

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210132Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 27, 2018
From	Shelley R. Slaughter, M.D., Ph. D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 210132
Applicant	Therapeutics MD Pharmaceuticals
Date of Submission	December 28, 2017 (receipt date)
PDUFA Goal Date	October 28, 2018
Proprietary Name	Bijuva
Established or Proper Name	Estradiol and progesterone capsules, for oral use
Dosage Form(s)	Capsule
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe vasomotor symptoms due to menopause
Applicant Proposed Dosing Regimen(s)	One combined 1 mg estradiol and 100 mg progesterone capsule administered orally once per day (b) (4)
Recommendation on Regulatory Action	<i>I do not recommend approval. My rationale for this recommendation is presented in the body of this review (See Section 7.</i>
Recommended Indication(s)/Population(s) (if applicable)	If approved, the indication will be as proposed by the applicant, treatment of moderate to severe vasomotor symptoms, due to menopause. The intended population is nonhysterectomized postmenopausal women.
Recommended Dosing Regimen(s) (if applicable)	A single Bijuva (estradiol and progesterone) capsule, 1 mg/100 mg, administered orally once per day

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Estrogens without and with progestogens are indicated to treat symptoms (vasomotor and vulvar and vaginal atrophy) due to menopause. With the application of Noncontraceptive Estrogen Class Labeling across all estrogen-containing products irrespective of dosage strength or route of administration, FDA has determined that in the absence of data to establish otherwise, all such products are associated with the same risks. The most serious risks associated with estrogen plus progestogen products, such as the proposed fixed dose combination Bijuva (estradiol and progesterone) capsule which include increased risks of Cardiovascular disorder, Probable Dementia, Breast Cancer and Ovarian Cancer.

The applicant, Therapeutics MD, submitted on December 28, 2017, a new drug application (NDA) seeking approval for (b) (4) Bijuval (estradiol and progesterone) capsules 1mg/100 mg (b) (4) for the indication of treatment of moderate to severe vasomotor symptoms, due to menopause. The clinical development program included five phase 1 pharmacokinetic, bioavailability or comparative bioavailability/bioequivalence trials and one 52-week phase 3 clinical Trial TXC12-05 conducted to support efficacy (from data collection in the first 12 weeks) and safety (entire 52-week trial).

This reviewer does not believe that the applicant has established an acceptable benefit:risk profile, due to failure to establish efficacy (b) (4) according to prospectively-identified efficacy criteria (See Section 7. Efficacy of this review).

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Menopause is a natural condition of aging in a woman that represents the time when her menstrual periods permanently cease, and she is no longer capable of reproduction (i.e. she is no longer fertile). Operationally menopause is defined by the absence of menstrual periods for 12 consecutive months without any other biological or physiological cause. Menopause results from diminished ovarian primordial follicles, failure of monthly development of an ovarian dominant follicle and ovulation, and eventual exhaustion of primordial follicles. This process is accompanied by greatly diminished ovarian production of the sex hormone estrogen (as well as progesterone) resulting in both very low serum concentrations of estrogens and cessation of menstruation.	Moderate to severe menopausal symptoms including vasomotor symptoms, though not life-threatening, constitute a significant public health concern often requiring medical intervention.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Menopause may be characterized by the following symptoms:</p> <ul style="list-style-type: none"> • Vasomotor symptoms (or hot flashes) - feeling of warmth and excessive sweating (throughout the day), thought to result from the effects of estrogen withdrawal on hypothalamic thermoregulating system. Night sweats may interfere with the woman’s ability to sleep at night. • Vulvar and vaginal atrophy symptoms – vaginal dryness, dyspareunia (pain with intercourse) and vaginal irritation resulting from withdrawal of estrogen stimulation to the lower genital tract (vulva and vagina) <p>While not life-threatening moderate to severe menopausal symptoms can be debilitating, affecting the woman’s ability to carry out her day-to-day normal personal and or employment-related activities.</p> <p>The 2010. Census estimates 53.1 million women, age 50 or above living in the U.S.¹</p> <p>About 75% - 80% of postmenopausal women experience hot flashes on and off up to a decade post menopause. About 46% of women suffer from moderate to severe vasomotor symptoms requiring medical intervention.</p> <p>An additional 40% of menopausal women experience symptoms of vulvar and vaginal atrophy.² The proposed product is intended to treat moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause</p>	

¹ <https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf>

² <https://www.sciencenews.org/sn-magazine/january-20-2018>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	<ul style="list-style-type: none"> Numerous oral and transdermal estrogen plus progestogen products or an estrogen plus progestin agonist/antagonist product (See Tables 1 and Table 2, respectively) and oral, transdermal gels, sprays, a solution; and transdermal system products containing estrogen-alone (See Tables 13 in the Appendix) are approved for the treatment of vasomotor symptoms. 	<p>Estrogen-alone and estrogen plus progestogen products are approved in multiple dosage strengths allowing for up-titration or down-titration to control the frequency and severity of a postmenopausal woman’s vasomotor symptoms when present and may differ at different phases of her menopause</p>
Benefit	<ul style="list-style-type: none"> Approved estrogen-alone and estrogen plus progestogen products have been demonstrated to be efficacious in the treatment of moderate to severe vasomotor symptoms. 	<p>The applicant proposes for approval, (b) (4) [redacted] Bijuva (estradiol and progesterone) capsules, (estradiol and progesterone) 1mg/100 mg (b) (4) [redacted]. No dosage strength of Bijuva met the recommended criteria to demonstrate efficacy according to the 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.</p> <p>The applicant offers that an additional benefit of this product accrues for women with peanut allergies as this combination hormone therapy product with estradiol and progesterone does not contain peanut oil. There are other oral and non-oral estrogen plus progestin products that do not contain peanut oil and are approved for the treatment of moderate to severe vasomotor symptoms, due to menopause (See Table 1). These products contain the synthetic progestins, drospirinone, levonorgestrel, medroxyprogesterone acetate, and norethindrone acetate. The Women’s Health Initiative Estrogen plus Progestin Substudy,</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		<p>after a mean follow-up of 5.6 years, reported use of an estrogen plus progestin (conjugated estrogen and medroxyprogesterone acetate), increased the risk of invasive breast cancer. There is some suggestion in the professional/scientific community that progesterone may offer a benefit over synthetic progestins with respect to breast health. To this reviewer’s knowledge there have not been results from head-to-head, well-designed and controlled clinical trial to support this position.</p>
<p>Risk and Risk Management</p>	<p>Noncontraceptive Estrogen Class Labeling include in the Boxed WARNINGS and/or WARNINGS AND PRECAUTIONS sections, the following serious adverse outcome risks with long-term (chronic) use:</p> <p><u>Estrogen-alone therapy:</u></p> <ul style="list-style-type: none"> • Endometrial Cancer • Cardiovascular Disorders (Stroke, Coronary Heart Disease and Venous Thromboembolism) • Ovarian Cancer • Probable Dementia <p><u>Estrogen plus progestogen therapy:</u></p> <ul style="list-style-type: none"> • Cardiovascular Disorders • Probable Dementia • Breast Cancer • Ovarian Cancer <p>Noncontraceptive Estrogen Class Labeling, applied to all estrogen products and in part to some non-estrogen products (particularly those acting at the estrogen receptor) approved to treat moderate to severe vasomotor symptoms, due to menopause, recommends risk mitigating strategies such as: including the addition of progestogen opposition of</p>	<p>If any dosage strength of Bijuva (estradiol and progesterone) capsules, is approved, that product will receive Noncontraceptive Estrogen Class Labeling</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the effects of estrogen in no hysterectomized women, appropriate endometrial assessment of women demonstrating persistent vaginal spotting or bleeding, use of the lowest approved dosage strength of the approved estrogen product and use for the shortest duration appropriate to the woman’s treatment goals and individuals risks.	

DRAFT

Table 1 presents estrogen plus progestin products and Table 2 presents an approved estrogen plus progestin agonist/antagonist product, respectively, approved for the treatment of moderate to severe vasomotor symptoms.

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 or 1 mg E2 plus 0.5 mg NETA, taken daily
Angeliq® [E2 plus drospirenone (DRSP)]	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 mcg EE plus 0.5 mg NETA or 5 mcg EE plus 1 mg NETA, taken daily
Premphase® [conjugated estrogens (CE) plus medroxyprogesterone acetate (MPA)]	0.625 mg CE taken daily for days 1 - 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 or 0.625 mg CE plus 2.5 mg or 5.0 mg MPA taken daily
Transdermal Estrogen Plus Progestin Products	Available Dosage Strengths
ClimaraPro® (E2 plus levonorgestrel)	0.045 mg E2 plus 0.015 mg levonorgestrel, transdermal system applied weekly
CombiPatch® (E2 plus NETA)	0.05 mg E2 plus 0.14 mg NETA or 0.05 mg E2 plus 0.25 mg NETA, transdermal system applied twice weekly

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

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

2. Background

The following is an abbreviated and high-level presentation of the regulatory history and clinical development program for Bijuva (estradiol and progesterone capsules. Refer to the medical officer’s review of Dr. Theresa van der Vlugt for a complete presentation of the regulatory history:



- **August 2012** – IND 114477 was opened by TherapeuticsMD. The sponsor stated at the time that the clinical safety assessment would be based on comparison to two approved oral products Estrace® and Prometrium® and DBRUP agreed that previous findings of safety and efficacy for the listed drugs (LD), and published literature data could provide the nonclinical support for the proposed IND.

Key review comments included:

- The Agency agreed, at the pre-IND meeting conducted with you on April 10, 2012, that it was possible to conduct a single large and adequately controlled dose and regimen finding phase 3 clinical trial with multiple treatment groups per regimen that evaluate efficacy during the first 12 weeks of the trial and safety for protection of the endometrium in an extension to 12 months. We continue to remind you, however, that such a trial would be large and complex and would need to demonstrate that the lowest effective dose of each component in the combination product is identified for both treatment of moderate to severe vasomotor symptoms and protection of the endometrium. We also continue to recommend that you consider conducting an independent 12-week dose-finding and efficacy study to demonstrate a non-effective dose of each component as well as effective doses.
- Per the combination drug rule (21 CFR § 300.50), two or more drugs may be combined in a single dosage form when each component makes a contribution to claimed effect and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined

in the labeling for the drug. It is not clear how you plan to demonstrate the contribution of progesterone in your estradiol plus progesterone combination product to the claimed effect, “treatment of moderate to severe vasomotor symptoms due to menopause”.

- **November 7, 2013** – DBRUP provided an Advice Letter to TherapeuticsMD

-  (b) (4)
”
This is not acceptable. We continue to recommend that your development program identify the lowest effective dose of each component of your combination drug product for the treatment of moderate to severe vasomotor symptoms, and also the lowest progesterone dose that will protect the endometrium.
- Per the Agency’s 2003 draft clinical evaluation Guidance for Industry, we recommend that the endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory. For the evaluation of protection of the endometrium, we recommend 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. We also recommend that standardized criteria be used for the diagnosis of endometrial hyperplasia, and that endometrial polyps be fully characterized as to glandular proliferation and atypia. 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 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/UC M133343.pdf>
- We do not concur with the proposed duration of study medication exposure that should trigger the performance of an endometrial biopsy on women who discontinue the study. We recommend that any subject who discontinues Study TXC12-05 after week 12 of study medication onward receive an endometrial biopsy.
- We recommend that a woman who discontinues the study early should have a mammogram one year after her initial mammogram for study entry.
- 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.

- We advise you that only data collected on the primary endpoint will be presented in product labeling. Data collected for the proposed secondary endpoints in the Vasomotor Substudy will not be used to determine the effectiveness of the drug product for the indications sought, nor will this data appear in product labeling.
- Be advised 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.
- **February 3, 2014** –DBRUP provided Preliminary Responses to Type A Meeting Request from TherapeuticsMD for stalled clinical development. Therapeutics MD cancelled the face-to-face meeting and accepted the Preliminary Responses. The following question and responses were the key issues addressed:
 - **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-12-001-HR? 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 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.

- **May 29, 2014** – DBRUP provided an Advice Letter to TherapeuticsMD
Key comments included:

- We continue to recommend that concurrent readings by three independent expert pathologists be conducted for instances of “for cause” endometrial biopsies obtained during the conduct of Study TXC12-05 and for End-of-Treatment (or early withdrawal when treated ≥ 12 weeks) endometrial biopsies. Each of these three pathologists should be blinded to the study treatment group and to the readings of the other pathologists.
 - We do not agree with your proposal [REDACTED] (b) (4)
 - Provide the Pathology Committee Charter as proposed.
 - Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting.
- **July 30, 2014** – DBRUP provided an Advice Letter to TherapeuticsMD

We also refer to your amendment dated, June 11, 2014, containing Protocol Amendment for Study TXC12-05 entitled “A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study to Evaluate the Safety and Efficacy of Estradiol in Combination with Progesterone in Postmenopausal Women with an Intact Uterus: Estradiol to Reduce the Frequency and Severity of Vasomotor Symptoms and Progesterone to Manage the Incidence of Endometrial Hyperplasia.”

We have the following comments and recommendations:

- We continue to recommend that concurrent readings by three independent expert pathologists be conducted for instances of “for cause” endometrial biopsies obtained during the conduct of Study TXC12-05 and for End-of-Treatment (or early withdrawal when treated ≥ 12 weeks) endometrial biopsies. Each of these three pathologists should be blinded to the study treatment group and to the readings of the other pathologists.
- We do not agree with your proposal [REDACTED] (b) (4)
- Provide the Pathology Committee Charter as proposed.



- **August 25, 2017** –DBRUP provided Preliminary Responses to Type B Pre-IND Meeting Request from TherapeuticsMD. Therapeutics MD cancelled the face-to-face meeting and accepted the Preliminary Responses. The following key items were addressed:

Chemistry, Manufacturing and Controls (CMC):

- 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 ^(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.

