 mL of clear serosanguinous fluid was removed. She was discharged from the hospital on trial Day 65; discontinued from the trial, and informed the site she would meet with the oncologist on trial Day 73. She did not appear for her early termination visit scheduled on trial Day 91 as she had returned to the hospital. She died on trial Day 116 (site became aware of death from a local newspaper). Per the death certificate, the cause of death was metastatic non-small cell lung cancer with contributing conditions of

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ischemic MCA cerebrovascular accident, C. Difficile colitis, and abdominal aortic thrombus.

The investigator considered the event severe and unrelated to trial medication. This reviewer concurs with the investigator's assessment.

8.4.2. Serious Adverse Events

A total of 46 women experienced 57 serious adverse events (SAEs) that occurred on/after the first dose of trial medication. A total of 40 women (38 in the active treatment groups and 2 in placebo treatment group) experienced 47 treatment-emergent adverse events (TEAEs) that occurred while receiving trial drug or within 15 days of last dose. A summary of SAEs that occurred on/after the first dose of trial medication for the Safety population by SOC and PT and treatment group is presented in Table 36. SAEs that occurred more than 15 days after the last dose of trial medication are denoted in the same table.

Table 36: Serious Adverse Events on Therapy and Post-Therapy for the Safety Population in Trial TXC12-05 – Number of Women with Adverse Event – A Woman May Have More Than One Adverse Event

Treatment	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)
Women with at least one SAE	9 (2.2)	15 (3.5)	9 (2.1)	11 (2.6)	2 (1.3)
<b>Cardiac disorders</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>
- Cardiac tamponade	0 (0.)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Coronary artery disease	1 (0.2)	0.(0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Stress cardiomyopathy	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Gastrointestinal Disorders</b>	<b>2 (0.5)</b>	<b>1 (0.2)</b>	<b>3 (0.7)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>
- Colitis ischemic <sup>a</sup>	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Colitis ulcerative	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Gastroduodenal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Gastroduodenitis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Pancreatitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Pancreatitis acute	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Small intestinal obstruction	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
<b>General disorders and administrative site conditions</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>
- Non-cardiac chest pain <sup>a</sup>	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
<b>Hepatobiliary disorders (0.0)</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>
- Hepatic steatosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Immune system disorders</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>
- Angioedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2) 1 (0.2)	0 (0.0)
<b>Infections and infestations</b>	<b>3 (0.7)</b>	<b>4 (0.9)</b>	<b>2 (0.5)</b>	<b>0 (0.0)</b>	<b>1 (0.7)</b>
- Bronchitis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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- Cholecystitis infective	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
- Clostridium difficile <sup>a</sup>	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Diverticulitis	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Gastroenteritis viral	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Mononucleosis <sup>a</sup>	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Pneumonia	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
- Urosepsis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Injury, poisoning and procedural complications</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>2 (0.5)</b>	<b>0 (0.0)</b>
- Ankle fracture	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Foot fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Humerus fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Incisional hernia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Jaw fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Tibia fracture	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
<b>Musculoskeletal and connective tissue disorders</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>
- Chondrocalcinosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Disc protrusion	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Osteoarthritis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Neoplasms benign, malignant and unspecified (cysts and polyps)</b>	<b>2 (0.5)</b>	<b>4 (0.9)</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>
- Breast cancer female	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Invasive ductal breast carcinoma	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
- Lung cancer metastatic <sup>a</sup>	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Myelodysplastic syndrome	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
- Non-small cell lung cancer stage IV	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
<b>Nervous system disorders</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>2 (0.5)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>
- Balance disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Cerebellar infarction	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Cerebrovascular accident <sup>a</sup>	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Seizure <sup>a</sup>	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Subarachnoid hemorrhage	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
<b>Psychiatric disorders</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>
- Psychotic disorder	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Reproductive system and breast disorders</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>	<b>1 (0.7)</b>
- Uterine leiomyoma	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>1 (0.2)</b>	<b>3 (0.7)</b>	<b>0 (0.0)</b>
- Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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- Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
- Pleural infusion	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
- Pneumonia aspiration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vascular disorders	1 (0.2)	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)
- Aortic aneurysm	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Aortic thrombosis <sup>a</sup>	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Deep vein thrombosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Peripheral arterial occlusive disease	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from NDA 210132, Trial TXC12-05 clinical Study Report, Table 45, page 129 of 1539.

a SAE that occurred more than 15 days after last dose of trial medication.

Abbreviations: E2 = estradiol; P = progesterone.

Note: At each level of summation (overall, SOC, PT, participants reporting more than one adverse event are counted only once.

Clinical Reviewer’s Comments:

Numerically, the 0.5 mg estradiol/100 mg progesterone treatment group produced the highest number of SAEs in Trial TXC12-05, primarily influenced by the 4 events occurring in the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps). The remaining three dosage strengths produced similar incidences of SAEs. All active treatment group SAEs exceeded the placebo treatment group.

Narratives for selected trial participants with SAEs follow in this review. The narratives for the all trial participants presented in Table 35 can be viewed in NDA 210132, Section 14.3.3

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the Safety population, 164 (8.9%) of Trial TXC12-05 participants experienced an adverse event (AE) on/after the first dose of study drug that was the primary reason for withdrawal from the trial (9.1% from all combined active treatment groups, and 6.6% from the placebo group). A summary of AEs leading to discontinuation from Trial TXC12-05 is presented in Table 37.

Table 37: Adverse Events on Therapy and Post-Therapy Leading to Withdrawal from Trial TXC12-05 (Safety Population)

Treatment	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)
Women with at least one AE	46 (11.1)	33 (7.8)	34 (8.1)	41 (9.7)	10 (6.6)
Cardiac disorders	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.7)
- Stress cardiomyopathy	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)

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Eye disorders	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
- Eye edema	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Vision blurred	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Gastrointestinal disorders	8 (1.9)	1 (0.2)	8 (1.9)	4 (0.9)	2 (1.3)
- Abdominal discomfort	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Abdominal distention	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Abdominal pain	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
- Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
- Abdominal pain upper	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Colitis ischemic <sup>a</sup>	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Colitis ulcerative	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Constipation	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Diarrhea	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Dry mouth	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Gastrointestinal pain	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Gastrointestinal reflux disease	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Nausea	1 (0.2)	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)
- Pancreatitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Stomatitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Vomiting	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
General disorders and administration site conditions	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	2 (1.3)
- Chest discomfort	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Fatigue	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.7)
- Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2) <sup>a</sup>	1 (0.7)
Hepatobiliary disorders	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Hepatic steatosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Hypersensitivity	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	1 (0.2)	2 (0.5)	2 (0.5)	1 (0.2)	0 (0.0)
- Erysipelas	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Furuncle	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Hepatitis C	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Herpes simplex	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Herpes zoster <sup>a</sup>	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Ankle fracture	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (1.4)	2 (0.5)	1 (0.2)	8 (1.9)	1 (0.7)
- Prolonged activated partial thromboplastin time	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
- Abnormal Endometrial biopsy	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Alkaline phosphatase increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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- Decreased blood fibrinogen	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Increased blood glucose	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Increased lipids	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Liver function test abnormal	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Weight increased	1 (0.2)	2 (0.5)	1 (0.2)	4 (0.9)	1 (0.7)
<b>Musculoskeletal and connective tissue disorders</b>	<b>2 (0.5)</b>	<b>2 (0.5)</b>	<b>3 (0.7)</b>	<b>2 (0.5)</b>	<b>0 (0.0)</b>
- Joint swelling	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Muscle spasm	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Musculoskeletal chest pain	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
- Myalgia	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Pain in extremity	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Neoplasms benign, malignant and unspecified (cysts and polyps)</b>	<b>1 (0.2)</b>	<b>2 (0.5)</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>0 (0.0)</b>
- Basal cell carcinoma	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
- Breast cancer female	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Lung cancer metastatic <sup>a</sup>	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Non-small cell lung cancer stage IV	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
<b>Nervous system disorders</b>	<b>4 (1.0)</b>	<b>2 (0.5)</b>	<b>4 (1.0)</b>	<b>11 (2.6)</b>	<b>0 (0.0)</b>
- Carpal tunnel syndrome	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Dizziness	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
- Dysarthria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Headache	1 (0.2)	0 (0.0)	0 (0.0)	6 (1.4)	0 (0.0)
- Hypoaesthesia	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
- Lethargy	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Memory impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Migraine with aura	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Morton's neuralgia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Motor dysfunction <sup>a</sup>	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Subarachnoid hemorrhage	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Tension headache	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
<b>Psychiatric disorders</b>	<b>4 (1.0)</b>	<b>4 (0.9)</b>	<b>2 (0.5)</b>	<b>2 (0.5)</b>	<b>1 (0.7)</b>
- Adjustment disorder <sup>a</sup>	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Agitation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Anxiety	2 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Depression	1 (0.2)	2 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
- Insomnia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Irritability	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.7)
- Mood swings	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Reproductive system and breast disorders</b>	<b>16 (3.9)</b>	<b>6 (1.4)</b>	<b>8 (1.9)</b>	<b>8 (1.9)</b>	<b>2 (1.3)</b>

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- Atrophic vulvovaginitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Breast pain	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
- Breast swelling	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Breast tenderness	6 (1.4)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
- Endometriosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Hot flash	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.7)	1 (0.7)
- Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Postmenopausal hemorrhage	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Uterine hemorrhage	2 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Uterine leiomyoma	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Uterine polyp	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
- Uterine spasm	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Vaginal hemorrhage	3 (0.7)	4 (0.9)	1 (0.2)	2 (0.5)	0 (0.0)
- Vulvovaginal pain	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (0.2)	7 (1.2)	2 (0.5)	0 (0.0)	0 (0.0)
- Alopecia	1 (0.2)	3 (0.7)	2 (0.5)	0 (0.0)	0 (0.0)
- Dermatitis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Rash erythematous	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Rash pruritic	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Skin hyperpigmentation	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	2 (0.5)	0 (0.0)	1 (0.2)	2 (0.5)	1 (0.7)
- Aortic aneurysm	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Deep vein thrombosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Hypertension	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.7)

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report. Table 46. Page 132 of 1539.

a AE leading to discontinuation more than 15 days after last dose of trial drug.

Note: At each level of summation (overall, SOC, PT), participants reporting more than one AE are counted only once.

Clinical Reviewer's Comments:

TEAEs were the primary reason for withdrawal from Trial TXC12-05 for 158 women [148 (8.8%) in active treatment groups and 10 (6.6%) in the placebo treatment group]. An unexpected active treatment non-linear dose response is shown in Table 37. While the 1 mg estradiol/100 mg progesterone treatment group had the largest number of withdrawals (11.1%, 46 of 415 participants), the 0.25 mg estradiol/50 mg progesterone treatment group had the next highest number of withdrawals (9.7%, 41 of 424 participants) with breast tenderness occurring more frequently in the 1 mg estradiol/100 mg progesterone treatment group and headaches occurring more frequently in the 0.25 mg estradiol/50 mg progesterone treatment group. The two remaining active treatment groups in Trial TXC12-05 (0.5 mg estradiol/100 mg progesterone and 0.5 mg estradiol/50 mg progesterone) had similar incidences of

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withdrawal (7.8% and 8.1%, respectively). Nonetheless, all active treatment group withdrawals exceeded the placebo treatment group.

As shown in Table 37, 6 women in the active treatment groups experience one AE each (ischemic colitis, metastatic lung cancer, motor dysfunction, adjustment disorder, Herpes zoster, and non-cardiac chest pain), that occurred more than 15 days after the last dose of trial medication, withdrew from Trial TXC12-05.

Narratives for selected trial participants withdrawn from Trial TXC12-05 follow in this review. The narratives for the all trial participants withdrawn from Trial TXC12-05 presented in Table 37 can be viewed in NDA 210132, Section 14.3.3

#### 8.4.4. Significant Adverse Events

##### Applicant-Identified Life Threatening Adverse Events:

Four (4) trial participants in Trial TXC12-05 had application identified life threatening AEs (3 events occurred during trial participation, and 1 event occurred more than 15 days after last dose of trial medication. See Table 38.

Table 38: Life-Threatening Adverse Events in Trial TXC12-05 (Safety Population)

Treatment	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)
Women with Life-Threatening Adverse Events	0 (0.0)	2 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
- Cardiac tamponade	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
- Gastrointestinal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
- Breast cancer female	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
- Lung cancer metastatic <sup>a</sup>	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 47, page 136 of 1539.

Abbreviations: E2 = estradiol; P = progesterone.

Note: At each level of summation (overall, SOC, PT), participants reporting more than one AE are counted only once.

##### Clinical Reviewer's Comments:

No "life-threatening events" occurred in the 1 mg estradiol/100 mg progesterone treatment group or in the placebo treatment group.

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Two of these reported events occurred in the 0.5 mg estradiol/100 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a White female 48 years of age, with a medical history of current smoker x 30 years, bilateral tubal ligation, hot flashes, and no history of relevant prior medications had a single day of rectal bleeding on trial Day 9 (considered mild in severity and not related to trial medication by investigator), and had weight loss on trial Day 82 (considered moderate in severity and not related to trial medication by the investigator). She reported being hospitalized trial Days 132 and 133 for a diagnosis of “brain metastasis due to lung cancer”. She also reported having “chemotherapy” on trial Day 151. At her early termination visit on trial Day 183, she refused all end-of-treatment procedures. Her last day of trial medication was reported as trial Day 102. Attempts to contact her were unsuccessful. The investigator considered “brain metastasis due to lung cancer” as severe and not related to trial medication. This reviewer concurs with the investigator’s assessment.
- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 60 years of age, with a medical history of mitral valve prolapse, multiple sclerosis, left breast lumpectomy (benign), headaches, and a BI-RADS 2 finding at Screening (normal breast exam) had a BI-RADS 4 finding on trial Day 363. An ultrasound guided needle biopsy was performed on trial Day 371 with no malignancy identified. On post-trial Day 439, she had a left breast lumpectomy which revealed invasive carcinoma with ductal and lobular features. She was estrogen and progesterone receptor positive, HER2/neu negative. She began chemotherapy on post-trial Day 527. The investigator considered this SAE as severe and possibly related to the trial medication. This reviewer concurs with the investigator’s assessment.

One event occurred in the 0.5 mg estradiol/50 mg progesterone treatment group:

- Participant Number (b) (6) – See a discussion of this participant on page 116 of this review.

One event occurred in the 0.25 mg estradiol/50 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a White female 54 years of age with a medical history of irritable bowel syndrome, back pain, and migraine, and a history of use of Mylanta (1 tsp as needed), ibuprofen 600 mg as needed, and Aleve and Excedrin as needed. She presented to the hospital on trial Day 86 with multiple episodes of vomiting blood, syncope, and weight loss (16 pounds). Her diagnosis was upper gastrointestinal bleed and she was treated with a Protonix drip. An esophagogastroduodenoscopy with biopsy was performed that revealed a deep ulcer in the duodenal bulb with a visible vessel

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and a clot. She underwent an open pyloromyotomy with oversew of bleeding gastroduodenal artery. She was discharged from the hospital on trial Day 93. Her trial drug that was interrupted on trial Day 86 was restarted on trial Day 95. She completed the trial and the last dose of trial drug was on Day 371. The investigator assessed the event as severe and not related to trial medication. This reviewer concurs with the investigator's assessment.

Applicant-Identified Venous Thrombotic Event of Interest:

One deep vein thrombosis (DVT) was reported in Trial TXC12-05:

- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 58 years of age randomized to the 0.5 mg estradiol/50 mg progesterone treatment group with a medical history of left femoral popliteal bypass surgery in 1999 was admitted to the hospital on trial Day 111 with complaints of swelling and pain of her left lower extremity that began on trial Day 108. Venous Doppler of the left leg revealed a total acute DVT in the groin and thigh as well as a partial acute DVT behind the knee. She denied a recent history of immobility. She was treated with subcutaneous enoxaparin and warfarin and was discharged on trial Day 112 with medications including enoxaparin, warfarin, pantoprazole, atorvastatin, hydrochlorothiazide, potassium chloride and tramadol. She was discontinued from the trial due to this SAE on trial Day 126. Her treatment was ongoing. The investigator and medical monitor assessed this event as severe and possibly related to trial medication. The event resolved on trial Day 218. This reviewer concurs with the trial investigator's assessment.

Applicant-Identified Cardiac Adverse Events of Interest:

Three cardiac adverse events of interest are reported in Trial TXC12-05:

- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 53 years of age randomized to the 1 mg estradiol/100 mg progesterone with a medical history of angina, coronary heart disease, and cocaine abuse (all not reported during Screening but later confirmed in medical records) was seen by her private cardiologist on trial Day 73. On trial Day 82, she underwent a cardiac catheterization which revealed significant coronary artery disease (LAD with 70% proximal stenosis and 90% distal stenosis; LCx with up to 50% stenosis; OM2 with 70% stenosis). The investigator discontinued her from the trial on trial Day 108. Her last dose of trial medication was on trial Day 79. On trial Day 148 she underwent a planned two vessel coronary artery bypass grafting. She was discharged from the hospital on trial Day 155 with stable vital signs and laboratory values within normal limits. The investigator assessed the event as severe and not related to trial medication. This reviewer concurs with the investigator's assessment.
- Participant Number (b) (6) – A woman who self-identified as a White female 49 years of age randomized to the 0.5 mg estradiol/100 mg progesterone treatment group with a

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medical history of high cholesterol, chronic headaches, and hypertension entered the trial with an abnormal not clinically significant (NCS) ECG showing sinus bradycardia/cannot rule out lateral infarct, age undetermined. She presented to the emergency department on trial Day 22 following a severe headache with hypertension and chest pain. She was admitted to the hospital. Her cardiac catheterization and ventriculogram were reported normal. She was diagnosed with stress cardiomyopathy. Her last dose of trial medication was trial Day 36 and she discontinued the trial on trial Day 42. The investigator assessed the event as serious, mild in severity, resolved, and not related to trial medication. This reviewer concurs with the investigator's assessment.

- Participant Number (b) (6) – A woman who self-identified as a Native Hawaiian/Pacific Islander female 58 years of age randomized to the 0.5 mg estradiol/50 mg progesterone treatment group with a medical history of current smoker (for 43 years), hypertension, hyperlipidemia, hot flashes, headaches, and mononeuritis neuropathy presented to the emergency room with nausea, vomiting and acute severe headache on trial Day 99. Her computed tomography (CT) of the head demonstrated subarachnoid blood filling the basal cisterns with a 7-mm basilar tip aneurism. She underwent a transcatheter coil embolization of the ruptured basilar tip aneurism. She was discharged from the hospital on trial Day 105 in stable condition with aspirin, Fioricet, famotidine and nimodipine. On trial Day 106, she was hospitalized again with a new small infarct in the left cerebellar hemisphere. Plavix was added to her treatments. She was discharged to rehabilitation on trial Day 113. A SAE was reported for cerebral infarction beginning trial Day 110 and resolving on trial Day 113. The investigator assessed the event as moderate in severity and not related to the trial medication. She continued trial participation. This participant did not reveal her subarachnoid hemorrhage until trial Day 272, at which time her trial medication was stopped. She was discontinued on trial Day 277 due to her SAE of subarachnoid hemorrhage. The investigator assessed the subarachnoid hemorrhage as severe and not related to trial medication. This reviewer concurs that the subarachnoid hemorrhage was severe and not related to trial medication.

Applicant-Identified Cerebrovascular Adverse Events of Interest:

Two trial participants experienced cerebrovascular events of interest in Trial TXC12-05:

- Participant Number (b) (6) – See the immediately preceding discussion above for this trial participant.
- Participant Number (b) (6) – A White female 49 years of age randomized to the 0.5 mg estradiol/50 mg progesterone treatment group who was diagnosed with metastatic lung cancer to the brain and experiences a SAE of cerebrovascular accident. See page 116 of this review for a full discussion.

Applicant-Identified Syncope Adverse Events of Interest:

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Ten women experienced AEs of syncope in Trial TXC12-05: two women in the 1 mg estradiol/100 mg progesterone treatment group (Numbers (b) (6) and (b) (6)), four women in the 0.5 mg estradiol/100 mg progesterone treatment group (Numbers (b) (6)), one woman in the 0.5 mg estradiol/50 mg progesterone treatment group (Number (b) (6)), and two women in the 0.25 mg estradiol/50 mg progesterone treatment group (Numbers (b) (6) and (b) (6)). Participant Number (b) (6) is discussed on page 125 of this review. Two participants, of special interest to this reviewer, are discussed below. Narratives for the remaining participants can be viewed in NDA 210132, Section 14.3.3.

- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 49 years of age randomized to the 0.5 mg estradiol/100 mg progesterone treatment group with a medical history of migraines, intermittent left side numbness, and tremor experienced an episode of syncope on trial Day 22 and aphasia on trial Day 24. She presented to the hospital on trial Day 66 after a generalized convulsive seizure episode with bladder incontinence after several days of left sided arm and leg weakness. Magnetic resonance imaging (MRI), transthoracic echocardiogram, head CT, and magnetic resonance angiogram (MRA) of the neck were negative. Her urine was positive for cannabis, but negative for other substances. She was diagnosed with seizure, bradycardia and substance abuse (cannabis). She was discharged on trial Day 67 with instruction to follow up with her primary care physician and outpatient Neurology. Her last dose of trial medication was trial Day 29. She discontinued Trial TXC12-05 on trial Day 71 with anxiety due to intermittent left-sided numbness. The investigator assessed the event as moderate in severity and not related to trial medication. This reviewer concurs with the trial investigator’s assessment.
- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 57 years of age randomized to the 0.25 mg estradiol/50 mg progesterone treatment group with a medical history of incomplete right bundle branch block on no prior medications was taken by ambulance to the hospital after a syncopal episode on trial Day 39. At Screening, her ECG was abnormal but not clinically significant. Per the participant, no conclusive cause for her syncope was provided. She did not authorize for the release of her medical records. Her last dose of trial medication was on trial Day 38. She discontinued from Trial TXC12-05 on trial Day 88 due to this event. The investigator assessed the event as moderate in severity and possibly related to trial medication. This reviewer feels that the available information is inconclusive to assess relationship to trial medication.

Applicant-Identified Breast Cancer Adverse Events of Interest:

Breast cancer AEs were reported for six (6) women participating in the active treatment groups in Trial TXC12-05. There were no reported cases of breast cancer in the placebo treatment group. Narratives for these six cases are as follows by treatment group:

- 1 mg estradiol/100 mg progesterone treatment group:
  - Participant Number (b) (6) – A woman who self-identified as a White female 56

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years of age with no known use of hormone therapy, a BMI of 24.6 kg/m<sup>2</sup>, with a medical history of benign right breast mass/needle biopsy, benign left breast mass/needle biopsy, and human Papilloma virus (HPV). Her Screening mammogram was reported as Breast Imaging-Reporting and Data System (BI-RADS) 2. Trial participant had an out of trial mammogram done (annual mammogram) on trial Day 317 which was BI-RADS 0, but revealed a suspicious mass in her right breast. A repeat mammogram with an ultrasound on trial Day 323 showed a 1.2 cm irregular right breast mass. An ultrasound-guided biopsy on trial Day 329 showed intermediate grade infiltrating ductal carcinoma of 0.5 cm size with a benign core needle biopsy of the right axillary lymph node. A breast needle localization lumpectomy with sentinel node biopsy and a left power port placement was performed on trial Day 351. Adjuvant chemotherapy was administered with radiation therapy administered post-chemotherapy. This woman was on trial medication for 331 days. She discontinued on trial Day 351. The investigator and medical monitor assessed the right breast cancer as severe and possibly related to trial medication. This reviewer concurs with this assessment.

- Participant Number (b) (6) – A woman who self-identified as a White Hispanic female 53 years of age with no history of hormone use, with a BMI of 31.30 kg/m<sup>2</sup>, with a medical history of heartburn, genital herpes, moodiness, insomnia, hot flashes, benign right breast mass/biopsy (2009), former smoker (quit 2005), and a significant family history of breast/uterine cancer. Her Screening mammogram was BI-RADS 2. End-of-trial mammogram on trial Day 256 showed two right breast masses:

- 0.8 cm x 0.9 cm x 0.6 cm irregular mass at 1 o'clock position
- 1.8 cm x 1.5 cm mass at 12 o'clock position

On trial Day 366, an ultrasound-guided biopsy of the 1 o'clock position mass revealed malignant invasive ductal carcinoma and invasive cancer and in-situ cancer (II). The mass at the 12 o'clock position indicated high risk benign radial sclerosing lesion. She tested positive for low-grade ductal carcinoma in situ with calcifications, ER 100%, 2+, PR 5%, 2+, HER-2 2+, on trial Day 379. An ultrasound-guided local excision and sentinel node biopsy was performed on post-trial Day 415. Pathology report lists diagnosis as 9 mm invasive ductal adenocarcinoma; sentinel and regional lymph nodes tested negative for metastasis. Brachytherapy via SAV1 device was administered post-trial Days 435 through 441. She continues with routine follow-up with her Oncologist. This participant completed Trial TXC12-05 and was on trial medication for 356 days. The investigator and medical monitor assessed the right breast cancer a severe and possibly related to trial medication. This reviewer concurs with this assessment.

- 0.5 mg estradiol/100 mg progesterone dosage strength:
  - Participant Number (b) (6) - See page 125 of this review for the narrative for

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this trial participant. This participant was diagnosed with invasive carcinoma of the left breast. The investigator considered this SAE as severe and possibly related to the trial medication. This reviewer concurs with the investigator's assessment.

- Participant Number (b) (6) – A woman who self-identified as a White female 53 years of age with a BMI of 31.10 kg/m<sup>2</sup> with no relevant medical history and no prior medication use. Her Screening mammogram was BI-RADS 1. Her end-of-trial mammogram on trial Day 344 was BI-RADS 4. A left breast ultrasound and additional mammographic views showed a 5-mm left breast mass in the lower outer quadrant. A stereotactic core biopsy on trial Day 367 identified invasive ductal carcinoma, micropapillary type, Nottingham Combined Histological Grade 2-3 of 3; focal associated ductal carcinoma in situ, solid type, intermediate grade. She was referred for surgical consultation, but decided to self-administer cannabidiol oil and eat a healthy diet for 3 months. She completed the trial. Her last dose of trial medication was on trial Day 358. She had follow-up magnetic resonance imaging of her left breast on post-trial Days 429 and 480, but refused to release her medical records. The investigator and medical monitor assessed the left breast carcinoma as serious and possibly related to trial medication. This reviewer concurs with this assessment.
- 0.5 mg estradiol/50 mg progesterone dosage strength:
  - Participant Number (b) (6) – A woman who self-identified as a White female 57 years of age with a BMI of 33 Kg/m<sup>2</sup> with a medical history of hypercholesterolemia, hypopituitarism, hyperthyroidism, hypertension, asthma, mitral valve prolapse on Ventolin, Advair, levothyroxine. Her Screening mammogram was BI-RADS 2. Her end-of-trial mammogram on trial Day 357 was BI-RADS 4. She completed the trial, and was on trial medication for 356 days. A right breast incisional biopsy on post-trial Day 400 revealed invasive ductal carcinoma, grade 2/3. She was estrogen and progesterone receptor positive and HER2/neu negative. A complete surgical lumpectomy and sentinel node biopsy was performed on post-trial Day 434 confirming diagnosis (sentinel nodes negative for metastatic disease). On post-trial Day 471, she completed SAVI radiation treatment. She was placed on aromatase inhibitor for 90 days. The investigator and medical monitor assessed the invasive ductal cancer as severe and possibly related to trial medication. This reviewer concurs with this assessment.
- 0.25 mg estradiol/50 mg progesterone dosage strength:
  - Participant Number (b) (6) – A woman who self-identified as a White female 52 years of age with a BMI of 24.79 kg/m<sup>2</sup> with a medical history of hypertension, hot flashes, bilateral breast implants hyperopia, former 22-year smoker, and significant family history of breast cancer on Atenolol, fexofenadine hydrochloride, magnesium, calcium. Her Screening mammogram was BI-RADS 2.