- Your proposal to submit 12 months long-term stability data for three registration batches for each product strength manufactured by Catalent, is acceptable. Provide accelerated stability data through 6 months 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)
- 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.
 - 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 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.
 - 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., $\pm 10\text{-}20\%$ 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:

- The sponsor's approach to bridge for the formulation and manufacturing site changes, appears reasonable. Provide, in the 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:

- The sponsor's approach to 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, appears acceptable.

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.

Clinical Pharmacology:

- The proposed food effect trial design appears reasonable. At this time, we have not identified any clinical safety concerns.
- 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 TXC 17-02). Whether the results of Trial TXC16-01 are adequate to support the Clinical Pharmacology section of your labeling will be a review issue.
- The assessment of estrone sulfate is not required for approval of TX-001HR
- Considering the linear pharmacokinetics of progesterone and estradiol within the 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.
- We have not currently identified a need for further Clinical Pharmacology trials.

Clinical:

- 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.

- 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 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.
 - 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.
- **December 28, 2017** – TherapeuticsMD submitted NDA 210132 to the Agency
 - **May 25, 2018** – TherapeuticsMD submitted to the Agency, the 120-Day Safety Update to NDA 210132. Therapeutics MD states, “No studies are ongoing, and no new safety information has become known to TherapeuticsMD since the application was submitted.”

3. Product Quality

The Chemistry and Biopharmaceutics data for this NDA were reviewed by the Office of Product Quality (OPQ). The Review Team is listed in Table 3.

Table 3: OPQ reviewers for NDA 210132

DISCIPLINE	REVIEWER	DIVISION / BRANCH
Drug Substance	Soumya Mitra	BII / DNDAPI / ONDP
Drug Product/Labeling/ Environmental Analysis	Zhengfang Ge	BV / DNDPII / ONDP
Process/ Facility	Jingbo Xiao	PABV / DPAII / OPF
Microbiology	Denise Miller	BI / DMA / OPF
Biopharmaceutics	Sandra Suarez	BII / DB / ONDP
Laboratory (OTR)	N/A	DPA /OTR
Application Technical Lead	Mark Seggel	ONDP/DNDPII/Br V
RPM	Thao Vu/Florence Aisada	BI/DRBPM I/OPRO

Abbreviations: ONDP = Office of New Drug Products; DNDAPI = Division of New Drug Active Pharmaceutical Ingredient; DPA = Division of Pharmaceutical Analysis; DMA = Division of Microbiology Assessment; DIA = Division of Inspectional Assessment; DB = Division of Biopharmaceutics; DNDP = Division of Non-prescription Drug Product; OPF= Office of Process and Facility; DPA = Division of Pharmaceutical Analysis; RPM = Regulatory Project Manager

Source: Application Technical Lead

Most of the following chemistry, manufacturing and control (CMC) information is adapted from Mark Seggel’s Executive Summary of the Office of Pharmaceutical Quality (OPQ) Review.

BIJUVA (estradiol and progesterone) capsules is an immediate-release formulation of estradiol and progesterone in a soft gelatin capsule for oral administration. (b) (4)

Drug Substance:

Estradiol and progesterone are well characterized and have long histories of use in medical drug products. Both active pharmaceutical ingredient (API) manufacturers have provided Letters of Authorization to reference their respective Drug Master File (DMF). The CMC of estradiol and progesterone are documented in Type II DMFs # (b) (4) and # (b) (4) respectively. Both DMFs have been found adequate to support use of the drug substances in the manufacture of the drug product. Both drug substances are subjects of United States Pharmacopeia (USP) and European Pharmacopoeia (EP) monographs.

(b) (4)

The levels of individual and total impurities in estradiol drug substance are adequately controlled and meet ICH requirements.

(b) (4)

The progesterone USP is sourced from (b) (4). To ensure consistent product performance (i.e., dissolution of progesterone), the acceptance criteria include particle size controls. Levels of impurities are controlled at levels specified in the EP monograph for progesterone. While the limits for EP Impurities B, C and I exceed

the ICH Q3A threshold of 0.15%, the proposed limits are consistent with those established for progesterone drug substances used in other approved drug products.

From the Drug Substance perspective, the NDA is recommended for approval.

Drug Product:

BIJUVA capsules consist of a gelatin capsule shell, which is soft in consistency and containing (b) (4) (b) (4) estradiol (b) (4) progesterone. The soft gelatin capsule shell is prepared from (b) (4)

with (b) (4) The capsule fill is prepared (b) (4)

The formed and filled capsules are (b) (4)

(b) (4) 1 mg/100 mg dosage (b) (4) contain (b) (4) mg of fill. (b) (4)

The fill mass components, their functions, suppliers, and quantities per capsule for the (b) (4) 1 mg/100 mg dosage (b) (4) are provided in Table 4

Table 4: Composition of the Fill Mass in TX-001HR Capsules

Table 1: Composition, Fill Mass Estradiol and Progesterone Capsules

Component [Compendial name (trade name)]	Quality Standard	Manufacturer	Function	Quantity/capsule (in mg)
(b) (4)				

BIJUVA will be supplied in 30-count blister cards with an outer carton. (Initially, a (b) (4)-count blister was proposed, but in the September 13, 2018 submission, with prior agreement from the Agency, the applicant changed to a 30-count configuration (b) (4). A 5-count blister pack physician sample will also be available.

The product manufacturing process consists of (b) (4). The information in the NDA, as amended, regarding the batch formula, manufacturing process parameters, and in-process controls, is supportive of a robust process.

Note that the manufacture of the proposed commercial scale batches by **Catalent** uses the same formulation, follows the same unit operations and sequence, utilizes equipment with the same design and operating principle used in the manufacture of the clinical batches by (b) (4).

The regulatory specification for the finished product includes tests for the identification, assay, and content uniformity of estradiol and progesterone, tests for estradiol and progesterone related compounds, (b) (4)%, and dissolution of estradiol and progesterone (see discussion below). The analytical procedures are adequately described and appropriately validated.

The applicant proposed limit of NMT (b) (4)% for process impurity and degradant identified as EP Impurity M ((17 α)-pregn-4-ene-3,20-dione; 17-isoprogestrone), a stereoisomer of progesterone. It has been observed in drug product at levels up to (b) (4)%.

Because this is above the ICH qualification threshold, the nonclinical review team was asked to CDER Cross Discipline Team Leader Review NDA 210132 Bijuva (estradiol and progesterone) capsules

assess any risk associated with (b) (4) % Impurity M. Dr. Frederic Moulin determined that, “[t]he no-more-than (NMT) (b) (4) % limit for EP Impurity M does not create a safety risk for patients and is therefore acceptable.” See **Section 4. Nonclinical Pharmacology/Toxicology** of this review.

The drug product is also tested for Microbial Limits at release and on stability using methods consistent with USP Chapters <61> and <62> for non-sterile products. The acceptance criteria are consistent with USP Chapter <111>.

The applicant’s proposed dissolution test employs USP Apparatus III (reciprocating cylinder) at 30 dips per minute (DPM) and a medium consisting of 250-mL 3% w/v (b) (4) in 0.1 N HCl (b) (4). Acceptance criteria of Q = (b) (4) % at (b) (4) minutes were proposed. Sample work-up and analyses differ somewhat to accommodate (b) (4).

However, the proposed test conditions with (b) (4) do not provide any discriminating power. Under these conditions, more than (b) (4) % of progesterone is dissolved within 15 minutes. Concerns about the test conditions and requests for additional data were conveyed to the Applicant on several occasions. The applicant-initiated development and validation of an improved dissolution test, the results of which will be reported under a PMC. While use of the current test conditions with an acceptance criterion of Q = (b) (4) % at 15 minutes and to which the applicant has agreed to implement in the interim, is not ideal, it will ensure that the product meets minimum clinically-relevant performance criteria.

During this review cycle, OPQ identified the following deficiency: *The lack of a discriminatory dissolution test method precludes use of dissolution data to bridge phase 1 clinical materials to phase 3 clinical materials (both manufactured by (b) (4), and of the phase 3 product to the commercial product manufactured by Catalent.* The bioavailability of a 2 mg estradiol and 200 mg progesterone phase 1 product was compared to Prometrium 200 mg capsule. *While the phase 1 and phase 3 products manufactured by (b) (4) have similar composition, the absence of meaningful dissolution data precludes bridging of the 2 mg / 200 mg product to the 1 mg / 100 mg product used in the phase 3 trials.* During formulation development a change was made to the (b) (4)

The manufacture of the investigational drug product by (b) (4) and the manufacture of the commercial product by **Catalent** are also considered sufficiently similar to, under usual circumstances, allow reliance on dissolution data to bridge the products. However, because of the deficiencies already noted, the available dissolution data are not useful in this context. Per Dr. Seggel, given the comparability of the formulations and manufacturing processes, significant differences in the performance of the phase 1, phase 3 and commercial product is not expected from the CMC perspective. This position is *supported* by the available pharmacokinetic data. See **Section 5. Clinical Pharmacology** of this review for discussion of the pharmacokinetic bridge across products.

Verification of the analytical procedures by the CDER/OPQ/OTR laboratory in St. Louis (DPA) was not requested, as neither active ingredient is an NME, and the methods appear relatively

straightforward and employ common analytical methodologies.

The applicant initially proposed an expiration dating period of (b) (4) months based on up to 18 months of long-term data at 25°C/60% RH. (b) (4)

The applicant has acknowledged the 18-month expiration dating period. Continued stability testing will be performed to confirm the current expiration dating period, and if appropriate, extension of the shelf-life.

Overall, TherapeuticsMD has provided adequate information on the drug product, including appropriate raw material controls, adequate manufacturing and in-process controls, a suitable regulatory specification, and suitable packaging, to assure the identity, strength, purity, quality and bioavailability throughout an 18-month expiration dating period when stored at 25°C/60%RH (b) (4).

From the Drug Product and Process perspective, the application, *as amended*, is recommended for Approval.

Product Quality Microbiology

The product is non-sterile product (b) (4). The drug product is also tested for Microbial Limits at release and on stability using methods consistent with USP Chapters <61> and <62> for non-sterile products. The acceptance criteria are consistent with USP Chapter <1111>, and acceptable risk assessment.

Biopharmaceutics

To ensure consistent product performance, an in vitro dissolution test employing USP Apparatus Type 3 at 30 dips per minute and a dissolution medium consisting of 250 mL of 0.1 N HCl with (b) (4)%, sodium laurel sulfate at 37°C was developed. The applicant has agreed to an acceptance criterion of NLT (b) (4)% (Q) of the labeled contents dissolved in (b) (4) minutes.

To demonstrate that the manufacturing process used by *Catalent* for the registration/stability batches and the process used at (b) (4) for clinical and registration/stability batches produces equivalent product, a comparison of the dissolution profiles for one batch of 25 mcg estradiol strength capsule manufactured at Catalent and one manufactured at (b) (4) was performed. The two-sample T-test concludes that the means at the 30, 60, 90, and 120-minute time points do not differ from each other. Data provided for 4 mcg and 10 mcg products demonstrate that about (b) (4)% or more API is dissolved at the first few time points, and although a similarity factor f2 could not be calculated, the in vitro release profiles are considered comparable.

Note that the USP Estradiol Vaginal Inserts monograph specifies dissolution testing with Apparatus 1 and a pH 4.75 phosphate buffer dissolution medium, and sampling at 3, 5 and 10 hours.

From a Biopharmaceutics perspective, NDA 208564 is recommended for approval. In addition to recommending that the applicant petition the USP to incorporate the new test and acceptance criterion into the compendial monograph, it is recommended that the applicant

perform dissolution method validation in accordance with US<1092>, The Dissolution Procedure: Development And Validation, and adopt appropriate acceptance criteria.

Manufacturing Facilities

All manufacturing, packaging and testing facilities associated with the drug substances and drug product have acceptable CGMP status. The OPF Division of Inspectional Assessment issued an Overall Inspection Recommendation of *APPROVE* on August 13, 2018. No changes in facility status have been reported as of the date of this review.

Labeling

Based on the chemist's labeling review, and comments from DMEPA and ODPP, revisions to the labels (carton and blister) and Prescribing Information, were conveyed to the Applicant. Those changes include corrections to nomenclature and formatting, and deletion of potentially promotional wording (e.g., (b) (4)).

The carton and blister labels, and the Prescribing Information, as revised on October 24, 2018, are adequate from the chemist's perspective.

From an overall CMC perspective, the application is recommended for approval

4. Nonclinical Pharmacology/Toxicology

The NDA nonclinical pharmacology/toxicology data submitted was reviewed by Dr. Frederic Moulin.

The sponsor submitted a 505(b)(2) application partially relying on the FDA's previous finding of safety for Prometrium® (NDA 019781) as the Listed Drug (LD) for progesterone. Published literature is provided to support the safety of estradiol for the 505(b)(2) application, and inform Sections 8 (Use in Specific Populations) and 13 (Nonclinical Toxicology) of Prescribing Information.

The safety assessment of this new estradiol plus progesterone capsule formulation (TX-001HR) is based on previous findings of safety for the progesterone Listed Drug (LD) Prometrium® and relevant published literature to support the safety of estradiol. The highest proposed clinical doses of estradiol and progesterone in TX-001HR are also equal to or less than the approved doses for marketed oral estradiol and Prometrium® (oral progesterone).

Estradiol is an endogenous sex hormone present in many approved drug products for diverse indications, including the treatment of moderate to severe vasomotor symptoms as a single daily dose of 1 or 2 mg (e.g. Estrace®, Climara®, EstroGel®, Vagifem®, Vivelle®). The safety of estradiol is well-established and documented in the published literature following many years of clinical use. For this reason, the sponsor has not conducted any nonclinical studies of their own for estradiol and relied on relevant published literature to support the nonclinical safety and to inform nonclinical sections of the label. The literature that the sponsor has submitted is adequate for this purpose without requiring reliance on previous findings of safety for a reference drug product.