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Her end-of-trial mammogram on trial Day 366 was Bi-RADS 4 (ill-defined 1 cm lesion within the axillary tail of the left breast). She completed the trial, and was on trial medication for 365 days. Left breast core biopsies performed on post-trial Day 391 determined invasive ductal carcinoma Nottingham grade 1, estrogen and progesterone receptor positive. BRACA gene testing showed no clinically significant gene mutation. She underwent a total bilateral mastectomy, left sentinel node biopsy, removal of breast implants with immediately breast reconstruction on post-trial Day 447. Pathology report indicated fibrocystic mastopathy in the right breast with no evidence of malignancy. Histology of the left breast confirmed invasive carcinoma with ductal and lobular features (mixed type carcinoma). Ductal carcinoma in situ was present. No regional lymph node metastasis was identified. The investigator and medical monitor assessed left breast invasive ductal carcinoma as severe and possibly related to the trial medication. This reviewer concurs with this assessment.

Clinical Reviewer's Comments:

The 6 cases of breast cancer, discussed above, are evenly distributed across the 4 active estradiol/progesterone treatment groups in Trial TXC12-05. Four (4) of these 6 cases of breast cancer occurred in the 1 mg estradiol/100 mg progesterone treatment group (2 cases), and the 0.5 mg estradiol/100 mg progesterone treatment group (2 cases) (b) (4). (b) (4). The remaining 2 cases occurred in the lower dosage strengths of combined estradiol and progesterone (one in each dosage strength) (b) (4).

The 4 cases of breast cases identified in Trial TXC12-05, in the dosage strength requested for approval, are similar to the cases of breast cancers reported in The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial conducted to assess pairwise differences between placebo, unopposed estrogen [0.625 mg conjugated estrogen (CE)], and three estrogen/progestogen regimens [0.625 mg CE plus cyclic 10 mg medroxyprogesterone acetate (MPA); 0.625 mg CE plus continuous 2.5 mg MPA; and 0.625 mg CE plus 200 mg cyclic micronized progesterone (MP)] on selected heart disease risk factors. In the 3 year PEPI trial, two (2) women were diagnosed with breast cancer between 6 months and 1 year (one assigned to CE plus cyclic MP; one assigned to CE plus cyclic MPA). At the first-year examination in the PEPI trial, three (3) other breast cancers were diagnosed (2 assigned to CE plus cyclic MP, and 1 assigned to CE plus cyclic MPA).<sup>10</sup> One (1) additional case of breast cancer occurred in the CE plus cyclic MP group in the PEPI trial (duration of exposure not provided).

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<sup>10</sup> The Writing Group for the PEPI trial. Effects of Estrogen or estrogen/Progestin Regimens on Heart Disease Risk factors in Postmenopausal Women. JAMA. 1995; 273(#):199-208.

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In the US, breast cancer is diagnosed more often in woman who self-identified as White compared to woman who self-identified as Black/African American, Hispanic/Latina, Asian/Pacific Islander, or Native American/Alaska Native women.<sup>11</sup> In 2012, the incidence of breast cancer was reported as 130 cases per 100,000 women. In the US, about 1 in 8 women (12.4%) will develop invasive breast cancer.

In Trial TXC12-05, 5 of the 6 cases of breast cancer occurred in woman who self-identified as White. These 6 cases of breast cancer do not raise safety concerns for the combined estradiol/progesterone product. Labeling should include information on these 6 cases of breast cancer. FDA will monitor for breast cancer occurrence should this product gain approval.

Eight (8) additional women had “abnormal mammograms/procedure of interest” in Trial TXC12-05. All 8 women had normal mammograms at Screening, and end-of-treatment mammograms reported as BI-RADS 3 or 4, necessitating a right or left breast biopsy. Three women were in the 1 mg estradiol/100 mg progesterone treatment group:

- Participant Number (b) (6): A woman who self-identified as a White female 61 years of age; her stereotactic-guided right breast biopsy obtained on trial Day 367 contained benign findings.
- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 54 years of age who had a core biopsy of the left breast on trial Day 386 that was indeterminate with stromal fibrosis; no evidence of neoplasm.
- Participant Number (b) (6) – A woman who self-identified as a White female 58 years of age who had a stereotactic left breast biopsy on trial Day 366 reported as negative.

Two women were in the 0.5 mg estradiol/100 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a White female 54 years of age who had an ultrasound needle biopsy of the left breast on trial Day 383; the biopsy was read as benign breast tissue.
- Participant Number (b) (6) – A woman who self-identified as a White female 51 years of age had an ultrasound guided needle biopsy of the right breast on trial Day 383, which showed fibrocystic changes with apocrine metaplasia; she was recommended to have a follow-up ultrasound in 6 months.

Two women were in the 0.5 mg estradiol/50 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a White female 57

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<sup>11</sup> Howlander N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistic Review, 1975-2009 (Vintage 2009 populations), National Cancer Institute. Bethesda, MD, 2012.

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years of age who had a right breast biopsy on trial Day 399 which showed fibrocystic changes; no carcinoma.

- Participant Number (b) (6) – A woman who self-identified as a White female 58 years of age who had a stereotactic biopsy of the left breast on trial Day 374, which showed benign fibrocystic changes, microcalcifications; no carcinoma.

One woman was in the 0.25 mg estradiol/50 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a White female 45 years of age underwent an ultrasound-guided right breast biopsy on trial Day 358 reported as cystic and papillary apocrine metaplasia, no evidence of malignancy

These 8 cases of abnormal, but benign breast tissue findings, do not raise additional safety concerns for the combined estradiol/progesterone product.

Applicant-Identified Cervical Adverse Events of Interest:

Adverse events that involved an end-of trial abnormal Pap Smear are shown in Table 39.

Table 39: Summary of Pap Smear Results in Trial TXC12-05 at Month 12/End-of-Treatment (Safety Population)

	1 mg E2/ 100 mg P (n=325)	0.5 mg E2/ 100 mg P (n=338)	0.5 mg E2/ 50 mg P (n=347)	0.25 mg E2/ 50 mg P (n=334)	Placebo (n=112)
Negative (%)	306 (94.2)	324 (95.9)	332 (95.7)	320 (95.8)	112 (100.0)
ASCUS	12 (3.7)	5 (1.5)	8 (2.3)	7 (2.1)	0 (0.0)
HSIL	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
LSIL	7 (2.2)	6 (1.8)	5 (1.4)	3 (0.9)	0 (0.0)
NOS	0 (0.0)	1 (0.3)	5 (1.4)	3 (0.9)	0 (0.0)
Unsatisfactory specimen	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 69, Page 196 of 1539.

Abbreviations: E2 = estradiol; P = progesterone; ASCUS = atypical cells of undetermined significance; HSIL = high-grade squamous intraepithelial lesion; LSIL – low-grade squamous intraepithelial lesion; NOS = atypical glandular cells – not otherwise specified.

Clinical Reviewer’s Comments:

As shown in Table 39, a total of 32 cases of ASCUS were reported in active treatment groups in Trial TXC12-05 versus zero (0) cases in the placebo treatment group. ASCUS is a common finding in a Pap smear. ASCUS may be a sign of certain types of human papilloma virus (HPV) infection. There are hundreds of strains of HPV virus. Some are low risk causing warts. Some are high-risk and can cause cell changes that can turn into cervical dysplasia or cancer. ASCUS may also be a sign of a benign growth, such as a cyst or polyp. It is unusual, however, that the placebo treatment group had no reported

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cases of ASCUS on a final Pap smear in Trial TXC12-05. This discrepancy is not explained.

The following Table 40 shows women with a diagnosis of high-grade squamous intraepithelial lesion (HSIL) or low-grade squamous intraepithelial lesion (LSIL) on a final/end-of-treatment Pap smear in Trial TXC12-05.

Table 40: Women with High-Grade Squamous Intraepithelial Lesion (HSIL) or Low-Grade Squamous Intraepithelial Lesion (LSIL) in Trial TXC12-05 at Month 12/End-of-Treatment Pap Smear

Treatment Group Participant Number	Screening Pap Screening HPV	On Therapy Pap Smear	On Therapy HPV	Colposcopy Results	Follow-Up
1 mg Estradiol/100 mg Progesterone Treatment Group					
Number (b) (6)	Normal Not performed	LSIL (trial Day 176; early termination)	Negative	Colposcopy results reported as cervical intraepithelial neoplasia grade 2-3  Endocervical curettage (ECC) results reported as benign squamous and endocervical epithelium	Loop electrosurgical excision procedure (LEEP) procedure results reported as HSIL and LSIL (CIN 1 and CIN 2) and LSIL at cauterized biopsy margin
Number (b) (6)	Normal Not performed	LSIL (trial Day 402)	Negative	Refused colposcopy procedure	Preferred to see private physician
Number (b) (6)	Normal Not performed	LSIL (trial Day 358)	Negative	Colposcopy results reported as normal	A repeat Pap smear 6 months post-trial was reported as normal
Number (b) (6)	Normal Not performed	LSIL (trial Day 356)	Positive	Colposcopy results reported as normal  ECC results reported as negative for dysplasia	Instructed to have repeat Pap smear in 6 month; unknown if completed
Number (b) (6)	Normal Not performed	LSIL (trial Day 366)	Positive	Colposcopy results reported as mild dysplasia (CIN 1)	Instructed to have repeat Pap smear in 6 months; unknown if completed
Number (b) (6)	Normal Not performed	LSIL (trial Day 352)	Positive	Colposcopy results reported as mild dysplasia	Instructed to have repeat Pap smear in 1 year;

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				(CIN 1) ECC results reported cervicitis with inflammatory atypia	unknown if completed
Number (b) (6)	Normal Not performed	LSIL (trial Day 105; early termination)	Negative	No colposcopy performed	Colposcopy performed post-trial Day 514 reported as negative  ECC also performed; reported as negative
0.5 mg Estradiol/100 mg Progesterone Treatment Group					
Number (b) (6)	Normal Not performed	LSIL (trial Day 358)	Private physician performed testing on trial Day 28 reported as positive	Private physician performed colposcopy on trial Day 28 reported as squamous atypia  ECC revealed no abnormalities	Private physician repeated Pap smear post-trial reported as normal
Number (b) (6)	Normal Not performed	LSIL (trial Day 372)	Negative	Colposcopy results reported as normal	Instructed to have repeat Pap smear in 6 months; unknown if completed
Number (b) (6)	Normal Not performed	LSIL (trial Day 361)	Negative	Refused colposcopy procedure	No additional information is available
Number (b) (6)	Normal Not performed	LSIL (trial Day 356)	Positive	Colposcopy results show chronic cervicitis with squamous metaplasia  ECC results report benign endocervical glands; squamous epithelium	No additional information is available
Number (b) (6)	Normal Not performed	HSIL (trial Day 356)	Positive	Colposcopy results report endocervical mucosa, negative for dysplasia  ECC results reported as negative for	No additional information is available

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				dysplasia	
Number (b) (6)	Normal Not performed	LSIL (trial Day 359)	Positive	Colposcopy results report benign squamous epithelium	No follow-up information is provided
Number (b) (6)	Normal Not performed	LSIL (trial Day 360)	Positive	Colposcopy results report tissue consisted with cervix with focal chronic inflammation  ECC results reports fragments of squamous epithelium with focal high-grade dysplasia; tissue insufficient	Instructed to follow-up with private physician; no follow-up information is provided

Source: Adapted from NDA 210132 Clinical Study Report; Table 70, page 198 of 1539.

Abbreviations: Pap = Papanicolaou smear; HPV = human papillomavirus; HSIL = high-grade squamous epithelial lesion; LSIL = low-grade squamous intraepithelial lesion; ECC = endocervical curettage; LEEP = loop electrosurgical excision procedure

Clinical Reviewer’s Comments:

Only 1 of the 14 women in Table 40 had a diagnosis of HSIL (participant Number (b) (6) in the 0.5 mg estradiol/100 mg progesterone treatment group); the remaining 13 women has a diagnosis of LSIL. All 14 women had HPV testing (participant Number (b) (6) outside of Trial TX12-05); 8 reported as positive and 6 reported as negative. Colposcopy results are available for 11 of the 14 women. Participant Number (b) (6), had a LEEP procedure post-trial which showed HSIL and LSIL. All other finding are considered normal.

These 14 cases do not raise safety issues for the combined estradiol/progesterone product with respect to an increase in observed cervical intraepithelial lesions.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Common treatment-emergent adverse events (TEAEs) are presented in Table 41, in descending order of frequency, for each individual active treatment group and all active estradiol/progesterone treatment groups combined and the placebo treatment group.