The nonclinical evidence supporting the safety of progesterone in TX-001HR are based on the Agency's determination of safety for the Listed Drug, Prometrium® (NDA 19-781). Prometrium® is an approved drug product (progesterone; 100 mg and 200 mg oral capsules) that is indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets (single daily dose of 200 mg at bedtime for 12 days sequentially per 28-day cycle), as well as for use in secondary amenorrhea (single daily dose of 400 mg at bedtime for 10 days). The scientific bridge between TX-001HR and oral Prometrium® is provided by two comparative bioavailability (BA) trials (studies EPROG-1K-351-12 and EPROG-1K-352-12) and one bioequivalence (BE) trial (EPROG-1K-459-12). In the pivotal comparative bioavailability/bioequivalence trial, the applicant demonstrated that the progesterone exposure from an estradiol and progesterone capsule, 1 mg/100 mg, administered under fed conditions was less than or comparable to the reference drug (Prometrium®). See **Section 5. Clinical Pharmacology** for discussion of the scientific bridge.

There is no novel excipient in TX-001HR. There is no novel excipient in TX-001HR. All excipients are below IID limits. The specifications for impurities in the progesterone drug substance are based on the European Pharmacopoeia (EP) monograph, as well as the (b) (4) DMF Technical Package acceptance criteria. (b) (4) has included potential impurities, their acceptance limits and quantitation methods in their DMF, and TherapeuticsMD transferred these methods to its manufacturing process. Among the (b) (4) specification for impurities in progesterone USP, a process impurity referred as "EP Impurity M" ((17 α)-pregn-4-ene-3,20-dione; 17-Isoprogesterone; CAS# 2000-66-0) has an acceptance limit of no-more-than (NMT) (b) (4) %.

"EP Impurity M" was observed above the ICH identification limit of 0.2% on accelerated stability conditions for phase 3 clinical batches manufactured at (b) (4). During the evaluation of clinical stability data, "EP impurity M" was identified in both room temperature and accelerated stability conditions samples. This impurity/degradant was present between (b) (4) % in the drug product at release, with the proportion increasing under accelerated stability conditions. For (b) (4) lot number PN0082-25, this impurity/degradant was at (b) (4) % in the 6-month accelerated stability conditions samples, and the retest values ranged from (b) (4) %.

"EP Impurity M" is chemically (17 α)-isoprogesterone, a stereoisomer of progesterone with no reported toxicity in the literature. Since "EP Impurity M" was present in the clinical batches manufactured by (b) (4) at up to (b) (4) %, 23 months after manufacturing, it is "qualified" for safety at up to (b) (4) % through its administration in the phase 3 trial without adverse effect. "EP impurity M" was not predicted to react with DNA by two separate QSAR models (Leadscope and Derek Nexus) and is considered of no mutagenic concern following ICH M7(R1) guidance. ICH M7(R1) does not recommend further genotoxicity testing.

The request by TherapeuticsMD to increase the acceptance limits from (b) (4) % to (b) (4) % is within the guidance of "allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristic". In addition, there are no significant toxicities

associated with this impurity. *The no-more-than (NMT) ^(b)(4)% limit for “EP Impurity M” does not create a safety risk for patients and is therefore acceptable.*

^(b)(4) is used as ^(b)(4) in ^(b)(4) of the synthesis process employed by ^(b)(4) to manufacture the estradiol API. TherapeuticsMD proposes to fix the acceptance limits in the final drug product to NMT ^(b)(4) parts per million (ppm). However, ^(b)(4) is not a ^(b)(4) included in the guidelines for ^(b)(4)), and its permitted daily exposure limits have not been specified in guidance.

The central nervous system is a primary target for ^(b)(4) toxicity in humans and animals. Acute exposure to high concentration of ^(b)(4) vapors can lead to central nervous system depression, loss of consciousness, and even death. Prolonged exposures produce neurobehavioral and vision changes with inhaled concentrations as low as ^(b)(4) ppm. In addition to the central nervous system, nonclinical studies have identified the kidney, liver, reproductive system, and developing fetus as targets of ^(b)(4) toxicity. The liver and kidney toxicities are believed to be mediated by metabolites, while the parent compound is considered the active neurotoxicant. Neurobehavioral changes occur at lower concentrations than any other effects.

Because of its neurological toxicity and non-genotoxic mouse carcinogenicity, ^(b)(4) should be considered a ^(b)(4) per ICH ^(b)(4) guidance. IARC has classified ^(b)(4) as a ^(b)(4) carcinogen (probably carcinogenic to humans) (IARC 2013).

Most of the evidences supporting the neurological and neurobehavioral effects of low exposures to ^(b)(4) comes from inhalation exposure. However, pharmacokinetics studies in animals have found similar blood concentrations after inhalation and oral administration, and the toxicity is expected to be similar.

The Agency for Toxic Substances and Disease Registry (ATSDR) indicates that the “Minimal Risk Levels (MRL) for chronic (≥ 365 days) oral exposure to ^(b)(4) is ^(b)(4) mg/kg/day. An MRL is an “estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure”. For a female patient of 60 kg, the permissible daily exposure (PDE) would be ^(b)(4) x 60 = ^(b)(4) mg/day. The PDE can be used with the known maximum daily dose of the drug substance to determine the concentration of ^(b)(4) allowed in the drug product. Such limits are considered acceptable if the ^(b)(4) has been reduced to the practical minimum.

The PDE is ^(b)(4) mg/day and the maximum daily dose of estradiol in TX-001HR is 1 mg per day. Hence the maximum permissible concentration of ^(b)(4) in the estradiol component of TX-001HR is greater than the proposed specification of NMT ^(b)(4). The proposed specification is therefore an acceptable limit for ^(b)(4) in TX-001HR as per ^(b)(4).

Also, according to ICH M7(R1), a Threshold of Toxicological Concern (TTC)-based acceptable intake of a mutagenic impurity of 1.5 μg per person per day is associated with a CDER Cross Discipline Team Leader Review NDA 210132 Bijuva (estradiol and progesterone) capsules

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negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure). The *TTC* is used for most pharmaceuticals as a default to derive acceptable limits to control mutagenic impurities present in pharmaceuticals when no definitive carcinogenicity data are available (*Classes 2 and 3*). Because [REDACTED] (b) (4) is classified as a [REDACTED] (b) (4), the *TTC* does apply to it. A daily intake of 1 mg estradiol from TX-001HR containing [REDACTED] (b) (4) would result in a daily intake of [REDACTED] (b) (4) ng of [REDACTED] (b) (4) which is well below the *TTC* of 1.5 µg per day. The proposed specification of NMT [REDACTED] (b) (4) ppm is also an acceptable limit for [REDACTED] (b) (4) in TX-001HR as per ICH M7(R1).

There are no other impurities or degradants of concern in TX-001HR.

From a Nonclinical Pharmacology/Toxicology perspective, approval is recommended for estradiol and progesterone capsules (TX-001HR) for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause in nonhysterectomized women with a uterus.

5. Clinical Pharmacology

The Clinical Pharmacology data for NDA 210132 was reviewed by Dr. Peng Zou.

The applicant conducted five phase 1 and one phase 3 trial in support of their product.

The Applicant proposed that one estradiol and progesterone capsule (TX-001HR) be taken orally each evening with food. After oral administration of multi-dose TX-001HR, the steady-state *C*_{max} of E2 and P4 were attained at approximately 5 and 3 hour, respectively. Food ingestion had no effect on the AUC of E2 but decreased *C*_{max} by approximately 54% compared to that under fasting conditions and prolonged *T*_{max} to 12 hours. Food ingestion did not affect systemic exposure of estrone (E1). A high-fat meal increased AUC_{0-t} and *C*_{max} of single-dose P4 by 79% and 162%, respectively.

Steady-state pharmacokinetics (PK) of E2, E1 and P4 were achieved within 7 days. The PK was variable [REDACTED] (b) (4). For the 1 mg /100 mg dose, the mean effective half-lives of E2 and E1 were 26 and 22 hours, respectively. The mean elimination half-life of P4 was 10 hours. The baseline-adjusted AUC of E2, E1 and P4 on Day 7 increased by 93%, 91% and 28%, respectively, compared to the AUC on Day 1. [REDACTED] (b) (4)

[REDACTED] The applicant also relies on general knowledge regarding metabolism and excretion of E2 and P4.

In the pivotal phase 3 trial (TXC12-05), blood was collected from the safety population to assess serum levels of E2, E1, and P4 over the course of the study. Blood samples were collected 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 P4 were assessed at Screening and Visits 4 and 7 (Week 12 and Month 12, respectively). Dose-dependent increase in E2 concentrations (See Table 1 in Dr. Peng Zou's review) and P4 concentrations (see Table 2 in Dr. Peng Zou's review) were observed. Consistent concentrations of E2 and P4 were maintained over 12

months for each treatment arm, which provided supportive evidence of effectiveness of TX-001HR.

To support the nonclinical safety of TX-001HR and support Sections 8 (Use in Specific Populations) and 13 (Nonclinical Toxicology) of the label, the applicant proposed to submit nonclinical published literature for E2. For P4, the applicant relied upon the FDA's finding of nonclinical safety for Prometrium® (progesterone capsules USP, NDA 019781) as the reference drug using Trial EPROG-1K-459-12 as the primary bridge to FDA's finding of safety. Bioequivalence (BE) Trial EPROG-1K-459-12 *successfully bridged the proposed to-be-marketed (TBM) product to the FDA's previous finding of nonclinical safety* for the listed drug Prometrium 200 mg.

Per Biopharmaceutical reviewer, the *to-be-marketed formulation (Catalent 1 mg E2/100 mg P)* is bridged to the phase 3 trial formulation [(b) (4) 1 mg E2/100 mg P4] using in vitro dissolution data and CMC data. No clinical bioequivalence (BE) study is required. A cross-study comparison between phase 1 Trial TXC16-01 (*Catalent 1 mg E2/100 mg P*) and phase 3 Study TXC12-05 ((b) (4) 1 mg E2/100 mg P, sparse PK sampling) did not show a dramatic difference in the plasma concentrations of E2 or P4.

The reader is referred to Dr. Zou's review for the details of the above determinations. The Office of Clinical Pharmacology Division of Clinical Pharmacology-3 recommends approval of this NDA.

6. Clinical Microbiology

This section is not applicable to the approvability decision for this review.

7. Clinical/Statistical- Efficacy

The primary review of the efficacy information in NDA 201132 was performed by Theresa van der Vlugt, M.D., Office of New Drugs (OND)/Office of Drug Evaluations (ODE) 3/DBRUP and Statistical Reviewer, Jia Guo, Ph.D., Office of Translational Science/Division of Biometrics III.

DBRUP recommends that trials conducted to support the treatment of moderate-to-severe (MS) vasomotor symptoms, due to menopause, evaluate four patient-reported co-primary endpoints consisting of frequency of vasomotor symptoms at **Week 4**, frequency of vasomotor symptoms at **Week 12**, severity of vasomotor symptoms at **Week 4** and severity of vasomotor symptoms at **Week 12**. The primary analyses of the four co-primary endpoints should demonstrate statistically significant improvement (reduction) from baseline in frequency of moderate to severe vasomotor symptoms at **Week 4 and Week 12** and statistically significant improvement from baseline in severity of moderate to severe vasomotor symptoms at **Week 4 and Week 12**. Additionally, the statistically significant relative reduction in frequency of vasomotor symptoms should be associated with a clinically meaningful threshold of a relative two per day or 14 per week greater decrease in the frequency of moderate to severe vasomotor

symptoms of the proposed trial product when compared to placebo. Because of the depth of knowledge attained over a long history of evaluation and approval of estrogen-containing products, the Agency requires demonstration of efficacy in only a single trial alone for non-new chemical entity (non-CME) estrogen-alone or a non-CME fixed dose combination estrogen plus progestogen product. The Agency recommends demonstration of efficacy for new CME estrogen in two or more trials. To demonstrate safety, the Agency requires a single 52-week trial (See **Section 8. Safety** of this review)

The applicant, TherapeuticsMD, submitted a single, randomized, double-blind, placebo controlled (first 12-weeks), 52-week duration, parallel-group, phase 3 trial, TXC12-05, to support the efficacy (b)(4) of their fixed dose combination estrogen (E2) plus progesterone (P4) product TX-001HR. As stated above for the determination of efficacy for a non-CME fixed dose combination estrogen plus progestogen product, a single trial is appropriate.

The primary objectives of Trial TXV14-01 were to determine whether TX-001HR given in a continuous fashion is effective at reducing the frequency and severity of moderate to severe VMS due to menopause when compared with placebo at Weeks 4 and 12 and to determine whether TX-001HR given in a continuous fashion is effective at achieving a $\leq 1\%$ incidence rate of endometrial hyperplasia following 12 months of therapy (see Section 8 Safety of this review).

Women were randomized in a 1:1:1:1:1 fashion to TX-001HR (fixed dose combinations of E2 and P4) cohorts of 1 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/ 50 mg, 0.25 mg/50 mg, and a placebo cohort. Trial participants were healthy (no active or ongoing chronic medical conditions/disease and no history of alcoholism or drug abuse) postmenopausal (defined by criteria of greater than 12 months of spontaneous amenorrhea, greater than 6 months but less than one year of spontaneous amenorrhea with screening follicle stimulating hormone (FSH) level of greater than 40 mIU/mL, or 6 weeks or greater postsurgical bilateral oophorectomy) women, who were to be between 40 and 65 years of age with normal mammogram [requirement of a breast imaging and reporting and database system (BI-RADS) of 1 or 2 to enroll; an incomplete mammogram result (for example, BI-RADS 0 was not acceptable)] within the previous 6 months of the initiation of trial medication. Women all were to have normal findings upon breast examination, normal Pap smear within the last 12 months [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 (ASCUS), cannot rule out HSIL, dysplastic cells, or malignant cells, were excluded], a body mass index (BMI) less than or equal to 34 kg/m², and normal hematology, clinical chemistry, and urinalysis. A woman was to have had an intact uterus and an acceptable result from an evaluable screening endometrial biopsy demonstrating 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.

Women at baseline were also to have reported ≥ 7 moderate to severe hot flushes per day, or ≥ 50 per week. These women participated in the first 12-week, blinded, placebo-controlled portion of TXC12-05 (VMS sub-trial). Women whose hot flushes were less frequent were still able enroll in 52-week TXC12-05 (safety), but efficacy results from these participants were not included the first 12 weeks VMS sub-trial. Trial TXC12-05 was conducted between August 5, 2013 and October 28, 2016.

The modified intent to treat (ITT) population consisted of all trial participants who were randomly assigned and had at least one dose of trial medication. To be included in the MITT of the vasomotor symptom sub-trial population of Trial TXC12-05, women must have been randomized to this portion of the trial, self-administered at least one dose (consisting of two capsules, one active and one placebo) of trial medication and have: 1) at least five (5) days of VMS diary data for Baseline measurement of frequency and severity of moderate to severe hot flushes and 2) 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. The modified intent-to-treat (MITT) population was the primary efficacy population with supportive efficacy analyses conducted on the efficacy evaluable population [(EE), those women without major protocol violations and 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.

For additional details of the design and conduct of Trial TXC12-05, including population definitions, evaluated primary and secondary endpoints and their analyses, the reader is referred to the reviews from Dr. van der Vlugt and Dr. Guo.

Of the 766 postmenopausal women randomized to the VMS sub-trial, 726 (94.8%) met the criteria to be included in the MITT-VMS population 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%)
- no trial medication and no post-Baseline VMS diary data (n = 3; 0.4%)
- no trial medication, no post-Baseline VMS diary data; and consumed less than two or more capsules (n = 2; 0.3%); and /or randomized twice into the study (n = 1; 0.1%)

The disposition of the mITT population in the initial 12-week vasomotor symptom sub-trial of phase 3 Trial TXC12-05 is summarized in Table 5.

Table 5: Disposition of the MITT Population on 12-Week Sub-trial of 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 completed, n (%)	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	1 (0.7)	0	0	1 (0.1)
Lack of Efficacy	2 (1.4)	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	1 (0.7)	1 (0.7)	0	0	2 (0.3)

Definitions: MITT-VMS = modified Intent-to-Treat – vasomotor symptoms; E₂ = estradiol; P = progesterone.

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

Overall, 71.2% (517 of 726 women in the vasomotor symptom sub-trial population) completed Trial TXC12-05. This is on par with completion rates seen with other vasomotor symptom trials. The most common reasons for discontinuation 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%).

The percentage of discontinuation across all dosage strength cohorts were similar (approximately 30%), except for the 0.5 mg/100 mg cohort (21% discontinuation). Discontinuations due to lack of efficacy was approximately 1 to 2% in each dosage strength cohorts, except for the 0.5 mg/100 mg cohort (0%). Adverse events as a reason for discontinuation were highest (14.5%) in the 1 mg estradiol/100 mg dosage strength cohort and lowest (3.4%) in the 0.5 mg estradiol/100 mg dosage strength cohort (even lower than the placebo cohort). Based on the data in Table 5, the 0.5 mg/100 mg dosage strength cohort stood out from the other dosage strength cohorts, it had a lower total discontinuation and reason for discontinuation than any of the other dosage strength cohorts except for discontinuations due sponsor/investigator decision (approximately the same as the other cohorts) and discontinuations due to patient withdrawal of consent, where the percentage of discontinuations for the 0.5 mg/100 mg dosage strength cohort exceeded the other dosage strength cohorts. The reason for the discrepancies in the 0.5 mg/100 mg cohort and other dosage strength cohorts, is not immediately obvious.

Selected demographics of postmenopausal women participating in the vasomotor symptom sub-trial are presented in Table 6 below:

Table 6: Selected Demographic and Baseline Characteristics for MITT-VMS

	1 mg E2/ 100 mg P4 (N=141)	0.5 mg E2/ 100 mg P4 (N=149)	0.5 mg E2/ 50 mg P4 (N=147)	0.25 mg E2/ 50 mg P4 (N=154)	Placebo (N=135)	Total (N=726)
Age (years)						
Mean (SD)	54.7 (4.80)	54.9 (4.45)	54.8 (4.63)	54.5 (3.78)	54.3 (4.29)	54.6 (4.39)
Median	55	55	55	54	54	54
Min, Max	40, 65	45, 65	41, 65	45, 65	45, 65	40, 65
Race, n (%)						
White	95 (67.4)	99 (66.4)	99 (67.3)	102 (66.2)	91 (67.4)	486 (66.9)
Black or African American	45 (31.9)	48 (32.2)	43 (29.3)	48 (31.2)	41 (30.4)	225 (31.0)
Other ^a	1 (0.7)	2 (1.3)	5 (3.4)	4 (2.6)	3 (2.2)	15 (2.1)
Weight (kg)						
Mean (SD)	71.7 (12.47)	72.7 (13.19)	72.0 (11.43)	71.1 (11.68)	71.7 (11.24)	71.9 (12.01)
Median	71	72	72	72	71	71
Min, Max	41, 106	45, 105	49, 100	45, 95	45, 98	41, 106
Height (cm)						
Mean (SD)	164.3 (6.96)	163.7 (7.49)	164.4 (6.51)	163.9 (6.41)	163.8 (6.05)	164.0 (6.70)
Median	164	163	165	163	165	164
Min, Max	149, 180	137, 183	151, 180	150, 185	146, 180	137, 185
BMI (kg/m²)						
Mean (SD)	26.45 (3.935)	27.05 (4.333)	26.57 (3.943)	26.42 (3.983)	26.64 (3.817)	26.63 (4.006)
Median	26.1	27.0	26.6	26.2	26.8	26.8
Min, Max	14.0, 34.2	18.2, 34.5	18.0, 34.4	17.0, 34.3	16.0, 34.1	14.0, 34.5

Source: Statistical Reviewer Table 18 and NDA 210132, Trial TXC12-05 report, Table 16, pages 81 - 82.

The demographics of women participating in the vasomotor symptom sub-trial consisted of women who self-identified their race as: White (67%), Black/African American (31%), and “Other” (2.1%). The percentage of non-White participants, particularly woman who self-identified as Black/African American, is substantially higher than typically seen in other trials submitted to support an indication of treatment of moderate to severe vasomotor symptoms, due to menopause. The mean weight and BMI values were very similar across all estradiol and progesterone dosage strength cohorts and placebo.

As previously indicated, the co-primary endpoints evaluated in Trial TXC12-05 were:

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

The primary efficacy analyses of all co-primary endpoints were performed on the modified Intent-to-Treat (ITT) sub-trial population of Trial TXC 12-05. The primary efficacy analysis was performed using a mixed model repeated measures (MMRM) analysis, applied to the 12 weekly change scores. The model included Baseline as covariate; and treatment, trial week, and treatment-by-trial week interaction as fixed factors; and participant as the repeated measure unit.

To account for the multiple comparisons of testing placebo to each of the evaluated fixed dose combination regimens (1 mg/100 mg, 0.5 mg/100mg, 0.5 mg/ 50 mg, 0.25 mg/50 mg) and the multiple testing of the four co-primary endpoints, a gatekeeping testing procedure was used. The testing started by examining the highest fixed dose combination of estradiol and progesterone (1 mg/100 mg) for each of the co-primary endpoints. If each of the four p-values for the co-primaries were significant ($p \leq 0.05$) then the hypothesis testing continued to the next highest dose and so forth. 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.

As indicated in the **Section 2. Background** discussion, TherapeuticsMD was notified during interactions with the Agency that the primary efficacy analyses should demonstrate for its product relative to placebo, a statistically significant improvement (reduction) from baseline in the frequency and severity of vasomotor symptoms at **Week 4 and Week 12** of treatment. In addition to statistical significance, the relative reduction in frequency should demonstrate a clinically meaningful threshold of a two per day or 14 per week greater decrease in the frequency of moderate to severe vasomotor symptoms of the applicant-proposed product when compared to placebo.

Efficacy results for the analyses of change from baseline in the frequency of moderate to severe vasomotor symptoms are provided in Table 7.

Table 7: Change from Baseline in the Mean Number (Frequency) of Weekly Moderate and Severe Vasomotor Symptoms, Weeks 1 Through Week 12, modified Intent to Treat (mITT) Population with Mixed Model Repeated Measures (MMRM) Analyses - Vasomotor Symptom Sub-trial of TXC12-05

Dosage Strengths Evaluated N = Number of Subjects Randomized)	1 mg E2/ 100 mg P4 (N=141)	0.5 mg E2/ 100 mg P4 (N=149)	0.5 mg E2/ 50 mg P4 (N=147)	0.25 mg E2/ 50 mg P4 (N=154)	Placebo (N=135)
Baseline					
Mean (SD)	74.4 (35.26)	72.1 (27.76)	75.9 (28.04)	77.0 (30.42)	72.4 (23.26)
Week 1 (n)	138	149	145	154	134
Mean (SD)	62.2 (38.71)	60.6 (29.74)	65.2 (32.25)	60.8 (32.03)	59.5 (26.02)
Mean (SD) change from Baseline	-12.2 (20.10)	-11.5 (20.19)	-11.0 (20.94)	-16.3 (22.28)	-13.0 (21.25)
LS Mean (SE) difference from placebo*	1.36 (2.51)	1.29 (2.47)	3.17(2.49)	-1.93 (2.46)	---
MMRM P-value vs placebo	0.588	0.601	0.202	0.431	---
Week 2 (n)	134	146	145	153	133
Mean (SD)	47.4 (37.80)	51.0 (30.16)	56.4 (36.62)	51.8 (33.23)	51.3 (26.31)
Mean (SD) change from Baseline	-26.6 (27.67)	-21.2 (24.79)	-19.0 (28.32)	-25.4 (26.63)	-21.3 (24.75)
LS Mean (SE) difference from placebo*	-4.35 (3.05)	-0.17(3.00)	3.54(3.01)	-2.77(2.98)	---
MMRM P-value vs placebo	0.154	0.956	0.240	0.353	---
Week 3 (n)	136	144	144	153	131
Mean (SD)	40.0 (38.71)	43.1 (29.55)	47.2 (33.47)	43.6 (32.54)	47.8 (27.65)
Mean (SD) change from Baseline	-34.3 (29.22)	-29.0 (26.73)	-28.1 (28.18)	-33.6 (27.76)	-25.1 (27.26)
LS Mean (SE) difference from placebo*	-8.56 (3.16)	-3.76 (3.11)	-1.65 (3.12)	-7.24 (3.08)	---
MMRM P-value vs placebo	0.007	0.227	0.597	0.019	---
Week 4 (n)	134	144	142	152	126
Mean (SD)	31.5 (29.45)	37.2 (26.68)	41.5 (33.85)	38.4 (32.79)	45.9 (27.52)
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) difference 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 5 (n)	131	144	142	152	126
Mean (SD)	26.7 (26.23)	32.6 (25.24)	38.0 (30.64)	34.2 (31.79)	40.9 (27.58)
Mean (SD) change from Baseline	-45.9 (32.3)	39.5 (28.53)	-37.1 (30.64)	-43.5 (33.1)	-31.6 (28.96)
LS Mean (SE) difference from placebo*	-15.59 (3.35)	-9.88 (3.29)	-5.90 (3.31)	-12.05 (3.27)	---
MMRM P-value vs placebo	< 0.001	0.003	0.075	< 0.001	---