Table 41: Incidence of Treatment-Emergent Adverse Events Occurring in ≥ 3 Percent in Any Treatment Group in Trial TXC12-05 (Safety Population)

	1 mg E2/ 100 mg P	0.5 mg E2/ 100 mg P	0.5 mg E2/50 mg P	0.25 mg E2/50 mg P	Total Active Treatment	Placebo

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	(N=415)	(N=424)	(N=421)	(N=424)	(N=1684)	(N=151)
Headache	31 (7.5)	24 (5.7)	45 (10.7)	43 (10.1)	143 (8.5)	4 (2.6)
Nasopharyngitis	25 (6.0)	41 (9.7)	37 (8.8)	24 (5.7)	127 (7.5)	4 (2.6)
Upper respiratory tract infection	22 (5.3)	26 (6.1)	34 (8.1)	15 (3.5)	97 (5.8)	6 (4.0)
Nausea	20 (4.8)	25 (5.9)	19 (4.5)	16 (3.8)	80 (4.8)	2 (1.3)
Back pain	22 (5.3)	11 (2.6)	15 (3.6)	15 (3.5)	63 (3.7)	1 (0.7)
Abdominal pain	22 (5.3)	10 (2.4)	14 (3.3)	15 (3.5)	63 (3.7)	4 (2.6)
Sinusitis	20 (4.8)	15 (3.5)	13 (3.1)	13 (2.0)	61 (3.6)	3 (2.0)
Dizziness	17 (4.1)	15 (3.5)	10 (2.4)	8 (1.9)	50 (3.0)	3 (2.0)
Pelvic pain	17 (4.1)	15 (3.5)	10 (2.4)	7 (1.7)	49 (2.9)	0 (0.0)
Diarrhea	13 (3.1)	13 (3.1)	11 (2.6)	11 (2.6)	48 (2.9)	2 (1.3)
Vulvovaginal mycotic infection	14 (3.4)	15 (3.5)	14 (3.3)	5 (1.2)	48 (2.9)	4 (2.6)
Abdominal distention	15 (3.6)	6 (1.4)	11 (2.6)	11 (2.6)	43 (2.6)	1 (0.7)
Vaginal discharge	16 (3.9)	13 (3.1)	7 (1.7)	7 (1.7)	43 (2.6)	1 (0.7)
Hypertension	7 (1.7)	13 (3.1)	9 (2.1)	12 (2.8)	41 (2.4)	2 (1.3)
Influenza	4 (1.0)	6 (1.4)	14 (3.3)	12 (2.8)	36 (2.1)	2 (1.3)
Vaginal hemorrhage	14 (3.4)	10 (2.4)	3 (0.7)	8 (1.9)	35 (2.1)	1 (0.7)

Source: Adapted from NDA 210132, Trial TXC Clinical Study Report, Table 43 on page 127 of 1539 and Table 14.4.4.2.4 on page 1354 of 1539.

Abbreviations: E2 = estradiol; P = progesterone.

Note: All information obtained from the adverse events case report form (AE CRF). At each level of summation (overall, SOC, PT), participants reporting more than one TEAE are counted only once.

Clinical Reviewer's Comments:

Overall, the most common TEAE ( $\geq 3\%$ ) across all active treatment groups in Trial TXC12-05 were headache (8.5%), nasopharyngitis (7.5%), breast tenderness (5.9%), upper respiratory tract infection (5.8%), nausea (4.8%), back pain (3.7%), abdominal pain (3.6%), sinusitis (3.6%), and dizziness (3.0%).

All common TEAEs occurred more frequently in the active treatment groups as compared to placebo. This finding is not unexpected.

The incidences of treatment-related TEAEs (investigator assessed event as “possibly related”, “probably related”, or “definitely related”) by descending order of frequency, are presented in Table 42.

Table 42: Incidence of Related Treatment-Emergent Adverse Events Occurring in  $\geq 3$  Percent in Any Treatment Group and More Commonly than Placebo in Trial TXC12-05 (Safety Population)

	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)

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Breast tenderness	43 (10.4)	17 (4.0)	25 (5.9)	10 (2.4)	1 (0.7)
Headache	14 (3.4)	17 (4.0)	22 (5.2)	24 (5.7)	1 (0.7)
Nausea	9 (2.2)	15 (3.5)	11 (2.6)	8 (1.9)	1 (0.7)
Pelvic pain	13 (3.1)	12 (2.8)	8 (1.9)	6 (1.4)	0 (0.0)
Vaginal hemorrhage	14 (3.4)	10 (2.4)	3 (0.7)	8 (1.9)	0 (0.0)
Vaginal discharge	14 (3.4)	8 (1.9)	6 (1.4)	6 (1.4)	1 (0.7)

Source: Adapted from NDA 210132, Trial TXc12-05 Clinical Study Report, Table 43, page 127 of 1539.

Abbreviations: E2 = estradiol; P = progesterone.

Note: All information obtained from the adverse events case report form (AE CRF). At each level of summation (overall, SOC, PT), participants reporting more than one TEAE are counted only once.

### Clinical Reviewer's Comments:

The events presented in Table 41 are those that would be expected with an estradiol/progesterone combined product. The incidence of these common events appears similar to that seen in a trial conducted with conjugated estrogens plus micronized progesterone given orally for 12 days sequentially per 28-day cycle. These TEAEs, determined to be treatment related, should appear in product labeling if the drug product is approved.

### 8.4.6. Laboratory Findings

Each clinical laboratory parameter for the Safety population was summarized using descriptive statistics (including mean and SD, median, minimum, and maximum) for each time point and change from Baseline. Shifts in laboratory values and potentially clinically important findings were also summarized. Individual laboratory values are available in the application and can be found in the listings for: hematology, chemistry, coagulation, and lipids.

Hematology parameters were evaluated at Screening (Baseline), Week 12, Month 6, Month 9, and Month 12 (or Early Termination). Five women in Trial TXC12-05 (participants Numbers (b) (6)) had hemoglobin and/or hematocrit values that were clinically significant. Participants Numbers (b) (6) and (b) (6) in the 1 mg estradiol/100 mg progesterone treatment group and participant Number (b) (6) in the 0.25 mg estradiol/50 mg progesterone treatment group had medical histories of anemia and low hematocrit prior to the start of Trial TXC12-05. These 3 trial participants had fluctuating hematocrits during trial participation. Trial participant Number (b) (6) had an AE for cold agglutinins on trial Day 209, and was evaluated by a hematologist on trial Day 281 with a follow-up on trial Day 302. She was clinically asymptomatic, hematologically stable, requiring no treatment. The investigator considered her AE for cold agglutinins moderate in severity and not related to trial medication. This reviewer agreed with the investigator's assessment.

Trial participant Number (b) (6) had a medical history of uterine fibroids at Screening. She reported intermittent vaginal spotting for a total of 11 days and heavy vaginal bleeding for a total of 16 days. She completed the clinical trial. Her end-of trial endometrial biopsy consensus

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diagnosis was endometrial tissue (other); endometrial polyp not present. The investigator assessed the vaginal bleeding as related to fibroid and trial medication use. This reviewer agrees with the investigator's assessment.

Trial participant Number (b) (6), with normal hematologic findings at Screening showed below normal findings at end-of-trial (trial Day 358), specifically a hemoglobin of 61 g/L (lab normal = 120-155 g/L), hematocrit of 18.0 L/L (lab normal = 36-46 L/L), erythrocytes of  $1.45 \times 10^{12}/L$  (lab normal =  $3.7-5.2 \times 10^{12}/L$ ), and a platelet count of  $52 \times 10^9/L$  (lab normal =  $150-450 \times 10^9/L$ ), deemed severe and not related to trial medication by the investigator. Her private physician diagnosed myelodysplastic syndrome. She was treated with blood transfusion and chemotherapy. She refused to release her medical records, and no further information is available. Full narratives for these 5 trial participants are available in NDA 210132, Section 14.3.3.

Clinical Reviewer's Comments:

Overall, there were no unexplained clinically meaningful changes in the mean hematology values over time or across groups, and no signals were detected.

Chemistry parameters were evaluated at Screening (Baseline), Week 12, Month 6, Month 9, and Month 12 (or Early Termination). Twelve (12) women had AST/ALT laboratory values that were clinically significant. In 6 women, liver function test (LFTs) were fluctuating and transient with return to normal (participant Number (b) (6) in the 1 mg estradiol/100 mg progesterone treatment group, participants Number (b) (6) and (b) (6) in the 0.5 mg estradiol/100 mg progesterone treatment group, participant Number (b) (6) in the 0.5 mg estradiol/50 mg progesterone treatment group, and participants Number (b) (6) and (b) (6) in the placebo treatment group). Two (2) women gave medical histories of significant alcohol use (participant Number (b) (6) in the 0.5 mg estradiol/100 mg progesterone treatment group, and participant Number (b) (6) in the 0.25 mg estradiol/50 mg progesterone treatment group); positively associated with increases in AST/ALT. Participant Number (b) (6) in the 1 mg estradiol/100 mg progesterone treatment group was diagnosed with Hepatitis C on trial Day 147. Participant Number (b) (6) in the 0.5 mg estradiol/100 mg treatment group was admitted to the hospital on trial Day 28 with hepatitis steatosis/cirrhosis and elevated LFTs. Elevated AST/ALT was assessed as not related to trial medication in these two women. Narratives are available in the application, in Section 4.3.3 for all these trial participants.

Clinical Reviewer's Comments:

Overall, the mean change from Baseline to end-of trial in ALT ranged from -2.1 to 0.0 U/L for the active treatment groups compared to 1.6 U/L for the placebo treatment group; and for AST, -0.7 to 0.3 U/L compared to 0.8 U/L. These changes do not present safety concerns for the combined estradiol/progesterone product.

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Coagulation parameters, including antithrombin III, activated partial thromboplastin time, fibrinogen, prothrombin international normalized ratio, Protein C (Factor XIV) and Protein S, and prothrombin time, were evaluated at Screening (Baseline), Week 12, Month 6, Month 9, and Month 12 (or Early Termination). Factor V Leiden was also measured at Screening. Trial participants Number (b) (6) (randomized to 0.25 mg estradiol/50 mg progesterone treatment group), and trial participant Number (b) (6) (randomized to the 0.25 mg estradiol/50 mg progesterone treatment group) had an AE of prolonged activated partial thromboplastin time (aPTT) that led to discontinuation:

- Participant Number (b) (6) – A woman who self-identified as a White female 49 years of age with reported normal coagulation parameters at Screening, had an elevated aPTT on trial Day 183 (49 seconds; laboratory normal = 22-36 seconds), repeated on trial Day 195 (44 seconds) that led to discontinuation (other coagulation parameters reported within normal range). Her last dose of trial medication was on trial Day 189. There was no treatment for this AE which was ongoing at discontinuation (trial Day 204). The investigator assessed this AE as mild in severity and not related to trial medication.
- Participant Number (b) (6) – A woman who self-identified as a White female 53 years of age with reported normal coagulation parameters at Screening, had an elevated aPTT on trial Day 109 (41 seconds; laboratory normal = 22-36 seconds; resolved on trial Day 124) that led to discontinuation (other coagulation parameters reported within normal range). Her last dose of trial medication was on trial Day 108. The investigator assessed the AE as moderate in severity and possibly related to trial medication.

Trial participant Number (b) (6) (randomized to the 0.25 mg estradiol/50 mg progesterone treatment group) experienced an AE of decreased blood fibrinogen that led to discontinuation:

- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 56 years of age with near normal coagulation parameters at Screening, had an increased aPTT (42 seconds), prothrombin time (PT; 13.1 seconds, laboratory normal = 9.4-12.9 seconds), prothrombin international normalized ratio (INR; 1.2, laboratory normal = 0.9-1.1 seconds) on trial Day 268; resolved on trial Day 338. There was no treatment for these AEs. She discontinued on trial Day 347. Her last dose of trial medication was on trial Day 332. The events were considered mild in severity and possibly related to trial medication.

Clinical Reviewer's Comments:

No clinical sequelae occurred from these reported AEs. All three cases of altered coagulation parameters could have been related to trial medication. (b) (4)

Lipid parameters were evaluated at Screening (Baseline), Week 12, Month 6, Month 9, and

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Month 12 (or Early Termination). A total of six (6) trial participant had elevated triglyceride values. Three (3) of these 6 women were in the 0.5 mg estradiol/100 mg progesterone treatment group (Numbers (b) (6)) and 1 was in the placebo treatment group (Number (b) (6)). The remaining 2 participants were in the two lower estradiol/progesterone treatment groups (1 each).

Clinical Reviewer's Comments:

Across Trial TXC12-05 visits, elevated triglycerides were transient, resolved by end-of-treatment, or not clinically significant for 2 participants in the 0.5 mg estradiol/100 mg progesterone treatment groups (participants Number (b) (6) and (b) (6)). Participant Number (b) (6), who completed Trial TXC12-05, had ongoing elevated triglyceride at end-of-treatment and was referred to her private physician for follow-up. These cases of elevated triglycerides do not raise safety concerns for the combined estradiol/progesterone product.

8.4.7. Vital Signs

Vital signs were measured at all visits. The application summarized the mean change from Baseline to Week 4, Week 8, Week 12, Month 6, Month 9, Month 12, and Month 12/ET. Per the information provided in the application, there were little changes in systolic and diastolic blood pressure, and heart rate.

Five (5) trial participants reported weight increase during trial participation with weight gains between 18.2 and 23.9 kilograms (40.1 to 52.7 pounds). Trial participant Number (b) (6) and Number (b) (6) were in the 1 mg estradiol/100 mg progesterone treatment group; and trial participant Number (b) (6) and (b) (6) were in the 0.5 mg estradiol/100 mg progesterone treatment group. The remaining trial participant was in the 0.5 mg estradiol/50 mg progesterone treatment group (participant Number (b) (6)). Each of these 5 trial participants self-identified as Black/African American. All completed the clinical trial except for participant Number (b) (6) who discontinued due to herpes simplex on lips that stated on trial Day 55.

Clinical Reviewer's Comments:

There were no trends or clinically meaningful differences in blood pressure or heart rate in Trial TXC12-05.

Weight gain is known to be associated with estrogen and progesterone use. Weight gain of 40.1 to 52.7 pounds is significant and could be related or result in other clinically adverse outcomes. It is to be noted that this excess weight gain occurred in women who self-identified as Black/African American.

8.4.8. Electrocardiograms (ECGs)

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ECG assessments at Screening (Baseline) and Month 12/ET are summarized in the NDA application. No ECG abnormalities were reported in any treatment group at Baseline. At end-of-trial, 10 clinically significant abnormal ECG results were reported across the 4 active treatment groups versus no reports of abnormal ECG in the placebo treatment group. Four (4) of these clinically significant abnormal results occurred in the two lower dosage strengths of combined estradiol/progesterone. Their narratives can be found in NDA 210132, Section 14.3.3. The remaining six cases occurred in the 1 mg estradiol/100 mg progesterone treatment group (1 case) and the 0.5 mg estradiol/100 mg progesterone treatment group (5 cases). Brief narrative descriptions follow:

1 mg estradiol/100 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 65 years of age with a Screening ECG read as abnormal, not clinically significant sinus rhythm anterior T wave changes are nonspecific. On trial Day 361, her ECG was read as abnormal, clinically significant ECG notable for sinus bradycardia, and non-specific anteroseptal and lateral T wave changes. She completed the clinical trial. She was referred to a Cardiologist and evaluated 6-months post-treatment. Her ECG was read as normal sinus rhythm with no-specific T wave changes. A stress test results were negative for ischemia. The investigator assessed the AE as mild in severity and not related to trial medication. This reviewer concurs with the investigator's assessment.

0.5 mg estradiol/100 mg progesterone treatment group:

- Participant Number (b) (6) – See narrative for this trial participant on page 126 of this review.
- Participant Number (b) (6) – A woman who self-identified as an Asian female 52 years of age with a Screening ECG read as sinus bradycardia, rate 55 beats per minute, not clinically significant. On trial Day 356, her ECG was read as abnormal ECG: normal sinus rhythm, T wave abnormality, consider anterior ischemia. She did not report any AEs, and completed the clinical trial. She was referred to a cardiologist, however, no further information is provided. The investigator assessed the AE as mild and not related to trial medication. This reviewer does not have enough information to agree or disagree.
- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 48 years of age with a Screening ECG read as abnormal, not clinically significant: sinus arrhythmia, possible left atrial enlargement. She had an AE of hypertension on trial Day 360, considered mild in severity and not related to trial medication. She was treated with Amlodipine 5 mg. Her ECG on the same day was read as sinus rhythm with frequent premature ventricular complexes in a pattern of bigeminy; right atrial enlargement. Her blood pressure was recorded as 155/100 mmHg. A follow-up ECG, done on trial Day 388, was read as normal. The investigator assessed the AE as mild in severity and not related to trial medication. This reviewer concurs with the investigator's assessment.

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- Participant Number (b) (6) – A woman who self-identified as a White female 60 years of age with a Screening ECG read as not clinically significant finding of sinus rhythm with prolonged PR interval. Her ECG on trial Day 358 was read as clinically significant abnormal ECG: sinus bradycardia with prolonged PR interval (atrioventricular block, first degree). She completed the clinical trial. No action was taken for this event. The investigator assessed the as mild in severity and possibly related to trial medication. The reviewer agrees with the investigator’s assessment. This participant should have been referred for follow-up with a cardiologist.
- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 52 years of age with a Screening ECG read as normal. Her ECG on trial Day 364 was read as clinically significant with findings of sinus rhythm with borderline first degree atrioventricular block. The participant completed the clinical trial, and saw her private physician. She reported that “everything was normal”. No investigator assessment is provided.

### Clinical Reviewer’s Comments:

None of these cases of clinically abnormal ECGs raise safety concern for the combined estradiol/progesterone product. Five (5) of the six women discussed above had Screening ECGs showing abnormal, but not clinically significant, findings.

### 8.4.9. QT

No thorough QT clinical trial was conducted during the development program for this combined oral estradiol/progesterone product. The application relies on relevant published literature to inform thorough QT. Endogenous and exogenous sex hormones have been shown to affect the QT interval.<sup>12</sup>

### 8.4.10. Immunogenicity

No immunogenicity safety issues are reported for the combined 1 mg estradiol/100 mg progesterone (b) (4) drug product.

## 8.5. Analysis of Submission-Specific Safety Issues

### 8.5.1. Endometrium

The primary safety endpoint in phase 3 Trial TXC12-05 was the incidence of endometrial hyperplasia at 12 months (to demonstrate a hyperplasia proportion that was  $\leq 1\%$  with an

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<sup>12</sup> Sedlah T, et al. J Women’s Health (Larchmt). Sex hormones and the QT interval: a review. 2012Sep;21(9):933-941.

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upper bound of the one-sided 95% CI for that rate that does not exceed 4%) based on an *a priori* plan in which a consensus among two out of three pathologists was the final endometrial pathology diagnosis. Per the protocol, trial participants who had an endometrial malignancy were not included in the numerator or denominator of the incidence calculation.

For the primary endpoint, all endometrial biopsies were centrally read by three pathologists. Each pathologist classified the biopsies into one of the following three categories:

- Category 1: Non-endometrial malignancy/non-hyperplasia - includes proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern, secretory endometrium, endometrial tissue (other) [that is, benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc], endometrial tissue insufficient for diagnosis, no endometrium identified, no tissue identified, other.
- Category 2: Endometrial hyperplasia includes simple hyperplasia with or without atypia and complex hyperplasia with or without atypia.
- Category 3: Endometrial malignancy.

Clinical Reviewer's Comments:

Per the protocol, the reads of the two primary pathologists, designated by the applicant *a priori*, were utilized. Consensus was reached when the two primary pathologist readers agreed on any of the above categories. For example, any two subcategories of "Non-endometrial malignancy/non-hyperplasia" was classified as "Category 1: Non-endometrial malignancy/nonhyperplasia"; if the primary pathologists disagreed on the presence of hyperplasia, the result of the third pathologist was utilized and the final decision regarding the presence of hyperplasia was based on the diagnosis of the majority.

We do not concur with the proposed Category 1, 2, and 3 classifications of endometrial histology. Per the Agency's 2003 draft Hormone Therapy Guidance for Industry, we recommend that the endometrial tissue obtained by endometrial biopsy at Screening, during the conduct of the trial, and at the end-of-trial be evaluated using standardized criteria for the diagnosis of endometrial hyperplasia as proposed in Blaustein's pathology test (Pathology of the Female Genital Tract) and not Category 1, 2, and 3 as presented in the application.

Standardized Histologic Characteristics of the Endometrium as provided in Blaustein's pathology text include the following:

0. No tissue
1. Tissue insufficient for diagnosis
2. Atrophic
3. Inactive
4. Proliferative

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- d. Weakly proliferative
  - e. Active proliferative
  - f. Disordered proliferative
5. Secretory
    - c. Cystic type
    - d. Progestational type
  6. Menstrual type
  7. Simple hyperplasia without atypia
  8. Simple hyperplasia with atypia
  9. Complex hyperplasia without atypia
  10. Complex hyperplasia with atypia
  11. Carcinoma

As shown, Category 1 is similar to Blaustein's standardized characteristics numbers 0 through 5 of Blaustein's pathology text, but does not include Blaustein's number 6. Menstrual type. Category 2 and Category 3 are in compliance with Blaustein's pathology text (Category 2 = numbers 7, 8, 9 and 10; Category 3 = number 11).

Per the application, a supplemental secondary analysis was performed based on the results from the three independent pathologists.

Clinical Reviewer's Comments:

This reviewer considers the analysis of the three individual pathologists of primary interest, not a supplemental secondary analysis. The 2003 draft Hormone Therapy Guidance for Industry recommends concurrent readings by three independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists is accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis.

The primary analysis population for endometrial safety in Trial TXC12-05 was the ES population. Analyses were also conducted for the overall Safety population for those women with a Screening and a post-Baseline endometrial biopsy. The application contains a by-woman listing of the endometrial biopsy results for the ES population and the Safety population. The application also presents by-woman listing of the endometrial biopsy results, by category and pathologists for the ES population and the Safety population.

No case of endometrial hyperplasia was reported, by the applicant, during phase 3, 52-weeks Trial TXC12-05. Per the application, all women with a uterus had a final diagnosis, per the Pathology Charter, of Category 1 (non-endometrial malignancy/non-endometrial hyperplasia),

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equivalent to Blaustein's Histology Characteristics of the Endometrium numbers 1 through 5. See Table 43.

Table 43: Incidence of Endometrial Hyperplasia in 52-Weeks Trial TXC12-05 (ES Population)

	1 mg E2/ 100 mg P (N=280)	0.5 mg E2/ 100 mg P (N=303)	0.5 mg E2/ 50 mg P (N=306)	0.25 mg E2/ 50 mg P (N=274)	Placebo (N=92)
Hyperplasia incidence rate (%)	0/280 (0.00)	0/303 (0.00)	0/306 (0.00)	0/274 (0.00)	0/92 (0.00)
One-sided upper 95% CI	1.06%	0.98%	0.97%	1.09%	3.20%

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 38, Page 121 of 1539.

Abbreviations: E2 = estradiol; P= progesterone; CI = confidence interval.

Clinical Reviewer's Comments:

As stated previously, the results of the three independent pathologists, using standardized Blaustein's Histologic Characteristics of the Endometrium, are of primary interest in determining the safety of this combined estradiol/progesterone drug product.

Applicant-Identified Adverse Events Related to the Endometrium:

Four trial participants had reported AEs of an abnormal biopsy of the endometrium in Trial TXC12-05: 3 (0.7%) in the 1 mg estradiol/100 mg progesterone treatment group (one of the two dosage strengths requested for approval), and 1 (0.2%) in the 0.25 mg estradiol/50 mg progesterone treatment group (a dosage strength not requested for approval). One of these 4 participant had a Screening endometrial biopsy reported as disordered proliferative endometrium (participant Number (b) (6)), and all 4 participants reported bleeding and/or spotting during Trial TXC12-05. These participants are discussed below:

1 mg estradiol/100 mg progesterone dosage strength:

- Participant Number (b) (6) - A woman who self-identified as a White female 50 years of age, one year since her last menstrual period, with a medical history of dysmenorrhea, menorrhagia, anemia, and no relevant prior medication use. Her Screening endometrial biopsy was reported as endometrial tissue (other) by two pathologists. She recorded vaginal spotting in her diary on trial Days 311, 324 to 325, and 333 to 334; and vaginal bleeding on trials Days 326 to 332. She reported pelvic pain on trial Day 326, resolved trial Day 333. A pelvic ultrasound performed on trial Day 331 showed an endometrial thickness of 12.8 mm with "thick, dense endometrium with cystic areas and normal adnexa". An end-of-trial endometrial biopsy on trial Day 358 was reported as follows:
  - Pathologist # 1: Disordered proliferative pattern; endometrial polyp not present
  - Pathologist # 2: Proliferative endometrium; endometrial biopsy not present
  - Pathologist # 3: Endometrial tissue (other); endometrial biopsy not present

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Provera (medroxyprogesterone acetate) 20 mg daily was started on trial Day 368 and completed on trial Day 374. She completed Trial TXC12-05, taking her last dose of trial medication on trial Day 357. A follow-up endometrial biopsy was performed on post-trial Day 526 which showed:

- Pathologist # 1: Endometrial tissue (other); endometrial polyp not present
- Pathologist # 2: Endometrial tissue (other); endometrial polyp not present
- Pathologist # 3: Endometrial tissue (other); endometrial polyp not present

The AE of “disordered proliferative pattern” was assessed by the investigator as mild in severity and definitely related to the trial medication. This reviewer concurs with the investigator’s assessment.

Clinical Reviewer’s Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as disordered proliferative pattern; endometrial polyp not present (disagreement between three pathologists; the most severe histologic classification is the final diagnosis). She was appropriately treated, and her follow-up endometrial biopsy showed normal results.

- Participant Number (b) (6) - A woman who self-identified as a Black/African American female 51 years of age, 6.5 years since her last menstrual period with a medical history of uterine fibroids and fibroidectomy with no relevant prior medication use. Her Screening endometrial biopsy was reported as endometrial tissue (other) by two pathologists. She reported intermittent vaginal spotting in her trial diary a total of 31 days beginning on trial Day 1 through trial Day 219, and intermittent vaginal bleeding a total of 21 days (beginning trial Day 73 through trial Day 221). A transvaginal ultrasound performed on trial Day 206 for vaginal bleeding showed an endometrial thickness of 14.7 mm with a “bulky posterior likely adenomyotic uterus”. An unscheduled endometrial biopsy performed on trial Day 219 was reported as follows:
  - Pathologist # 1: Disordered proliferative pattern; endometrial polyp not present
  - Pathologist # 2: Complex hyperplasia without atypia; polyp with hyperplasia without atypia
  - Pathologist # 3: Disordered proliferative pattern, endometrial polyp not presentShe was started on 10 mg medroxyprogesterone acetate twice daily starting on trial Day 245 through trial Day 318. A sonohysterogram was performed on trial Day 260. The results revealed 1.3 mm anterior and 1.7 mm posterior endometrial thickness and a 3.4 x 0.18 x 1.3 cm endometrial polyp with vascularity. A polypectomy was performed on trial Day 294. The pathology reports indicated “benign fragmented endometrial/encocervical polyp”. She was discontinued from Trial TXC12-05 on trial Day 294 due to abnormal endometrial biopsy. Her last date of trial medication was trial Day 233. The investigator assessed the abnormal endometrial biopsy as moderate in

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severity and probably related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as disordered proliferative pattern; endometrial polyp not present (agreement of pathologist # 1 and pathologist # 3). Note that pathologists # 2 diagnosed the endometrial histology as complex hyperplasia without atypia; polyp with hyperplasia without atypia. Under the 2003 Hormone Therapy Guidance for Industry recommendations, the final diagnosis was the agreement of pathologist #1 and pathologist # 3. Participant Number (b) (6) was appropriately treated, and her follow-up polypectomy showed benign fragmented endometrial/endocervical polyp.