Dosage Strengths Evaluated N = Number of Subjects Randomized)	1 mg E2/ 100 mg P4 (N=141)	0.5 mg E2/ 100 mg P4 (N=149)	0.5 mg E2/ 50 mg P4 (N=147)	0.25 mg E2/ 50 mg P4 (N=154)	Placebo (N=135)
Week 6 (n)	132	143	139	146	123
Mean (SD)	23.2 (26.28)	30.4 (25.05)	35.1 (31.25)	32.1 (31.69)	39.9 (27.54)
Mean (SD) change from Baseline	-49.4 (32.76)	-41.7 (29.97)	-40.1 (33.62)	-45.5 (33.14)	-32.7 (28.53)
LS Mean (SE) difference from placebo*	-17.8 (3.44)	-11.35 (3.39)	-7.81 ((3.40)	-12.51 (3.35)	---
MMRM P-value vs placebo	< 0.001	< 0.001	0.022	< 0.001	---
Week 7(n)	130	142	139	147	120
Mean (SD)	21.4 (24.74)	27.2 (25.05)	31.3 (29.27)	30.0 (30.10)	38.6 (27.00)
Mean (SD) change from Baseline	-51.5 (31.51)	-45.0 (30.73)	-43.8 (33.20)	-47.7 (32.18)	-33.4 (29.36)
LS Mean (SE) difference from placebo*	17.75 (3.41))	-13.29 (3.36)	-10.22 (3.37)	-13.61 (3.33)	---
MMRM P-value vs placebo	< 0.001	< 0.001	0.003	< 0.001	---
Week 8 (n)	129	140	137	147	120
Mean (SD)	21.4 (26.83)	25.7 (23.30)	29.3 (28.25)	29.4 (29.54)	36.2 (27.46)
Mean (SD) change from Baseline	-52.3 (31.63)	-46.8 (30.64)	-45.4 (32.55)	-48.4 (32.82)	-36.0 (30.66)
LS Mean (SE) difference from placebo*	-16.63 (3.42)	-12.97 (3.37)	-9.63 (3.38)	-11.97 (3.34)	---
MMRM P-value vs placebo	< 0.001	< 0.001	0.005	< 0.001	---
Week 9 (n)	124	137	132	141	119
Mean (SD)	19.3 (22.83)	22.3 (22.12)	27.2 (27.44)	27.1 (29.01)	35.7 (26.38)
Mean (SD) change from Baseline	-52.6 (32.57)	-50.5 (31.01)	-47.4 (30.13)	-50.1 (33.92)	-36.4 (29.09)
LS Mean (SE) difference from placebo*	-17.12 (3.40)	-15.58 (3.40)	-11.05 (3.36)	-13.02 (3.32)	---
MMRM P-value vs placebo	< 0.001	< 0.001	0.001	< 0.001	---
Week 10 (n)	126	133	129	140	118
Mean (SD)	18.9 (22.85)	21.1 (21.21)	26.0 (27.59)	26.2 (27.99)	35.0 (27.04)
Mean (SD) change from Baseline	-53.2 (32.58)	-51.9 (32.79)	-49.0 (30.24)	-50.6 (33.36)	-37.1 (29.74)
LS Mean (SE) difference from placebo*	-16.80 (3.45)	-15.66 (3.40)	-11.20 (3.41)	12.16 (3.37)	---
MMRM P-value vs placebo	< 0.001	< 0.001	0.001	< 0.001	---
Week 11 (n)	126	134	129	137	118
Mean (SD)	18.4 (21.36)	20.7 (22.22)	25.4 (27.34)	25.7 (28.63)	35.6 (28.01)
Mean (SD) change from Baseline	-53.7 (32.21)	-52.0 (31.24)	-49.4 (30.71)	-50.9 (34.33)	-36.7 (30.32)
LS Mean (SE) difference from placebo*	-18.11 (3.47)	-16.45 (3.42)	-12.41 (3.44)	-13.60 (3.39)	---
MMRM P-value vs placebo	< 0.001	< 0.001	< 0.001	< 0.001	---

Dosage Strengths Evaluated N = Number of Subjects Randomized)	1 mg E2/ 100 mg P4 (N=141)	0.5 mg E2/ 100 mg P4 (N=149)	0.5 mg E2/ 50 mg P4 (N=147)	0.25 mg E2/ 50 mg P4 (N=154)	Placebo (N=135)
Week 12 (n)	124	129	124	135	115
Mean (SD)	17.1 (20.65)	19.1 (21.87)	25.2 (27.45)	24.1 (28.42)	32.0 (26.24)
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)
LS Mean (SE) difference 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	---

*Least Square (LS) mean difference from placebo and P-values are obtained from MMRM model, which included baseline frequency as covariate, treatment, study week, and treatment-by-study week interaction as fixed factors, and subject as the repeated measure unit.

Source: Statistical Reviewer constructed table with modified presentation of the data presented in NDA 210132, Trial TXC12-05 report, Table 14.2.2.1, pages 613 -619.

Three dosage strengths of fixed dose combinations of E2 and P4, 1 mg/100 mg, 0.5 mg/100mg, and 0.25 mg/50 mg demonstrated a statistically significant reduction in the frequency (number) of moderate to severe vasomotor symptoms at **Week 4 and Week 12** (the timepoints of assessment of the co-primary endpoints). However, at Week 4 none of these statistically significant reductions for the fixed dose combination of E2 and P4 were associated with a least square mean differences of 14 per week (or 2 per day) hot flushes over placebo, the clinically meaningful threshold. For the highest dosage strength 1 mg/100 mg, this threshold was reached at Week 5 and maintained to Week 12. For the second highest dosage strength, the 14 per week per week clinically meaningful threshold was not reached until Week 9. For the 0.25 mg/50 mg dosage strength a clinically meaningful threshold was not reached in the 12 weeks trial duration.

Efficacy results for the analyses of change from baseline in the severity of moderate to severe vasomotor symptoms are provided in Table 8

Table 8: Change from Baseline in the Severity of Weekly Moderate and Severe Vasomotor Symptoms, Weeks 1 Through Week 12, modified Intent to Treat (mITT) Population with Mixed Model Repeated Measures (MMRM) Analyses - Vasomotor Symptom Sub-trial of TXC12-05

Dosage Strengths Evaluated N = Number of Subjects Randomized)	1 mg E2/ 100 mg P4 (N=141)	0.5 mg E2/ 100 mg P4 (N=149)	0.5 mg E2/ 50 mg P4 (N=147)	0.25 mg E2/ 50 mg P4 (N=154)	Placebo (N=135)
Baseline	2.5 (0.32)	2.5 (0.25)	2.5 (0.23)	2.5 (0.26)	2.5 (0.25)
Week 1 (n)	138	149	145	154	134
Mean (SD)	2.3 (0.36)	2.3 (0.38)	2.3 (0.37)	2.3 (0.39)	2.3 (0.37)
Mean (SD) change from Baseline	-0.2 (0.31)	-0.3 (0.27)	-0.2 (0.26)	-0.3 (0.33)	-0.3 (0.26)
LS Mean (SE) Difference*	0.01 (0.03)	0.00 (0.03)	0.02 (0.03)	0.00 (0.03)	---
P-value vs placebo	0.801	0.991	0.642	0.928	---
Week 2 (n)	134	146	145	153	133
Mean (SD)	2.2(0.45)	2.2(0.45)	2.2(0.43)	2.2(0.40)	2.2(0.40)
Mean (SD) change from Baseline	-0.3 (0.41)	-0.3 (0.39)	-0.3 (0.35)	-0.3 (0.31)	-0.3 (0.31)
LS Mean (SE) Difference*	-0.05 (0.04)	-0.06 (0.04)	0.02 (0.04)	-0.01 (0.04)	---
P-value vs placebo	0.231	0.173	0.717	0.849	---
Week 3 (n)	136	144	144	153	131
Mean (SD)	2.1(0.55)	2.1(0.48)	2.2(0.48)	2.1(0.50)	2.2(0.44)
Mean (SD) change from Baseline	-0.4(0.51)	-0.4(0.44)	-0.3(0.41)	-0.4(0.42)	-0.3(0.37)
LS Mean (SE) Difference*	-0.11(0.05)	-0.11(0.05)	0.00(0.05)	-0.05(0.05)	---
P-value vs placebo	0.039	0.030	0.946	0.309	---
Week 4 (n)	134	144	142	152	126
Mean (SD)	2.1 (0.57)	2.0 (0.60)	2.1 (0.52)	2.1 (0.58)	2.2 (0.45)
Mean (SD) change from Baseline	-0.5 (0.55)	-0.5 (0.56)	-0.4 (0.47)	-0.4 (0.51)	-0.3 (0.39)
LS Mean (SE) Difference*	-0.13 (0.06)	-0.17 (0.06)	-0.05 (0.06)	-0.10 (0.06)	---
P-value vs placebo	0.031	0.005	0.401	0.100	---
Week 5 (n)	131	143	139	147	124
Mean (SD)	1.9(0.71)	2.0(0.58)	2.1(0.50)	2.0(0.64)	2.1(0.58)
Mean (SD) change from Baseline	-0.6(0.70)	-0.6(0.56)	-0.4(0.46)	-0.5(0.61)	-0.4(0.55)
LS Mean (SE) Difference*	-0.23 (0.07)	-0.15 (0.07)	-0.02 (0.07)	-0.12 (0.07)	---
P-value vs placebo	0.001	0.034	0.790	0.086	---

Dosage Strengths Evaluated N = Number of Subjects Randomized)	1 mg E2/ 100 mg P4 (N=141)	0.5 mg E2/ 100 mg P4 (N=149)	0.5 mg E2/ 50 mg P4 (N=147)	0.25 mg E2/ 50 mg P4 (N=154)	Placebo (N=135)
Week 6 (n)	132	143	139	146	123
Mean (SD)	1.7 (0.87)	1.9 (0.68)	2.0 (0.58)	1.9 (0.76)	2.1 (0.60)
Mean (SD) change from Baseline	-0.8 (0.84)	-0.6 (0.64)	-0.5 (0.58)	-0.6 (0.76)	-0.5 (0.57)
LS Mean (SE) Difference*	-0.36 (0.08)	-0.18 (0.08)	-0.10 (0.08)	-0.19 (0.08)	---
P-value vs placebo	<0.001	0.030	0.247	0.022	---
Week 7(n)	130	142	139	147	120
Mean (SD)	1.7 (0.89)	1.8 (0.69)	1.9 (0.64)	1.9 (0.77)	2.1 (0.51)
Mean (SD) change from Baseline	-0.9 (0.85)	-0.7 (0.69)	-0.6 (0.64)	-0.6 (0.76)	-0.4 (0.48)
LS Mean (SE) Difference*	-0.37 (0.09)	-0.25 (0.08)	-0.18 (0.08)	-0.20 (0.08)	---
P-value vs placebo	<0.001	0.002	0.031	0.016	---
Week 8 (n)	129	140	137	147	120
Mean (SD)	1.7 (0.89)	1.8 (0.69)	1.8 (0.70)	1.9 (0.75)	2.0 (0.58)
Mean (SD) change from Baseline	-0.9 (0.85)	-0.7 (0.64)	-0.7 (0.69)	-0.6 (-0.75)	-0.5 (0.56)
LS Mean (SE) Difference	-0.38 (0.09)	-0.23 (0.09)	-0.15 (0.09)	-0.14 (0.09)	---
P-value vs placebo	<0.001	0.008	0.087	0.092	---
Week 9 (n)	124	137	132	141	119
Mean (SD)	1.6 (0.91)	1.8 (0.74)	1.8 (0.72)	1.8 (0.78)	2.0 (0.55)
Mean (SD) change from Baseline	-1.0 (0.89)	-0.7 (0.70)	-0.7 (0.72)	-0.7 (0.77)	-0.5 (0.54)
LS Mean (SE) Difference*	-0.48 (0.09)	-0.29 (0.09)	-0.24 (0.09)	-0.24 (0.09)	---
P-value vs placebo	<0.001	0.001	0.009	0.007	---
Week 10 (n)	126	133	129	140	118
Mean (SD)	1.5 (0.96)	1.7 (0.76)	1.7 (0.77)	1.9 (0.75)	2.00 (0.58)
Mean (SD) change from Baseline	-1.1 (0.95)	-0.8 (0.73)	-0.8 (0.77)	-0.6 (0.74)	-0.5 (0.58)
LS Mean (SE) Difference*	-0.52 (0.10)	-0.28 (0.09)	-0.23 (0.10)	-0.10 (0.09)	---
P-value vs placebo	<0.001	0.003	0.016	0.310	---
Week 11 (n)	126	134	129	137	118
Mean (SD)	1.5 (0.94)	1.7 (0.83)	1.7 (0.78)	1.8 (0.78)	2.0 (0.58)
Mean (SD) change from Baseline	-1.0 (0.93)	-0.9 (0.78)	-0.8 (0.78)	-0.7 (0.77)	-0.5 (0.57)
LS Mean (SE) Difference	-0.53 (0.10)	-0.37 (0.10)	-0.25 (0.10)	-0.17 (0.10)	---
P-value vs placebo	<0.001	<0.001	0.011	0.076	---

Dosage Strengths Evaluated N = Number of Subjects Randomized)	1 mg E2/ 100 mg P4 (N=141)	0.5 mg E2/ 100 mg P4 (N=149)	0.5 mg E2/ 50 mg P4 (N=147)	0.25 mg E2/ 50 mg P4 (N=154)	Placebo (N=135)
Week 12 (n)	124	129	124	135	115
Mean (SD)	1.4 (0.98)	1.6 (0.82)	1.7 (0.76)	1.8 (0.81)	2.0(0.62)
Mean (SD) change from Baseline	-1.1 (0.96)	-0.9 (0.78)	-0.8 (0.74)	-0.7 (0.81)	-0.6(0.60)
LS Mean (SE) Difference*	-0.57 (0.10)	-0.39 (0.10)	-0.24 (0.10)	-0.16 (0.10)	
P-value vs placebo	<0.001	<0.001	0.018	0.096	

*Least Square (LS) mean difference from placebo and P-values are obtained from MMRM model, which included baseline frequency as covariate, treatment, study week, and treatment-by-study week interaction as fixed factors, and subject as the repeated measure unit.

Source: Statistical Reviewer constructed table with modified presentation of the data presented in NDA 210132, Trial TXC12-05 report, Table 14.2.2.3, pages 627 – 623.

As noted above, three dosage strengths of fixed dose combinations of E2 and P4, 1 mg/100 mg, 0.5 mg/100mg, and 0.25 mg/50 mg demonstrated statistically significant reductions in the frequency (number) of moderate to severe vasomotor symptoms at **Week 4 and Week 12** (the timepoints of assessment of the co-primary endpoints). Only the 1 mg/100 mg and 0.5 mg/100 mg dosage strengths demonstrated statistically significant reductions in the severity of moderate to severe vasomotor symptoms at **Week 4 and Week 12** (the timepoints of assessment of the co-primary endpoints). The other evaluated dosage strengths, 0.5 mg/50 mg and 0.25 mg/50 mg did not show consistently statistically significant reductions in weekly severity assessments from Weeks 1 through Weeks 12.

This reviewer notes that to the best of her knowledge, all previous analyses performed on products seeking and eventually gaining approval for the indication of treatment of moderate to severe vasomotor symptoms, due to menopause, used an analysis of covariance (ANCOVA) with the last observation carried forward (LOCF) for efficacy analyses. Such analyses conducted as sensitivity analyses for this application (see Dr. van der Vlugt’s review), did not affect the outcome.