- Participant Number (b) (6) - A woman who self-identified as a White female 52 years of age, 9 months since her last menstrual period (FSH was 114.3 IU/L) with a medical history of dermoid cyst, fibroid, and no relevant prior medication use. Her Screening endometrial biopsy was reported as disordered proliferative pattern; endometrial polyp not present by two pathologists. She reported intermittent vaginal spotting in her trial diary for a total of 36 days beginning on trial Day 16 through trial Day 252. She also reported intermittent vaginal bleeding in her trial diary beginning of trial Day 17 through trial Day 249. She took her last dose of trial medication on trial Day 252. An endometrial biopsy performed at her early termination visit on trial Day 267 was reported as follows:

- Pathologist # 1: Disordered proliferative pattern; only focally disordered; endometrial polyp not present
- Pathologist # 2: Simple hyperplasia without atypia; endometrial polyp not present
- Pathologist # 3: Proliferative endometrium; endometrial polyp not present

The investigator offered this woman treatment, which she declined, indicating that she would follow up with her private Gynecologist. She withdrew her consent on trial Day 282. No further information is available. The investigator assessed the event as ongoing, moderate in severity, and probably related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for industry, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as simple hyperplasia without atypia; endometrial polyp not present (no agreement between pathologist; the most severe histologic

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classification is final diagnosis). It is not clear why this participant with a Screening diagnosis of disordered proliferative endometrium was allowed to participate in Trial TXC12-05. The outcome for participant Number (b) (6) is not known, as no further information is available.

0.25 mg estradiol/50 mg progesterone dosage strength:

- Participant Number (b) (6) - A woman who self-identified as a White female 63 years of age, 6 years since her last menstrual period with no relevant medical history or relevant prior medication use. Her Screening endometrial biopsy was reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She reported intermittent vaginal spotting in her trial diary for a total of 52 days beginning on trial Day 1 through trial Day 348. She did not report any vaginal bleeding. An endometrial biopsy performed at her end-of-trial visit on trial Day 352 was reported as follows:
  - Pathologist #1: Endometrial tissue (other); highly inflamed mildly atypical endocervical epithelial proliferation, favor reactive over neoplastic; endometrial polyp not present
  - Pathologist #2: Complex hyperplasia with atypia; atypical mucinous epithelium, appears associated focally with atrophic endometrial glands; endometrial polyp not present
  - Pathologist # 3: Endometrial tissue (other); endometrial polyp not presentA fractional dilation and curettage performed on trial Day 378 revealed scant detached fragments of benign ectocervical and endocervical mucosa in a background of mucinous debris, very scant fragments of inactive endometrium. The investigator assessed the event as moderate in severity and possibly related to trial mediation. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. This reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of pathologist # 1 and pathologist # 3). No further information is provided. I note that pathologist #2 provided a more severe diagnosis of complex hyperplasia with atypia, however, following the 2003 draft Hormone Therapy Guidance for Industry recommendations, the final diagnosis should follow the agreement of two out of the three pathologists.

Applicant-Identified Endometrial Biopsy Results of Interest:

Per the application, three trial participants in the Safety population had endometrial biopsy results of interest. One each in the 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone treatment groups, (b) (4)

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(participant Number (b) (6) and participant Number (b) (6), respectively). The third case was in the 0.5 mg estradiol/50 mg progesterone treatment group (b) (6). Narratives for participants Number (b) (6) and (b) (6) are not included in the application, but were requested on July 6, 2018.

1 mg estradiol/100 mg progesterone dosage strength:

- Participant Number (b) (6) -This trial participant is discussed under Applicant-Identified Adverse Events Related to the Endometrium on page 148 of this review.

0.5 mg estradiol/100 mg progesterone dosage strength:

- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 62 years of age, 6 years since her last menstrual period with no relevant medical history or prior medication use. Her Screening endometrial biopsy was reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She did not report any vaginal spotting or bleeding during the trial. She completed the trial and took her last dose of trial medication on trial Day 357. An endometrial biopsy performed on trial Day 358 was reported as follows:

- Pathologist # 1: Simple hyperplasia without atypia; tissue fragmentation prevents exact classification, also chronic endocervicitis; endometrial polyp not present
- Pathologist # 2: Proliferative endometrium; mostly detached glandular fragments, inflamed cervix present; endometrial polyp not present
- Pathologist # 3: Endometrial tissue (other); endometrial polyp not present

Per the investigator, no procedures were deemed necessary or performed as follow-up to the endometrial biopsy. The investigator did not classify severity of the adverse event or provide an assessment of relationship to trial medication.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as simple hyperplasia without atypia; endometrial polyp not present (no agreement between the three pathologists; the most severe histologic classification is the final diagnosis).

0.5 mg estradiol/50 mg progesterone dosage strength:

- Participant Number (b) (6) – A woman who self-identified as a White female 59 years of age, 10 years since her last menstrual period. Her Screening endometrial biopsy was reported as endometrial tissue (other); endometrial polyp not present, by two pathologists. She did not report any vaginal spotting or bleeding during the trial. She completed the trial and took her last dose of trial medication on trial Day 356. An

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endometrial biopsy performed on trial Day 357 was reported as follows:

- Pathologist # 1: Endometrial tissue (other); endometrial polyp not present
- Pathologist # 2: Proliferative endometrium; endometrial polyp not present
- Pathologist # 3: Complex hyperplasia without atypia; endometrial polyp not present

The investigator recommended that the participant follow-up with her Gynecologist and Primary Care Physician regarding the endometrial biopsy results. This action is not in compliance with agreed upon safety procedures to follow-up participant until adverse event stable or resolved. The investigator did not classify the severity of the adverse event or provide an assessment of relationship to trial medication.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as complex hyperplasia without atypia; endometrial polyp not present (no agreement between the three pathologists; the most severe histologic classification is the final diagnosis). (b) (4)

Applicant-Identified Endometrial Biopsy Results with Follow-up Dilatation and Curettage:

Four trial participants had dilatation and curettage performed following assessments of their end-of trial endometrial biopsy reports. These four trial participants are discussed below:

1 mg estradiol/100 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a Black/African American female 58 years of age, 10 years since her last menstrual period with no relevant medical history and no prior medications used. Her Screening endometrial biopsy was reported as endometrial tissue (other) by two pathologists. She reported vaginal bleeding on trial Days 214-215, 229-230, 243-244, and 331. She completed Trial TXC12-05. Her last day of trial medication was trial Day 358. Her end-of-trial endometrial biopsy performed on trial Day 359 reported as:
  - Pathologists # 1: Endometrial malignancy: few atypical glands with a mucinous component most consistent with endometrial neoplasia; endometrial polyp not present
  - Pathologist # 2: Endometrial tissue (other); endometrial polyp not present
  - Pathologist # 3: Endometrial tissue (other); endometrial polyp not present

Two dilatation and curettage samples collected on post-trial Day 408 showed:

First sample:

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- Pathologist #1: No endometrium identified, scanty benign squamous and endocervical epithelium; endometrial polyp not present
  - Pathologist # 2: No endometrium identified; endometrial polyp not present
- Second sample:
- Pathologist # 1: No endometrium identified; endometrial polyp not present
  - Pathologist # 2: Endometrial tissue (other); benign endometrial polyp
- The investigator determined results were normal. No additional follow-up is available. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of pathologist # 2 and pathologist # 3).

0.5 mg estradiol/100 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a White female 58 years of age with no relevant medical history and no prior medications use. Her Screening endometrial biopsy was reported as endometrial tissue (other) by two pathologists. She had a basal cell carcinoma (nose) diagnosed on trial Day 43 (assessed by the investigator as moderate in severity and not related to trial medication) which precipitated her early termination. Her early termination endometrial biopsy performed on trial Day 178 was reported as:
  - Pathologist # 1: Endometrial tissue (other); endometrial polyp not present
  - Pathologist # 2: Endometrial tissue (other); endometrial polyp not present
  - Pathologist # 3: Tissue insufficient for diagnosis; endometrial polyp not present

During the endometrial biopsy procedure, 3.5 cm of the Pipelle sheath was retained in the endometrial cavity and not retrievable with a curette. A hysteroscopy dilatation and curettage was performed on trial Day 188 to remove the Pipelle sheath. Endometrial curetting's were obtained with a pathology report of weakly proliferative endometrium. The investigator assessed this event as moderate in severity and not related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of pathologist # 1 and pathologist # 2).

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0.5 mg estradiol/50 mg progesterone treatment group:

- Participant Number (b) (6) – A woman who self-identified as a White female 49 years of age with a prior history of metrorrhagia and a cervical biopsy and no prior medication use who was two years since her last menstrual period. Her Screening endometrial biopsy was reported as endometrial tissue (other), endometrial polyp not present by two pathologists. She reported vaginal bleeding on trial Day 316. She completed Trial TXC12-05. Her last dose of trial medication was on trial Day 363. Her end-of trial endometrial biopsy performed on trial Day 364 was reported as:
  - Pathologist #1: Endometrial tissue (other); 3 mm polyp with hyperplasia without atypia
  - Pathologist # 2: Disordered proliferative pattern; benign endometrial polyp
  - Pathologist #3: Endometrial tissue (other); benign endometrial poly (b) (6)endometrium, fragments of benign endocervical mucosa, negative for hyperplasia or malignancy, no evidence of polyp within the current specimen. A levonorgestrel-releasing intrauterine system was placed in the uterus after the procedure was completed. The investigator assessed this AE of “endometrial polyp” as mild in severity and not related to trial medication. This reviewer does not agree the investigator’s assessment that this endometrial polyp without atypia is not related to trial medication.

Clinical Reviewer’s Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); 3 mm endometrial polyp with hyperplasia without atypia (no agreement between the three pathologists; endometrial polyp with hyperplasia without atypia is most severe diagnosis). (b) (4)

0.25 mg estradiol/50 mg progesterone treatment group:

- Participant Number (b) (6) – This trial participant is discussed under Applicant-Identified Adverse Events Related to the Endometrium on page 149 of this review.

Clinical Reviewer’s Overall Comments on the Endometrium:

This reviewer disagrees with the applicant’s conclusion that no hyperplasia occurred in Trial TXC12-05. Based on the histologic findings reported in endometrial biopsy specimens in Trial TXC12-05, this reviewer determines that the following three (3) cases of endometrial hyperplasia occurred in Trial TXC12-05:

- 1 mg estradiol/100 mg progesterone treatment group:

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- Participant Number (b) (6) with a diagnosis of simple hyperplasia without atypia; endometrial polyp not present based on no agreement between the three independent pathologists:
  - Pathologist 1: Disordered proliferative pattern; only focally disordered; endometrial polyp not present
  - Pathologist 2: Simple hyperplasia without atypia; endometrial polyp not present
  - Pathologist 3: Proliferative endometrium; endometrial polyp not present
- 0.5 mg estradiol/100 mg progesterone treatment group:
  - Participant Number (b) (6) with a diagnosis of simple hyperplasia without atypia; endometrial polyp not present based on no agreement between the three independent pathologists:
    - Pathologist 1: Simple hyperplasia without atypia; tissue fragmentation prevents exact classification, also chronic endocervicitis; endometrial polyp not present
    - Pathologist 2: Proliferative endometrium; mostly detached glandular fragments, inflamed cervix present; endometrial polyp not present
    - Pathologist 3: Endometrial tissue (other); endometrial polyp not present
- 0.5 mg estradiol/50 mg progesterone treatment group:
  - Participant Number (b) (6) with a diagnosis of complex hyperplasia without atypia; endometrial polyp not present based on no agreement between the three independent pathologists:
    - Pathologist 1: Endometrial tissue (other); endometrial polyp not present
    - Pathologist 2: Proliferative endometrium; endometrial polyp not present
    - Pathologist 3: Complex hyperplasia without atypia; endometrial polyp not present

Therefore, the incidence of endometrial hyperplasia in the ES Population, calculated by the Statistical Reviewer, is as follows for the treatment groups in Trial TXC12-05. See Table 44.

Table 44: Incidence of Endometrial Hyperplasia in 52-Weeks Trial TXC12-05 (ES Population)

	1 mg E2/ 100 mg P (N=281)	0.5 mg E2/ 100 mg P (N=303)	0.5 mg E2/ 50 mg P (N=306)	0.25 mg E2/ 50 mg P (N=274)	Placebo (N=92)
Hyperplasia incidence rate (%)	1/281 (0.36)	1/303 (0.33)	1/306 (0.33)	0/274 (0.00)	0/92 (0.00)
One-sided upper 95% CI	1.97%	1.83%	1.81%	1.34%	3.93%

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Source: NDA 210132 Statistical Review and Evaluation (FDA’s analysis using PROCREQ in SAS), dated October 16, 2018, Table 5, page 14 of 30.

Abbreviations: E2 -= estradiol; P = progesterone, CI = confidence interval.

**Clinical Reviewer’s Comments:**

Endometrial protection is demonstrated for the 1 mg estradiol/100 mg progesterone and the 0.5 mg estradiol/100 mg progesterone dosage strengths.

**Endometrial Polyps:**

Table 45 shows a summary of all reported endometrial polyps at Screening and Week 52 in Trial TXC12-05. Three (3) participants had polyps at both Screening and Week 52: participant Number (b) (6) and participant Number (b) (6) in the 0.5 mg estradiol/50 mg progesterone treatment groups; and participant Number (b) (6) in the 0.25 mg estradiol/50 mg progesterone treatment group.

The incidence of endometrial polyps is summarized in the Safety population in the application. Endometrial polyps, if identified, were categorized as follows: benign polyp, polyp with hyperplasia without atypia, polyp with hyperplasia with atypia, carcinomatous polyp, and polyp other. The histologic diagnosis was based on agreement of two of the three pathologist reads. Consensus was reached when two of the three pathologist readers agreed.

Table 45: Summary of Endometrial Polyps at Screening and Month 12 (Safety Population)

	1 mg E2/ 100 mg P (N=415) (n/%)	0.5 mg E2/ 100 mg P (N=424) (n/%)	0.5 mg E2/ 50 mg P (N=421) (n/%)	0.25 mg E2/ 50 mg P (N=424) (n/%)	Placebo (N=151) (n/%)
Screening	5/415 (1.2%)	9/424 (2.1%)	7/421 (1.7%)	8/424 (1.9%)	0/151 (0.0%)
Week 52	5/312 (1.6%)	7/330 (2.1%)	10/334 (3.0%)	7/308 (2.3%)	0/103 (0.0%)

Source: Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 14.3.8.4.1, page 1291 of 1539 and Listing 16.2.10.2.4, Page 4960 of 8473.

Abbreviations: E2 -= estradiol; P = progesterone.

**Clinical Reviewer’s Overall Comments on Endometrial Polyps:**

With the exception of the 3 mm polyp with hyperplasia without atypia, described above for participant Number (b) (6) in the 0.5 mg estradiol/50 mg progesterone treatment group, this reviewer confirms that the remaining endometrial polyps reported at Week 52/Early Termination in Trial TXC12-05 are all reported as benign endometrial polyps by consensus of two of three pathologists. (b) (4)

As shown in Table 45, a total of 29 polyps occurred in the four active treatment groups versus zero (0) polyps in the placebo treatment group in Trial TXC12-05. Twelve (12) polyps occurred in the (b) (4) 1 mg

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estradiol/100 mg progesterone treatment group (5 polyps), and 0.5 mg estradiol/100 mg progesterone treatment group (7 polyps)]. In the postmenopausal woman, an overgrowth of cells in the lining of the uterus (endometrium) leads to the formation of uterine/endometrial polyps. Endometrial polyps can also form in the pre-menopausal uterus.

This finding of 5 benign endometrial polyps in the 1 mg estradiol/100 mg progesterone versus no polyps in the placebo treatment group does not raise safety concerns for this reviewer.

Applicant-Identified Transvaginal Ultrasounds (TVU) Results:

Transvaginal/pelvic ultrasounds were performed in a total of 24 women (10 women in the 1 mg estradiol/100 mg progesterone treatment group; 4 women in the 0.5 mg estradiol/100 mg treatment group, 3 in the 0.5 mg estradiol/50 mg treatment group, 5 in the 0.25 mg estradiol/50 mg progesterone treatment group, and 2 in the placebo treatment group). Of these 24 women, 12 (50%) had a TVU performed for vaginal spotting and/or vaginal bleeding. Seven (7) of these 12 women had associated fibroids. Narrative for the 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone treatment groups, (b) (4) follow:

1 mg estradiol/100 mg progesterone treatment group:

1. Participant Number (b) (6) – A woman who self-identified as a White female 52 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. Participant recorded vaginal bleeding in her diary on trial Days 19-25, 58-59, 76-77, 79, and 110-112. A transvaginal ultrasound (TVU) performed on trial Day 84 showed endometrial thickness of 12 mm and suggestion of 1.3 x 0.9 cm endometrial polyp. A sonohystogram on trial Day 119 revealed a 1.05 cm endometrial polyp. An unscheduled endometrial biopsy on trial Day 119 reported as:
  - Pathologist # 1: Endometrial tissue (other); endometrial polyp not present
  - Pathologist # 2: Disordered proliferative pattern; benign endometrial polyp
  - Pathologist # 3: Weakly proliferative endometrium; benign endometrial polyp

This participant discontinued on trial Day 154. Her last day of trial drug was trial Day 118. She refused a repeat endometrial biopsy. The investigator assessed the event as moderate in severity and possibly related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final

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histologic diagnosis for participant Number (b) (6) as disordered proliferative endometrium; benign endometrial polyp (no agreement between the three pathologists; the most severe histologic classification is the final diagnosis).

2. Participant Number (b) (6) – A woman who self-identified as a White female 62 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. Participant recorded vaginal spotting in her diary on trial Days 163-174, 179-182, 192, 194, 196, 284-287, 290, and 292. She reported vaginal bleeding on trial Day 238. A TVU performed on trial Day 186 was reported a 3 mm. An end-of-trial endometrial biopsy obtained on trial Day 359 was reported as:
  - Pathologist # 1: Disordered proliferative endometrium; endometrial polyp not present
  - Pathologist #2; Disordered proliferative endometrium; endometrial polyp not present
  - Pathologist # 3: Weakly proliferative endometrium; endometrial polyp not present

She completed the clinical trial. Her last dose of trial medication was Day 359. A TVU performed on post-trial Day 389 showed an endometrial thickness of 4 mm. The investigator assessed the event as moderate in severity and probably related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as disordered proliferative endometrium; endometrial polyp not present (agreement of pathologist # 1 and pathologist # 2).

3. Participant Number (b) (6): A woman who self-identified as a White female 50 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. Participant reported vaginal spotting on trials Days 311, 324-325, and 333 to 334. She reported vaginal bleeding on trial Days 326-332. She also reported pelvic pain on trial Day 326 considered severe by the investigator and possibly related to trial medication. A TVU performed on trial Day 331 showed a thickness of 12.8 mm. Her end-of trial endometrial biopsy performed on trial Day 358 was reported as:
  - Pathologist # 1: Disordered proliferative pattern, endometrial polyp not present
  - Pathologist # 2: Proliferative endometrium; endometrial polyp not present
  - Pathologist # 3: Endometrial tissue (other); endometrial polyp not presentShe received medroxyprogesterone acetate 20 mg daily from trial Day 368 to Day 374. A repeat endometrial biopsy performed on post-trial Day 526 was reported as

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endometrial tissue (other); endometrial polyp not present by three pathologists. The investigator assessed the disordered proliferative endometrium as mild in severity and definitely related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as disordered proliferative endometrium; endometrial polyp not present (no agreement between the three pathologists; the most severe histologic classification is the final diagnosis).

4. Participant Number (b) (6) – A woman who self-identified as a Black/African American female 62 years of age with a Screening endometrial biopsy was reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She reported intermittent vaginal spotting for total of 31 days, and vaginal bleeding trial Days 52 to 59. A pelvic ultrasound performed on trial Day 220 revealed a 70 x 54 x 60 mm fibroid and a 13 x 16 mm fibroid. Her endometrial thickness was 2.68 mm. She completed the trial and had an endometrial biopsy performed on trial Day 357 which showed:
  - Pathologist # 1: Endometrial tissue (other); endometrial polyp not present
  - Pathologist # 2: Proliferative endometrium (with stromal breakdown); endometrial polyp not present
  - Pathologist # 3: Weakly proliferative endometrium; endometrial polyp not present

The investigator assessed the “fibroids” as mild in severity and not related to trial medication. This reviewer agrees that since a TVU was not obtained at Screening, the presence of fibroids is uncertain.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as active proliferative endometrium; endometrial polyp not present (no agreement between the three pathologists; the most severe histologic classification is the final diagnosis).

5. Participant Number (b) (6) – A woman who self-identified as a White female 50 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. Participant experienced vaginal spotting trial Days 145-146, and vaginal bleeding trial Days 147 to 150. A TVU performed on trial Day 154 showed endometrial thickness of 6.3 mm, and a right simple

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ovarian cyst. She had an unscheduled endometrial biopsy on trial Day 163 read by three pathologists as endometrial tissue (other); endometrial polyp not present. She completed the trial (last day of trial medication on trial Day 337). Her end-of trial endometrial biopsy performed on trial Day 358 was evaluated by all three pathologists as endometrial tissue (other); endometrial polyp not present. The investigator assessment the bleeding as mild and possibly related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of all three pathologists).

6. Participant Number (b) (6) – A woman who self-identified as a Black/African American female 51 years of age. See page 147 of this review for the narrative for this participant.
7. Participant (b) (6) – A White female 56 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She reported intermittent vaginal spotting a total of 26 days during trial participation. She also reported vaginal bleeding on trials Days 60 to 64, 77 to 78, 93 to 97, 102 to 114 and 126 to 134. A pelvic ultrasound performed on trial Day 107 for bleeding indicated an 11 mm endometrial stripe, abnormal endometrial echoes, two 1.0 cm uterine fibroids, and an enlarged right ovary. An unscheduled endometrial biopsy performed on trial Day 114 showed:
  - Pathologist # 1: Endometrial tissue (other); endometrial polyp not present
  - Pathologist # 2: Weakly proliferative endometrium; endometrial polyp not present
  - Pathologist # 3: Endometrial tissue (other); endometrial polyp not present

She discontinued the trial due to abnormal bleeding on trial Day 150. Her last dose of trial medication was trial Day 134. The investigator assessed the vaginal bleeding as moderate in severity and possibly related to trial medication. The AE of uterine fibroids was assessed as mild in severity and not related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement between pathologists #1 and # 3).

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8. Participant Number (b) (6) – A woman who self-identified as a Black/African American female 58 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She was hospitalized on trial Day 193 with a diagnosis of idiopathic acute pancreatitis. During her hospitalization, pseudocysts of the pancreas, hypokalemia, and a 1.9 cm “probable” uterine fibroid were detected. A pelvic ultrasound done on trial Day 194 revealed an endometrial thickness of 9.4 mm and a 1.5 x 1.9 cm uterine fibroid. She was discharged from the hospital on trial Day 197 and completed the clinical trial. Her last dose of trial medication was on trial Day 356. Her end-of-trial endometrial biopsy was read by three pathologists as endometrial tissue (other); endometrial polyp not present. The investigator assessed the acute pancreatitis as severe and possibly related to trial medication. This reviewer concurs with the investigator’s assessment.

Clinical Reviewer’s Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present based on the agreement of all three pathologists.

9. Participant Number (b) (6) – A woman who self-identified as a Black/African American female 59 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present, by two pathologists. She reported intermittent vaginal spotting in her diary for a total of 31 days. She reported vaginal bleeding on trial Days 124 to 127, 179, 208, 211 to 212, and 288 to 292. A TVU performed on trial Day 313 showed an endometrial thickness of 11.75 mm, a questionable fibroid measuring 18 x 12 x 11 mm, and a left adnexal simple cyst measuring 59 x 44 x 59 mm with no abnormal vascularity. A follow-up TVU performed on trial Day 356 reported an endometrial thickness of 10.64 mm, a fibroid measuring 17 x 15 x 11 mm and a left adnexal cyst measuring 63 x 44 x 57 mm. Her endometrial biopsy on trial Day 356 was reported as endometrial tissue (other); endometrial polyp not present by all three pathologists. A follow-up TVU performed on post-trial Day 51 reported an endometrial thickness of 8.91 mm, a fibroid measuring 13 x 16 x 15 mm, and a left adnexal cyst measuring 64 x 50 x 59. No further information is provided on this trial participant. The investigator assessed the vaginal bleeding as mild in severity and possibly related to trial medication. The investigator assessed the uterine fibroid as mild in severity, ongoing, and not related to trial medication. This reviewer concurs that the vaginal bleeding was possibly/probably related to trial medication. This trial participant appears not to have been followed-up in compliance with the agreed upon protocol.

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Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of all three pathologists).

10. Participant Number (b) (6) – A woman who self-identified as a White female 57 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She reported intermittent vaginal spotting in her diary for a total of 41 days during trial participation. She also reported vaginal bleeding on trial Days 65, 67 to 77, 287, and 355. A TVU and endometrial biopsy was performed at end-of-trial on trial Day 363 (last dose of trial medication on trial Day 355). Her TVU showed an endometrial thickness of 6 mm. Her endometrial biopsy was reported by three pathologists as endometrial tissue (other); endometrial polyp not present. Her trial investigator prescribed 10 mg medroxyprogesterone acetate once per day from trial Day 377 to trial Day 391 for her “endometrial thickness”. She was advised to follow-up with her Primary Care Physician. No additional information is provided.

Clinical Reviewer’s Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of all three pathologists).

0.5 mg estradiol/100 mg progesterone treatment group:

1. Participant Number (b) (6) – A woman who self-identified as a White female 61 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present, by two pathologists. She reported intermittent vaginal spotting in her diary for a total of 29 days during trial participation. She did not report any vaginal bleeding. A TVU performed on trial Day 270 reported an endometrial thickness on 4 mm, and endometrial fibroid (no further information provided), and “tiny polyps versus blood clots” in fundal endometrium. A follow-up TVU performed on trial Day 361 reported “stable fibroid”, and a 9 mm x 3.1 mm polyp. No endometrial thickness was recorded. She completed the trial (last dose of trial medication on trial Day 364). Her end-of-trial endometrial biopsy on trial Day 365 reported as endometrial tissue (other); endometrial polyp not present by all three pathologists. The investigator assessed the uterine fibroid as mild in severity and not related to trial medication, and the endometrial polyp as mild in severity and possibly related to trial medication. This reviewer concurs with the investigator’s assessment.

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Per the applicant, the final histologic diagnosis for participant Number [REDACTED] (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number [REDACTED] (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of all three pathologists).

- Participant Number [REDACTED] (b) (6) – A woman who self-identified as a White female 53 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She reported vaginal spotting in her diary on trial Days 86 and 97, and no vaginal bleeding. During Visit 5 on trial Day 176, the investigator noted an enlarged right ovary on palpation; resolved on trial Day 238. A TVU performed on trial Day 238 showed an endometrial thickness of 3 mm and both ovaries appearing normal. She completed the clinical trial (last dose of trial medication on trial Day 356). Her end-of-trial endometrial biopsy on trial Day 356 reported as endometrial tissue (other); endometrial polyp not present by all three pathologists. The investigator assessed the “enlarged right ovary” as mild in severity and not related to trial medication. This reviewer concurs with the investigator’s assessment.

Clinical Reviewer’s Comments:

Per the applicant, the final histologic diagnosis for participant Number [REDACTED] (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number [REDACTED] (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of all three pathologists).