In phase 3 Trial TXC12-05, 65 percent of women who participated in the trial self-identified as White (1201 of 1835 trial participants), 32.1 percent of participating women self-identified as Black or African American (589 of 1835 trial participants), and 2.4 percent of participating women self-identified as Other (including Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander) (45 of 1835 trial participants). In the course of her evaluation, Dr. Jia Guo alerted the review team that in the subgroup analyses by race, it was evident that women who self-identified as Black/African postmenopausal did not receive relief, based on the recommended frequency and severity co-primary endpoints at **Week 4 and Week 12**, from any dosage strength of Bijuva (estradiol and progesterone) capsules.

Table 9 provides the change from Baseline and the Least Square mean change from placebo for the frequency (number) of moderate to severe vasomotor symptoms at **Week 4 and Week 12** for women who self-identified as White and women who self-identified as Black/African American.

Table 9: Change from Baseline and Least Square Mean Change from Placebo in the Frequency of Weekly Moderate to Severe Vasomotor Symptoms 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)
White					
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	---
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	---

*Least Square (LS) mean difference from placebo and P-values are obtained from MMRM model, which included baseline frequency as covariate, treatment, study week, and treatment-by-study week interaction as fixed factors, and subject as the repeated measure unit

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.

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

Table 10 shown the change from Baseline and the least square mean change from placebo for the severity of moderate to severe vasomotor symptoms at **Week 4 and Week 12** for these two selected racial subgroups.

Table 10: Change from Baseline and Least Square Mean Change from Placebo in the Severity of Weakly Moderate to Severe Vasomotor Symptoms 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)
White					
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)	---
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	---

*Least Square (LS) mean difference from placebo and P-values are obtained from MMRM model, which included baseline frequency as covariate, treatment, study week, and treatment-by-study week interaction as fixed factors, and subject as the repeated measure unit

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.

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

In contrast to results in White postmenopausal women, the application of the co-primary analyses applied at **Week 4 and Week 12** to women who self-identified as Black/African American, demonstrated no statistically significant reduction in frequency at either **Week 4 or Week 12** in either the 1 mg /100 mg or 0.5 mg /100 mg dosage strength cohorts. In the CDER Cross Discipline Team Leader Review NDA 210132 Bijuva (estradiol and progesterone) capsules

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analyses for severity of moderate to severe vasomotor symptoms in women who self-identified as Black/African America, a statistically significant reduction was seen at **Week 12** (no statistically significant reduction in severity was seen at Week 4). Analyses of the two lower dosage strength cohorts in Trial TXC12-05 did not demonstrate statistically significant reductions in frequency or severity at either timepoint.

The applicant also performed a responder analysis as secondary. Responders were defined as the percent of women with 50% and, separately, 75% reduction 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 was also employed for the formulation of inferences concerning each comparison. The Agency did not concur with the definition of responder or use of responder analyses to support efficacy decisions. Therefore, the results of these analyses, have not been included in this CDTL review (See Dr. van der Vlugt's review for the secondary efficacy responder analyses results).

Conclusions on the Substantial Evidence of Effectiveness:

The 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 (subsequently referred to in this document as the 2003 draft Hormone Therapy Clinical Trial Guidance) was a revision of previous guidances (1995 and draft 1999) which provides the Agency's current thinking, as it stood at the time, for recommendations on the conduct and analyses of trials proposed to support an indication of treatment of moderate to severe vasomotor symptoms due to menopause for estrogen-containing products (estrogen-alone and estrogen plus progestogen/progestin) products. Certain recommendations from this guidance have also been extended to non-hormonal products seeking the same indication. The 2003 draft Hormone Therapy Clinical Trial Guidance recommends that to be considered efficacious in the treatment of moderate to severe vasomotor symptoms due to menopause products, clinical trial results for the evaluated product must demonstrate statistically significant improvement (reduction) from baseline in both frequency and severity of moderate to severe vasomotor symptoms (evaluated on a daily or weekly basis) relative to a comparison with placebo. Because of a realization that a statistically significant change **alone** may not reflect a clinically meaningful finding, FDA experts, in the late 1980's - early 1990's, took a look at products submitted to that time, and noted that clinical trials of postmenopausal women treated with those early products demonstrated, in addition to statistical significance, at a **minimum** (i.e., at the lowest) a relative two per day or 14 per week greater decrease in the frequency of moderate to severe vasomotor symptoms when compared to placebo. Thus, a two per day or 14 per week clinically meaningful threshold to the statistically significant improvement in frequency was proposed and adapted. This advice has also been provided to applicants since that time. The current clinical review team provided this same advice to the current applicant, Therapeutics MD, in at least one Advice Letters (See Section 2. Background in this review).

As discussed, the applicant submitted for approval, the fixed dose combination estradiol and progesterone 1 mg/100 mg (b)(4) Treatment with the 1

mg/100 mg (b) (4) demonstrated statistically significant reductions in both frequency and severity of moderate to severe vasomotor symptoms at Week 4 and Week 12 (the timepoints of assessment of the co-primary endpoints). (b) (4)

The 1 mg/100 mg dosage strength cohort met the clinically meaningful threshold at Week 5 and weekly continuing through **Week 12**. (b) (4)

. Nevertheless, the medical officer has recommended that the fixed dose combination estradiol and progesterone 1 mg/100 mg be approved because it just missed the Week 4 for efficacy criterion of the clinically meaningful threshold. On the face of it, this recommendation could be considered reasonable. However, this reviewer has concerns with this recommendation for several reasons: *1.)* At the most basic level, it is my belief that when criteria for efficacy for an indication have been discussed, and agreed-to prospectively, the Agency's evaluation should be based on those criteria. *2.)* The requested product dosage strength of the estrogen component is high (based on current standards), even for a product intended to treat moderate to severe vasomotor symptoms. Considering efficacy results from the clinical development trials of products with similar (or equivalent) dosage strengths, the expectation for the proposed fixed dose estradiol and progesterone product would be that it demonstrate a trend toward efficacy (i.e., begin to meet one or more, if not all, of the criteria) starting at Week 2 or 3 of treatment, and solidly meeting *all* criteria at **Week 4** and maintained through **Week 12**. Thus, this product would seem not to be in line with other products of similar (or equivalent) strengths. To approve this higher strength product when it did **not** meet *all* efficacy criteria, would allow drift in the expectations for approval. See entire discussion in the next paragraphs. *3.)* If approved, this product would be a "me-too" product with no relative benefit when compared to other approved products. The applicant offers that the benefit of this product accrues for women with a peanut allergy as it would be the only combination hormone therapy product with estradiol and progesterone that does not contain peanut oil (there is no previously-approved fixed-dose combination of estradiol and progesterone). While it would be true that, if approved, Bijuva would be the only combination hormone therapy product with estradiol and progesterone that does not contain peanut oil, there are alternative estrogen plus progestin products that don't contain peanut oil and are approved for the treatment of moderate to severe vasomotor symptoms, due to menopause. These products contain a progestin component.

I fully recognize that if the Division of Bone, Reproductive and Urologic Products (DBRUP) were to not approve (b) (4) the proposed fixed dose combination estradiol and progesterone capsules, the applicant, in defense of their product, would argue that the Agency has approved other products not meeting all recommended criteria at both **Weeks 4 and 12**. In this argument, the sponsor would be correct. However, acceptability of this argument, without providing the context to these approvals, as a rationale for approval would support the Agency's drifting away from, and weakening of the expected co-primary endpoint evaluation for the treatment of vasomotor symptoms, and undermine DBRUP's ability to provide

consistent recommendation to all sponsors that they should assess these co-primary endpoints to establish efficacy of their proposed products. There are five instances of products that were approved despite not fully meeting all efficacy criteria. I believe that an abbreviated review and discussion of the Agency's previous findings of safety and efficacy for these five products, as well as for product with the same (or equivalent) estrogen dosage strength, will clarify my concern for weakening the Agency criteria for approval. The five products in chronological order of approval, are discussed below.

I. *Cenestin (synthetic conjugated estrogens A*®

Cenestin (synthetic conjugated estrogens A) is an estrogen alone product. NDA 020992 for Cenestin was approved originally on March 24, 1999 for dosage strengths 0.625, 0.9 and 1.25 mg tablets. The 0.625 mg, 0.9 and 1.25 mg dosage strengths were analyzed and approved based on an unconventional trial not consistent with the 2003 draft Hormone Therapy Clinical Trial Guidance. This trial was a multicenter, randomized, placebo-controlled, dose titration, clinical trial in which 120 postmenopausal women, between 38 to 66 years of age inclusive (68% Caucasian) were randomized to receive either placebo (48 women) or 0.625 mg Cenestin (72 women) daily for 12 weeks. After seven days of treatment, if adequate clinical response was not achieved (defined as a 50% reduction in the baseline number of moderate-to severe vasomotor symptoms), the daily dose of Cenestin or placebo could be increased to two tablets of Cenestin or two tablets of placebo. No additional increase in dose was allowed during the 12-week study duration. However, at any time during the 12 weeks of treatment, the dose could be lowered to a minimum daily dose of a single 0.3 mg tablet of synthetic conjugated estrogens A, or placebo if women exhibited signs of study drug intolerance. By week 12, only 10% of the study participants remained on a single 0.625 mg Cenestin tablet daily while 77% required two (0.625 mg) tablets daily. Nevertheless, efficacy was assessed at 4 and 12 weeks of treatment. Per the labeling the combined 0.625 mg and 2 x 0.625 mg group demonstrated a statistically significant improvement (reduction) in frequency of vasomotor symptoms at Week 4 ($p=0.022$) and at Week 12 [$p=0.01$ (the labeling errantly states $p=0.1$)]. The combined 0.625 mg and 2 x 0.625 mg group met the clinically meaningful threshold of reduction of 14 per week or greater vasomotor symptoms above placebo at Week 4 (mean change for Cenestin 20 greater than placebo) and Week 12 (mean change for Cenestin 24 above placebo). It is *unclear* to this reviewer why the individual dosage strengths 0.625 mg or the 2 x 0.625, were approved based on combined data from both groups. According to the statistical review of Kate Meaker the 0.625 mg dosage cohort was *severely underpowered and demonstrated about the same treatment effect as placebo*, while the 2x 0.625 mg treatment group was also *likely underpowered but demonstrated a stronger treatment effect* compare to placebo (mean change difference of 26 above placebo at Week 4 and 28 at Week 12). Per the labeling, the 0.9 mg per day dosage strength of Cenestin was approved based on bracketing between the 0.625 mg and 2 x 0.625 mg dosage strengths. There was insufficient data submitted to assess the safety and efficacy of the 0.3 mg per day dosage strength for the treatment of moderate to severe vasomotor symptoms (MSVMS) and this dose was not recommended for approval.

A second randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of 0.45 mg Cenestin tablets, for the treatment of MSVMS in 104 menopausal women between 52 and 74 years of age (76% were Caucasian). Women were randomized to receive either placebo or 0.45 mg Cenestin daily for 12 weeks. Efficacy was assessed at 4 and 12 weeks of treatment. In ITT population analyses, the 0.45 mg dosage strength of Cenestin did **not** achieve a statistically significant improvement (reduction) in frequency of moderate to severe vasomotor symptoms at **Week 4** ($p=0.14$). However, statistically significant improvement (reduction) in frequency of moderate to severe vasomotor symptoms was met at **Week 12** ($p<0.001$) and the clinically meaning threshold of reduction of 14 per week or greater vasomotor symptoms above placebo was also met at **Week 12** (20). It is also unclear to this reviewer how the 0.45 mg dose of Cenestin was approved for the treatment of moderate to severe vasomotor symptoms based on this data. Intermediate weekly analyses were not presented or discussed in Cenestin labeling

Cenestin is no longer marketed. It is possible that lack of efficacy in marketing, may have had some role in this.

II. *femhrt*[®]

femhrt is a fixed combination estrogen (ethinyl estradiol) plus progestin (norethindrone acetate) product. NDA 021065 for *femhrt* was approved on October 15, 1999. Three dosage strengths of *femhrt* were evaluated in a standard 12-week multidose, placebo-controlled, multicenter, randomized clinical trial of 266 symptomatic women who had at least 56 moderate to severe hot flushes during the week prior to randomization. On average, patients had 12 hot flushes per day upon study entry.

(b) (4) *femhrt* (ethinyl estradiol and norethindrone acetate), 5 mcg/1 mg and 2.5 mcg/0.5 mg) were approved, based on the medical officer's determination (b) (4)

this information was not included in labeling. In the ANCOVA with LOCF analyses, the *femhrt* 5 mcg/1 mg treatment group was statistically significantly better compared to placebo in reduction of frequency and severity of vasomotor symptoms at both **Weeks 4 and Week 12**. The mean reduction from baseline in frequency of vasomotor symptoms for 5 mcg/1 mg was approximate 13 hot flushes greater than placebo at **Weeks 4 and 12** (note that this is not least square mean change). Data not shown in the labeling (b) (4)

The 2.5 mcg/0.5 mg treatment group was statistically significantly better compared to placebo in reduction of frequency at both **Weeks 4 and Week 12**. The mean reduction from baseline in frequency of vasomotor symptoms for *femhrt* 2.5 mcg/0.5 mg was approximate 10 hot flushes greater than placebo at **Week 4**, and 18 hot flushes greater than placebo at **Week 12** (again note that this is not least square mean change). With the 2.5 mcg/0.5 mg treatment group (the lowest dosage strength), a statistically significant reduction in severity did not occur until Week 5.

III. Femtrace®

Femtrace is an estrogen alone (estradiol acetate) product. NDA 021633 for Femtrace was originally approved on August 20, 2004 for dosage strengths 0.45, 0.9 and (b) (4) mg tablets. The trial conducted for the approval of Femtrace was a standard hormone therapy for vasomotor symptom trial conducted according to the 2003 draft Hormone Therapy Clinical Trial Guidance. In the ITT population analyses with last observation carried forward (LOCF) both of the higher dosage strengths 0.9 mg and (b) (4) mg met statistically significant improvement (reduction) in frequency of vasomotor symptoms ($p < 0.001$ for both doses) at **Weeks 4 and 12**, and the clinically meaning threshold of reduction of 14 per week or greater vasomotor symptoms above placebo at **Week 4** (16 and 19 for the 0.9 mg and (b) (4) mg dosage strengths, respectively) and **Week 12** (28 and 39 for the 0.9 mg and (b) (4) mg dosage strengths respectively). Likewise, the higher strengths both met statistically significant improvement in severity of vasomotor symptoms at **Week 4** ($p = 0.001$ and $p = 0.002$ for the 0.9 mg and (b) (4) mg dosage strengths, respectively) and **Week 12** ($p < 0.001$ for both doses).

In a modified ITT population analysis with LOCF the lower dosage strength of Femtrace, 0.45mg, met statistically significant improvement (reduction) in frequency of vasomotor symptoms at **Week 4** ($p = 0.014$) and **Week 12** ($p = 0.005$). However, the 0.45 mg lower dosage strength did **not** meet the clinically meaning threshold of reduction of 14 per week or greater vasomotor symptoms above placebo at **Week 4** (the 0.45 mg dose reduction from baseline in weekly frequency of vasomotor symptoms was approximately 7 greater than that of placebo) or **Week 12** (the 0.45 mg dose reduction from baseline in weekly frequency of vasomotor symptoms was approximately 10 greater than that of placebo). The 0.45 mg lower dosage strength also did not meet statistically significant improvement in severity of vasomotor symptoms at **Week 4** ($p = 0.787$) but did meet this criteria at Week 7 (data not shown in labeling) and **Week 12** ($p = 0.016$).

IV. Elestrin

Elestrin is an estrogen- alone (estradiol) topically-applied product, delivered via a pump. NDA 021813 was approved on December 15, 2006 for two dosage strengths, an 0.87 g dose, providing systemic delivery of 0.0125 mg of estradiol daily, and a 1.7 g dose, two pump actuations of which provides systemic delivery of 0.0375 mg daily. A randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy of 12-week treatment with three different daily doses of Elestrin for the treatment of vasomotor symptoms in 484 postmenopausal who had at least 60 moderate-to-severe hot flushes per week at baseline. Women applied placebo, Elestrin 0.87 g (0.52 mg estradiol), 1.7 g (1.02 mg estradiol), or 2.6 g (1.56 mg estradiol) once daily to the upper arm. Reduction in both the frequency and severity of moderate-to-severe hot flushes was statistically significant for the Elestrin 1.7 g per day dose compared to placebo at **Week 4**. Statistically significant reductions in both the frequency and severity of moderate-to-severe hot flushes when compared to placebo were delayed for the Elestrin 0.87 g/day dose to Week 5; the clinically meaningful threshold of 2 hot flush per day greater improvement with Elestrin compared to placebo was met at that time

point. Both the 0.87 g per day and 1.7 g per day doses were statistically significantly improved in frequency and severity compared to placebo at **Week 12**.

V. Divigel

Divigel is an estrogen- alone (estradiol) topically-applied product. NDA 022038 for Divigel was approved on June 4, 2007 for three dosage strengths, 0.25 grams per day, 0.5 grams per day and 1 gram per day. A randomized, double-blind, placebo-controlled trial evaluated the efficacy of 12-week treatment with three different daily doses of Divigel® for vasomotor symptoms in 495 postmenopausal women who had at least 50 moderate to severe hot flushes per week at baseline (in the two-week period prior to treatment). Subjects applied placebo, Divigel® 0.25 g (0.25 mg estradiol), Divigel® 0.5 g (0.5 mg estradiol), or Divigel® 1.0 g (1.0 mg estradiol) once daily to the thigh. Reductions in **both** the median daily frequency and the median daily severity of moderate to severe hot flushes were statistically significant for the 0.5 g per day and the 1.0 g per day Divigel® doses when compared to placebo at **Week 4**. The statistically significant reduction in vasomotor symptoms frequency from baseline for both dosage strengths met the clinically significant threshold of a 2 hot flush per day greater improvement with Divigel compared to placebo. Statistically significant reductions in both the median daily frequency and the median daily severity of moderate to severe hot flushes for the Divigel® 0.25 g per day dose when compared to placebo were delayed to week 7; at this timepoint a clinically significant threshold of a 2 hot flush per day greater improvement with Divigel compared to placebo, was met. There were statistically significant reductions in median daily frequency and severity of hot flushes for all three Divigel® doses (0.25 g per day, 0.5 g per day and 1.0 g per day) compared to placebo at **Week 12**.

This reviewer performed the Cross Disciplinary Team Leader review of two of the above products, Elestrin and Divigel. I was not involved in the review of the remaining three products. Therefore, I don't have firsthand knowledge of the thought on approval of these product. However, I note based on labeling, that the clinical trials submitted to support these product approvals were multiple dose efficacy trials. With the exception of Cenestin, it is evident from the review of the labeling for the other four products, that while the lower dosage strengths demonstrated inconsistent effectiveness at the earlier timepoint (**Week 4**), these lower strength dosages were associated with higher dosage strengths of the same product, which demonstrated efficacy with respect to each of the recommended four co-primary efficacy endpoints. Estrogen-alone and estrogen plus progestogen products have been typically approved in multiple dosage strengths allowing for up-titration or down-titration to control the frequency and severity of a postmenopausal woman's vasomotor symptoms at different phases of her menopause. Class labeling of estrogen plus progestin products and estrogen-only product states, "Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman." At least with Elestrin and Divigel, beyond the precedent, the thought in approving the lower dosage strengths that did not meet all efficacy requirements, was that these lower dosage strengths would be available for women who initially responded to a higher dosage strength, and whose improvement in vasomotor

symptoms was such that their dosage could be titrated down to a lower dosage, while still maintaining relief.

By today's standards for the treatment of moderate to severe vasomotor symptoms, the proposed fixed dose combination product of 1 mg E2 and 100 mg P4 would be considered at the higher range for estrogen dosing. 1 mg of E2 is considered to be dose equivalent to 0.625 mg of conjugated estrogen or esterified estrogens, 0.9 mg estradiol acetate or 0.01 to 0.015 mg of ethinyl estradiol. While the proposed and Medical Officer-recommended fixed dosage strength combination product Bijuva (estradiol and progesterone) 1 mg/ 100 mg was evaluated in a multidose trial, it was the highest dosage strength evaluated. Consider that in comparison, in the Health and Osteoporosis, Progestin and Estrogen (HOPE) clinical trial of Premarin (conjugated estrogen) 0.3mg, 0.45 mg and 0.625 mg dosage strengths and the fixed dose combination product Prempro (conjugated estrogen and medroxyprogesterone acetate) 0.3 mg/1.5 mg, 0.45 mg/1.5 mg, and 0.625 mg /2.5 mg, each evaluated dose of Premarin and each evaluated dose of Prempro demonstrated statistically significant improvement (reduction) from baseline in frequency **and** severity of moderate to severe vasomotor symptoms at **Week 4 and Week 12 and** met clinically meaning threshold of a 2 hot flush per day greater improvement in vasomotor symptom frequency compared to placebo.. The same stark contrast is noted for the efficacy result demonstration for Activella (NDA 020907, approved November 18, 1998), a fixed single dose combination of estradiol and norethindrone acetate, 1 mg/0.5 mg. In the phase 3 clinical trial submitted for approval of Activella demonstrated a statistically significant improvement (reduction) from baseline in frequency **and** severity of moderate to severe vasomotor symptoms at **Week 4 and Week 12 and** met clinically meaning threshold of a 14 hot flush per week greater improvement in vasomotor symptom frequency compared to placebo), compared to the efficacy results seen in the current review cycle for proposed fixed dosage strength combination product Bijuva (estradiol and progesterone) 1 mg/ 100 mg. The dosage strength of the estrogen component in Premarin, Prempro, and Activella is equivalent or lower than that of the proposed and recommended dosage strength of Bijuva.

Finally, I am concerned that this higher dosed estradiol containing product which failed to meet efficacy co-primary endpoint criteria recommendations for statistically significant improvement in **both** frequency (with a requirement that a clinically meaningful threshold be met along with statistical significance in frequency) **and** severity at **Weeks 4 and Weeks 12** (specifically the clinically meaningful threshold was missed), also appeared to **not** meet any frequency, or meet severity criteria until **Week 12** (at which only the one co-primary of severity was met) in women who self-identified as Black/African American. In this reviewer's opinion this fact diminishes further, the acceptability of the efficacy of the product.

My conclusion is that TherapeuticsMD's higher estrogen dosage strength fixed dose combination of Bijuva (estradiol and progesterone) capsules, 1 mg /100 mg, does not offer efficacy benefit or benefit overall for any patient group above that of existing products (See **Section 8. Safety** of this review). For this and the three reasons outlined above, I recommend that this dosage strength (b) (4) of Bijuva, **not** be approved

I realize that my recommendation, if upheld would likely lead to a sponsor appeal. Therefore, ahead of the completion of my review, I discussed this with the signatory for this application,

Dr. Christine Nguyen who indicated in informal Email communications that she would recommend approval of the combined 1 mg estradiol and 100 mg progesterone dosage strength based on: “Although clinically meaningful reduction in frequency did not occur until Week 5 (instead of the usual Week 4), I consider this delay acceptable for the trade-off that this is the first combined product of estradiol + progesterone and that it could be used by women with peanut allergy who would like to use a progesterone instead of a progestin. In addition, we have approved dosage strengths that did not meet the clinical meaningful threshold until Week 5 or Week 7”. As outlined above, I likewise disagree with this decision.

8. Safety

The primary review of the safety information in NDA 208564 was performed by Dr. Theresa van der Vlugt.

Overall safety assessments included: Adverse Events [(AEs), including serious adverse events (SAEs)], bleeding/spotting diary, clinical laboratory testing (including hormone levels), concomitant and prior medication use history, findings from a general physical examination, general medical and gynecological history, gynecological examination (including pelvic physical examination, Pap smear, and breast physical examination), histology from endometrial biopsy, pregnancy test, vital signs, and 12-lead ECG.

The disposition of women participating in the entire 52 weeks of Trial TXC12-05 (Safety Population) is provided in Table 11.

Table 11: Disposition of Enrolled Postmenopausal Women for the Entire 52-Week Trial TXC12-05 (Safety Population)

	1 mg E2/ 100 mg P4 (N=415)	0.5mg E2/ 100 mg P4 (N=424)	0.5 mg E2/ 50 mg P4 (N=421)	0.25 mg E2/ 50 mg P4 (N=424)	Placebo (N=151)	Total (N=1835)
Number of subjects completed, n (%)	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)
Investigator/Sponsor Decision	1 (0.2)	3 (0.7)	2 (0.5)	2 (0.5)	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	5 (0.3)

Source: Adapted from Statistical Review Table 2, page 10, Medical Officer Review Table 14, page 45 and NDA 210130, Clinical Trial Report for Trial TXC12-05, Table 10 page 73

The discrepancy between the 0.5 mg/ 100 mg dosage strength cohort and the other dosage strength cohorts seen in the disposition of women in the 12-week vasomotor symptom sub-trial portion of Trial TXC12-05, is not seen in the disposition of women in the entire trial. Discontinuation rates were approximately 30% in each dosage strength cohort. Discontinuations due to adverse events were similar with a range of 8 to 11%.

There was one death in a participating woman in Trial TXC12-05, from metastatic non-small cell lung cancer occurring on what would have been her trial Day 116. The participant had been discontinued from the trial on Day 65 following a hospitalization for a 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). The death was considered by the investigator as a severe event, unrelated to trial medication.

A total of 46 women experienced 57 SAEs that occurred on/after the first dose of trial medication. In the per dosage strength cohort consideration, women with at least one SAE numbered (%): 9 (2.2%) in the 1 mg/100 mg; 15 (3.5%) in the 0.5 mg/100mg; 9 (2.1%) in the 0.5 mg/ 50 mg, and 11(2.6%) in the 0.25 mg/50 mg dosage strength cohorts, and 2 (1.3%) in the placebo cohort. The reader is referred to Dr. van der Vlugt's review for a summary of SAEs (occurring on or after the first dose of trial medication) for the Safety population overall, by system organ class (SOC) and preferred term PT for each dosage strength, and placebo cohorts.

As shown in Table 11, 164 (8.9%) of Trial TXC12-05 Safety participants, experienced an adverse event (AE) on/after the first dose of study drug that was the primary reason for withdrawal from the trial. The reader is referred to Dr. van der Vlugt's review for a summary of AEs leading to discontinuation from Trial TXC12-05.