- Participant Number [REDACTED] (b) (6) – A woman who self-identified as a Black/African American female 50 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She reported intermittent vaginal spotting in her diary on trial Days 35, 43 to 46, and 140; and vaginal bleeding on trial Days 36 to 42, 64 to 74, 133 to 139, and 306 to 312. A TVU performed on trial Day 84 showed an endometrial thickness on 4.52 mm and “possible posterior subserous fibroid at fundus measuring 2.2 x 1.4 cm. No action was taken for this AE. She completed the clinical trial (last dose of trial medication on trial Day 355). An end-of-trial endometrial biopsy performed on trial Day 356 reported as:

- Pathologist # 1: Endometrial tissue (other); endometrial polyp not present
- Pathologist # 2: Weakly proliferative endometrium; endometrial polyp not present
- Pathologist # 3: Endometrial tissue (other); endometrial polyp not present

The investigator assessed the “subserous fibroid” as mild in severity and not related to trial medication. This reviewer concurs with the investigator’s assessment.

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Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of pathologist # 1 and pathologist # 3).

- Participant Number (b) (6) – A woman who self-identified as a White female 58 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She had a medical history of gastroesophageal reflux disease (GERD), dyspepsia, hypercholesterolemia, bladder neck suspension, and stress urinary incontinence. Her Screening liver function tests were within normal limits. She experienced biliary colic on trial Day 203 with cholelithiasis reported on trial Day 204. She underwent an out-patient laparoscopic cholecystectomy on trial Day 214. Both events were resolved on trial Day 214. She reported vaginal spotting in her diary on trial Days 217 to 218, 220, 225 to 229, 266 to 268, and 350; and no vaginal bleeding. She also reported pelvic cramping between trials Days 225 and 350. A TVU performed on trial Day 287 showed an endometrial thickness of 5 mm. She completed the clinical trial (last dose of trial medication on trial Day 359. Her end-of-trial endometrial biopsy performed on trial Day 360 reported as:

- Pathologist #1: Endometrial tissue insufficient for diagnosis; endometrial polyp not present
- Pathologist #2: No endometrium identified, endometrial polyp not present
- Pathologist #3: No endometrium identified; endometrial polyp not present

She did not consent to a repeat end-of trial endometrial biopsy. The investigator assessed the AEs of biliary colic/cholelithiasis as moderate/severe in severity and possibly related to trial medication. The reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as no endometrium identified; endometrial polyp not present (agreement of pathologist # 2 and pathologist # 3).

Placebo Treatment Group:

- Participant Number (b) (6): A woman who self-identified as a White female 52 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present, by two pathologists. She did not report any vaginal spotting or vaginal bleeding during trial participation. At Visit 5, the investigator noted a "fullness in the right lower quadrant" on palpation. A TVU was performed which noted no masses. The endometrial thickness was not reported. On trial Day 158 she

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reported right side abdominal pain which was ongoing at end-of trial. Her endometrial biopsy performed on trial Day 360 reported as:

- Pathologist # 1: Endometrial tissue insufficient for diagnosis; endometrial biopsy not present
- Pathologist # 2: Endometrial tissue (other); endometrial polyp not present
- Pathologist # 3: Endometrial tissue (other); endometrial polyp not present

The investigator assessed the abdominal pain as mild in severity and not related to trial medication. This reviewer concurs with the investigator's assessment.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 draft Hormone Therapy Guidance for Industry recommendations, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as endometrial tissue (other); endometrial polyp not present (agreement of pathologist # 2 and pathologist # 3).

2. Participant Number (b) (6) – A woman who self-identified as a Black/African American female 52 years of age with a Screening endometrial biopsy reported as endometrial tissue (other); endometrial polyp not present by two pathologists. She did not report any vaginal spotting or vaginal bleeding during trial participation. She completed the clinical trial (last dose of trial medication on trial Day 364). Her end-of trial endometrial biopsy performed on trial Day 365 was reported as no endometrium identified; endometrial polyp not present by all three pathologists. An attempt to repeat the endometrial biopsy on trial Day 386 was not successful. A TVU performed on trial Day 386 showed an endometrial thickness of 3.3 mm.

Clinical Reviewer's Comments:

Per the applicant, the final histologic diagnosis for participant Number (b) (6) was Category 1: Non-endometrial malignancy/non-hyperplasia. Per the 2003 Hormone Therapy Guidance for Industry, this reviewer classifies the final histologic diagnosis for participant Number (b) (6) as no endometrium identified; endometrial polyp not present (agreement of all three pathologists).

Clinical Reviewer's Overall Comments on TVU Results:

Eight (8) of the 10 women in the 1 mg estradiol/100 mg progesterone treatment group had TVU results reported > 4 mm (range 6 mm to 14.7 mm). Two (2) of the 4 women in the 0.5 mg estradiol/100 mg progesterone treatment group had TVU results reported > 4 mm (range 4.5 mm to 5 mm). Neither of the two (2) women in the placebo treatment group had a TVU result reported > 4 mm. Vaginal spotting/bleeding necessitated the performance of a TVU for the majority of women.

Proliferative Endometrium by Pathologist's Histological Classification:

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As discussed in the above narratives, four (4) women in the 1 mg estradiol/100 mg progesterone treatment group, recommended for approval by this reviewer, had a diagnosis of disordered proliferative endometrium by endometrial biopsy. Consensus diagnosis by two pathologists was reached for participant Number (b) (6) and Number (b) (6). Participant Number (b) (6) and Number (b) (6) are classified, by this reviewer, as disordered proliferative endometrium because of the lack of consensus diagnosis by three pathologists. Disordered proliferative endometrium is the most severe histologic diagnosis for these two participants.

Clinical Reviewer's Overall Comments on Disordered Proliferative Endometrium:

The finding of four (4) cases of disordered proliferative endometrium in the 1 mg estradiol/100 mg progesterone treatment group should appear in labeling.

Cases of proliferative endometrium (weakly proliferative, active proliferative, disordered proliferative) by endometrial biopsy at Week 52, as classified by this reviewer, are reported in all active treatment groups in Trial TXC12-05. No case of proliferative endometrium (weekly proliferative, active proliferative, or disordered proliferative) occurred in the placebo treatment group in Trial TXC12-05.

Clinical Reviewer's Selected Endometrial Histology Findings in Trial TXC12-05:

The following table summarized the Clinical Reviewer's selected endometrial histology findings in Trial TXC12-05 in the endometrial safety population.

Table 46: Summary of Clinical Reviewer's Selected Endometrial Histology Findings in Trial TXC12-05 – ES Population

Reviewer's Histologic Findings, n (%)	1 mg E2/ 100 mg P (N=281)	0.5 mg E2/ 100 mg P (N=303)	0.5 mg E2/ 50 mg P (N=306)	0.25 mg E2/ 50 mg P (N=274)	Placebo (N=92)
Weakly proliferative endometrium	1 (0.3)	2 (0.7)	2 (0.7)	2 (0.7)	0 (0.0)
Active proliferative endometrium	8 (2.8)	5 (1.7%)	1 (0.3)	3 (1.1)	0 (0.0)
Disordered proliferative endometrium	4 (1.4)	6 (2.0)	3 (1.0)	4 (1.4)	0 (0.0)
Simple hyperplasia without atypia	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Simple hyperplasia with atypia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complex hyperplasia without atypia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Complex hyperplasia with atypia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Cumulative Amenorrhea Reported in Trial TXC12-05:

Cumulative amenorrhea was defined as the absence of bleeding or spotting for a cumulative period, such as 1st to 13th cycle, 2nd to 13th cycle, and so on to 13th cycle.

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Cumulative amenorrhea from Cycle 1 to Cycle 13 in 52-week Trial TXC12-05 was reported as follows:

- 1 mg estradiol/100 mg progesterone treatment group = 56.1%
- 0.5 mg estradiol/100 mg progesterone treatment group = 67.6%
- 0.5 mg estradiol/50 mg progesterone treatment group = 68.1%
- 0.25 mg estradiol/50 mg progesterone treatment group = 73.1%
- Placebo treatment group = 78.9%

### Clinical Reviewer's Comments:

As expected, the placebo treatment group had the largest percentage of women with cumulative amenorrhea in 52-week Trial TXC12-05 (78.8%); the 1 mg estradiol/100 mg progesterone treatment group had the smallest percentage of women with cumulative amenorrhea (56.1%). This information will be provided in labeling.

## 8.6. Safety Analyses by Demographic Subgroups

No safety analyses by demographic subgroup was conducted by this reviewer. Single Trial TXC12-05 was not adequately powered to reach a conclusion regarding the safety among the demographic subgroups (age, BMI, race).

## 8.7. Specific Safety Studies/Clinical Trials

No PK drug interaction studies have been conducted with TX-001HR. In vitro and in vivo studies have shown that estradiol and progesterone are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect the metabolism of these active ingredients. Inducers of CYP3A4 may reduce plasma concentrations of estrogens and progestins, possibly resulting in a decrease in therapeutic effects. Inhibitors of CYP3A4, may increase plasma concentrations of estrogens and progestins resulting in side Effects. This information is available in labeling of approved estrogen plus progestin products.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

This review discussed the endometrial safety issues reported in 52-week, phase 3 Trial TXC12-05 conducted in postmenopausal women with a uterus. See Section 8.5 Analysis of Submission-Specific Safety Issues, Subsection 8.5.1 Endometrium in this review.

### 8.8.2. Human Reproduction and Pregnancy

No human reproductive and pregnancy safety explorations were conducted with the combined estradiol/progesterone product. No pregnancies were reported during the combined estradiol/progesterone development program.

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### 8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric and assessment of effects on growth was conducted for the combined estradiol/progesterone product. The estrogen/progesterone development program addresses an indication which is applicable only to postmenopausal women.

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdose, drug abuse potential, withdrawal or rebound potential was demonstrated in the application.

## 8.9. Safety in the Postmarket Setting

### 8.9.1. Safety Concerns Identified Through Postmarket Experience

No safety concerns have been identified through postmarketing experience with this combined oral estradiol/progesterone product. This combined estradiol/progesterone product is not approved for use in the US or internationally.

### 8.9.2. Expectations on Safety in the Postmarket Setting

The potential safety issues in the postmarketing setting is expected to be the same as for approved individual estradiol product used for the treatment of moderate to severe vasomotor symptoms, due to menopause. The potential safety issues for the progesterone component of the combined estradiol/progesterone product should be the same as for the approved individual micronized progesterone product approved for use in conjunction with conjugated estrogens to protect the endometrium.

### 8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues have been reported by other review disciplines.

## 8.10. Integrated Assessment of Safety

Single, 52-week Trial TXC12-05 was conducted during the estradiol/progesterone development program.

## 9. Advisory Committee Meeting and Other External Consultations

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No Advisory Committee was conducted for NDA 210132. Estradiol and progesterone are approved drug products.

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## 10. Labeling Recommendations

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### 10.1 Prescription Drug Labeling

(b) (4)  
This reviewer is recommending approval of (b) (4) the 1 mg estradiol/100 mg progesterone dosage strength for the treatment of moderate to severe vasomotor symptoms in a woman with a uterus.

The format and content of the proposed labeling was updated for consistency with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLT). Labeling format and content, and Section 8 Use in Specific Populations were revised as follows:

- (b) (4) was changed to “Lactation”.
- Risk Summary text under Section 8 Use in Specific Populations, Subsections 8.1 Pregnancy and 8.2 Lactation were modified for consistency with other approved estrogen plus progestin products with the same indication.
- Subsection 8.3 Females and Males of Reproductive Potential under Section \* Use in Specific Populations was deleted for consistency with other approved estrogen plus progestin products with the same indication
- Subsection 8.6 Renal Impairment and Subsection 8.7 Hepatic Impairment under Section 8 Use in Specific Populations were removed. There is no relevant trial data to present in these subsections

## 11. Risk Evaluation and Mitigation Strategies (REMS)

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No Risk Evaluation and Mitigation Strategies (REMS) are proposed for this combined estradiol/progesterone drug product.

## 12. Postmarketing Requirements and Commitments

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One (1) Chemistry, Manufacturing and Controls (CMC) Postmarketing Commitment (PMC) is proposed.

### Clinical Reviewer's Comments:

See the CMC review dated October 24, 2018, for a discussion of the elements of the proposed PMC for the combined oral estradiol/progesterone product.

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## 13. Appendices

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### 13.1. References

See the references reviewed and discussed throughout this primary clinical review.

### 13.2. Financial Disclosure

Dan Cartwright, Chief Financial Officer, signed Form FDA 3455 on August 10, 2017 indicating, “I certify that I have not entered into any financial arrangement with the listed clinical investigators (a list of clinical investigators is attach list) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Only one subinvestigator, (b) (6), at Site # (b) (6) of phase 3 Trial TXC12-05, had a significant equity interest that met the criteria for disclosure. At the time of his trial participation, (b) (6) had stock options that could potentially exceed \$50,000 US in aggregate. He disclosed ownership of a total of 216,000 options in TherapeuticsMD stock. Of these, the first 108,000 options were at \$0.10 per option and the second 108,000 options were at \$0.25 per option.

The circumstances which prevent potential bias are as follows:

- (b) (6) was a subinvestigator at Site # (b) (6) and not directly responsible for conduct of the trial at this site.
- Trial TXC12-05 was a multicenter, randomized, placebo-controlled trial. A total of 117 sites consented trial participants during Screening, with 111 sites randomizing 1847 participants to the trial. Site # (b) (6) screened (b) (6) participants and randomized (b) (6) participants. These (b) (6) participants represent less than (b) (6) % of the randomized trial population.

The required Form FDA 3455 for (b) (6) is provided in the application.

#### Clinical Reviewer’s Comments:

This primary reviewer concluded that TherapeuticsMD had adequately disclosed financial agreements for participating investigators/sub-investigators in the primary clinical trial conducted to support the NDA application (phase 3 Trial TXC12-05).

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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THERESA H VAN DER VLUGT  
10/26/2018

SHELLEY R SLAUGHTER  
10/26/2018

I concur with Dr. van der Vlugt's presentation of data. However, I do not concur with the recommendation to approve Bijuva (estradiol and progesterone) capsules 1 mg/ 100mg. My rationale for this conclusion will be presented in my review.