Significant adverse events of interest per the applicant included:

- *Four applicant-identified life-threatening events* [two (neoplasms benign, malignant and unspecified (including cysts and polyps) in the 0.5 mg/ 100 mg dosage strength cohort, one (cardiac disorder) in the 0.5 mg /50 mg dosage strength cohort and one (gastrointestinal disorder) in the 0.25 mg /50 mg dosage strength cohort]
- *One deep venous thrombosis* (occurring in the 0.5 mg/50 mg dosage strength cohort); *three cardiac events of interest* (one diagnosis of coronary artery disease requiring two vessel coronary artery bypass grafting in the 1 mg/100mg dosage strength cohort, one diagnosis of stress cardiomyopathy in the 0.5 mg /100 mg dosage strength cohort and one diagnosis of ruptured basilar tip aneurism with transcatheter coil embolization in the 0.5 mg/50 mg dosage strength cohort)
- *Two cerebrovascular adverse events of interest* (same participant with ruptured basilar tip aneurism in the 0.5 mg/50 mg dosage strength cohort and one diagnosis of metastatic lung cancer to the brain also in the 0.5 mg/50 mg dosage strength cohort)

- *Ten syncopal events* (two women in the 1 mg /100 mg dosage strength cohort, four women in the 0.5 mg /100 mg dosage strength cohort, one woman in the 0.5 mg /50 mg dosage strength cohort, and two women in the 0.25 mg /50 mg dosage strength cohort) *and*
- *Six applicant-identified Breast Cancer adverse events of interest* [two women in the 1mg/100 mg dosage strength cohort (one case of intermediate grade infiltrating ductal carcinoma of 0.5 cm size with a benign core needle biopsy of the right axillary lymph node and undergoing 1a breast needle localization lumpectomy with sentinel node biopsy and adjuvant chemotherapy with radiation therapy administered post-chemotherapy, and one case of invasive ductal adenocarcinoma; sentinel and regional lymph nodes negative for metastasis with brachytherapy via SAVI device), two women in 50 mg/100 mg dosage strength cohort (one case of invasive carcinoma of the left breast and one case of invasive ductal carcinoma, micropapillary type, Nottingham Combined Histological Grade 2-3 of 3 with focal associated ductal carcinoma in situ, solid type, intermediate grade), one woman in the 0.5 mg/50 mg dosage strength cohort [a case of invasive ductal carcinoma, grade 2/3, estrogen and progesterone receptor positive and HER2/ negative. She underwent a complete surgical lumpectomy and sentential node biopsy (negative for metastatic disease) with SAVI radiation treatment and aromatase inhibitor therapy] and one woman in the 0.25 mg/ 50 mg dosage strength cohort (invasive ductal carcinoma Nottingham grade 1, estrogen and progesterone receptor positive, and BRACA gene testing with nonclinical significant gene mutation. She underwent a total bilateral mastectomy, left sentinel node biopsy. Histology of the left breast confirmed invasive carcinoma with ductal and lobular features (mixed type carcinoma) with ductal carcinoma in situ and negative sentinel node. The reader is referred to Dr. van der Vlugt's review for details on each of these significant adverse events of interest. There did not appear to be an increase incidence of any severe adverse event to call into question the safety of this product.

Overall, the most common TEAEs ($\geq 3\%$) across all active treatment groups in Trial TXC12-05 was 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%).

The primary safety endpoint was the incidence of endometrial hyperplasia at 12 months. The applicant did not follow the 2003 draft Clinical Trial for Hormone Therapy Guidance and Agency recommendations that all endometrial histology slides be concurrent read 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 applicant did not follow 2003 draft Clinical Trial for Hormone Therapy Guidance recommendations 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. The applicant also did not consider endometrial cancer in an evaluation of the rate of endometrial hyperplasia or cancer. Participating women who had an endometrial malignancy were not included in the numerator

or denominator of the incidence calculation. The reader is referred to Dr. van der Vlugt’s review for details on the applicant’s assessment of endometrial hyperplasia. Per the applicant, no case of endometrial hyperplasia was diagnosed in 52-week, phase 3, Trial TXC12-05. The applicant’s results are presented in Table 12.

Table 12: Incidence of Endometrial Hyperplasia in 52-Weeks Trial TXC12-05 (ES Population)

Dosage Strength Cohort	1 mg E2/ 100 mg P4 (N=280)	0.5 mg E2/ 100 mg P4 (N=303)	0.5 mg E2/ 50 mg P4 (N=306)	0.25 mg E2/ 50 mg P4 (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%

Abbreviations: E2 = estradiol; P4= progesterone; CI = confidence interval.

Source: Medical Officer Table 43, Adapted from NDA 210132, Trial TXC12-05 Clinical Study Report, Table 38, Page 121

Using analyses of endometrial hyperplasia and cancer from the endometrial histology diagnoses of the three individual pathologists, based on Blaustein’s pathology text (Pathology of the Female Genital Tract), per the 2003 draft Clinical Trial for Hormone Therapy Guidance recommendations, the medical officer re-adjudicated cases of endometrial hyperplasia as follows:

- Two cases - one case each of simple hyperplasia without atypia; endometrial polyp not present in the 1mg/ 100 mg dosage strength cohort (Participant Number (b) (6)) and in the 0.5 mg/ 100 mg dosage strength cohort (Participant Number (b) (6))
 - Participant Number (b) (6)
 - Diagnosis per pathologist:
 - ✓ 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
 - Re-adjudication per the recommendation of the 2003 draft Clinical Trial for Hormone Therapy Guidance. Because there was no agreement on the histologic diagnosis between the three pathologists, the final diagnoses would be the most severe: Simple hyperplasia without atypia; endometrial polyp not present.
 - Participant Number (b) (6)
 - Diagnosis per pathologist:
 - ✓ 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

in that the data provided in NDA 210132 demonstrated that the role for the progesterone component was the protection of the endometrium from estradiol-induced increased risk for hyperplasia/cancer; thus, satisfying the fixed dose combination drug product rule, 21 CFR § 300.50.

Overall, there are no unexpected safety signals that were revealed in the Bijuva (estradiol and progesterone) capsules clinical development program.

The applicant offers that an additional benefit of this product accrues for women with peanut allergies, as this combination hormone therapy product with estradiol and progesterone does not contain peanut oil. There are other oral and non-oral fixed dose combination estrogen plus progestin products that do not contain peanut oil and are approved for the treatment of moderate to severe vasomotor symptoms, due to menopause. These products contain the synthetic progestins, drospirone, levonorgestrel, medroxyprogesterone acetate, and norethindrone acetate. The Women's Health Initiative Estrogen plus Progestin substudy, after a mean follow-up of 5.6 years, reported use of an estrogen plus progestin (conjugated estrogen and medroxyprogesterone acetate), increased the risk of invasive breast cancer. There is some suggestion from the professional/scientific community that progesterone may offer a benefit over synthetic progestins with respect to this risk. To this reviewer's knowledge there have not been results from head-to-head, well-designed and controlled clinical trial to support this position.

9. Advisory Committee Meeting

Advice of the Reproductive Health Advisory Committee was not sought during the period of consideration and recommendation for this product. The primary review concern was efficacy of the product based on the pre-specified endpoints. As there was internal disagreement as to whether approval could be recommended despite this fact, the Clinical Team did not think that presentation to and Advisory Committee input, would be helpful.

10. Pediatrics

A full pediatric waiver for ages 0 to 18 was requested by TherapeuticsMD with the rationale that the condition (b) (4)

(b) (4) does not apply to children. DBRUP concurs with the Applicant's assessment that the product would not be indicated in children. TherapeuticsMD's request for a full pediatric waiver for NDA 210132 for Bijuva (estradiol and progesterone) capsules, with an approved iPSP, was discussed at the September 5, 2018 meeting of the Pediatric Review Committee (PeRC). The committee determined that Bijuva would be granted a full waiver based on the fact that vasomotor symptoms, due to menopause is a condition that qualifies for waiver because studies would be impossible or highly impractical, as agreed-to in the iPSP. DBRUP concurs that a full pediatric waiver be granted from the study requirements of PREA.

11. Other Relevant Regulatory Issues

Clearance by 505(b)(2) Committee

NDA 201132 was discussed at the September 24, 2018 505(b)(2) clearance meeting. The application was cleared for action from a 505(b)(2) perspective.

Good Clinical Practices and Office of Scientific Investigations (OSI) Findings

To ensure compliance with Good Clinical Practice (GCP), TherapeuticsMD undertook a 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 the NDA submission for the following site audits:



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

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:

- 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 7th Avenue, Crystal River, FL 34429.
- 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.
- 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

On August 23, 2018, OSI/DCCE provided an evaluation of the clinical inspection as follows for Site # 127 (Scott Redrick, MD), Site # 105 (Arthur S. Waldbaum, MD), and Site # 142 (Sandra M. Hurtado, MD):

- Site # 127 (Scott Redrick, MD): Inspection was conducted between March 20 through March 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 # 105 (Arthur S. Waldbaum, MD): Inspection was conducted between March 26 through March 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. Dr. van der Vlugt determined that two protocol deviations are unlikely to have an impact on the efficacy or safety results of Trial TXC12-05.
- Site # 142 (Sandra M. Hurtado, MD): Inspection was conducted between April 24 through April 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.

All three sites received a No Action Indicated (NAI) classification.

Dr. van der Vlugt and I concur with OSI's recommendations and general conclusions that the quality of the data generated in the NDA appear acceptable for evaluation.

Financial Disclosure

On August 10, 2017, Dan Cartwright, Chief Financial Officer, signed Form FDA 3455 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).

One sub-investigator, (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 (U.S. currency) 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.

Per Dr. Cartwright, the circumstances which prevent potential bias are as follows:

- (b) (6) was a sub-investigator 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) was provided in the application submission.

Dr. van der Vlugt 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 TXV12-05). I concur with Dr. van der Vlugt's conclusion with respect to financial disclosure.

Tradenname Review

On January 31, 2018, TherapeuticsMD requested review of the proprietary name, Bijuva. On April 30, 2018, Division of Medication Error Prevention and Analysis (DMEPA) completed their review and concluded that the name Bijuva was conditionally approved.

12. Labeling

DBRUP sent labeling recommendations to the applicant on September 27, and October 23, 2018. Following these rounds of a labeling negotiations, an agreed-to labeling was received on October 24, 2018.

Prescribing Information:

The product will receive Noncontraceptive Estrogen and Progestin Class Labelling.

Section 14.1 Effects on Vasomotor Symptoms will also include findings in women who self-identified as Black/ African American

Other Labeling:

Division of Medication Error Prevention and Analysis (DMEPA)

Refer to DMEPA reviews archived August 6, 2018 and October 15, 2018 for labeling recommendations. All DMEPA recommendations were relayed to the applicant and DMEPA agreed to final labeling.

The Office of Prescription Drug Promotion (OPDP)

Refer to OPDP reviews, both archived on October 9, 2018 for labeling comments. All OPDP recommendations were relayed to the applicant and OPDP agreed to final labeling

Office of Medical Policy/Division of Medical Policy Programs (DMPP)

DMPP and DBRUP comments were included in labeling revisions provided to the applicant on September 27, 2018 and October 23, 2018 and included in final agreed-to labeling received October 24, 2018.

13. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

This reviewer recommends that should [REDACTED] ^{(b) (4)} Bijuva (estradiol and progesterone) capsule be approved, a post marketing commitment be included in the decisional letter to [REDACTED] ^{(b) (4)}

14. Recommended Comments to the Applicant

I do not recommend [REDACTED] (b) (4)
[REDACTED] Bijuva (estradiol and progesterone) 1mg/100 mg as requested by the applicant. My rationale for this recommendation is presented in **Section 7. Efficacy** of this review.

DRAFT

Appendix I – Approved Hormone Therapy Products for Vasomotor Symptoms

The following Table 13 presents the estrogen-alone products approved for the treatment of moderate-to-severe vasomotor symptoms.

Table 13: Estrogen-Alone Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Estrogen-Alone Products	Dosage Strengths
<ul style="list-style-type: none"> • Cenestin® (synthetic conjugated estrogens, A)* 	<ul style="list-style-type: none"> • 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
<ul style="list-style-type: none"> • Enjuvia® (synthetic conjugated estrogens, B)* 	<ul style="list-style-type: none"> • 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
<ul style="list-style-type: none"> • Menest® (esterified estrogens) 	<ul style="list-style-type: none"> • 0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
<ul style="list-style-type: none"> • Ogen® (estropipate) 	<ul style="list-style-type: none"> • 0.625 mg, 1.25 mg, or 2.5 mg once daily
<ul style="list-style-type: none"> • Femtrace® (estradiol acetate tablets) * 	<ul style="list-style-type: none"> • 0.45 mg, 0.9 mg, 1.8 mg once daily
<ul style="list-style-type: none"> • Premarin® (conjugated estrogens) Tablets 	<ul style="list-style-type: none"> • 0.3 mg, 0.45 mg, 0.625 mg, 0.9 m, or 1.25 mg once daily
<ul style="list-style-type: none"> • Various Generics (estradiol) Tablets 	<ul style="list-style-type: none"> • 0.5 mg, 1.0 mg, 2.0 mg
Transdermal Products	Available Dosage Strengths
<ul style="list-style-type: none"> • Alora® (estradiol matrix transdermal system) 	<ul style="list-style-type: none"> • 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
<ul style="list-style-type: none"> • Climara® (estradiol matrix transdermal system) 	<ul style="list-style-type: none"> • 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied once weekly
<ul style="list-style-type: none"> • Estraderm® (estradiol reservoir transdermal system) 	<ul style="list-style-type: none"> • 0.05 mg or 0.1 mg; patch applied twice weekly
<ul style="list-style-type: none"> • Vivelle® (estradiol transdermal system, extended release) 	<ul style="list-style-type: none"> • 0.05 mg, 0.1 mg; patch applied twice weekly
<ul style="list-style-type: none"> • VivelleDot® (estradiol matrix transdermal system) 	<ul style="list-style-type: none"> • 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
<ul style="list-style-type: none"> • Minivelle® (estradiol matrix transdermal system) 	<ul style="list-style-type: none"> • 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
<ul style="list-style-type: none"> • Esclim® (estradiol transdermal system)* 	<ul style="list-style-type: none"> • 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
<ul style="list-style-type: none"> • Various Generics (estradiol matrix transdermal system) 	<ul style="list-style-type: none"> • 0.05 mg or 0.1 mg; patch applied once or twice weekly

*Discontinued

Appears this way on original

DRAFT

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.

/s/

SHELLEY R SLAUGHTER
10/28/2018