CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210132Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Christine P. Nguyen
Subject	Division Deputy Director for Safety Summary Review
NDA/BLA # and Supplement #	210132
Applicant	TherapeuticsMD
Date of Submission	December 28, 2017
PDUFA Goal Date	October 28, 2018
Proprietary Name	Bijuva
Established or Proper Name	Estradiol and progesterone
Dosage Form(s)	Oral capsule (1 mg estradiol and 100 mg progesterone; (b) (4))
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe vasomotor symptoms due to menopause in women with an intact uterus
Action or Recommended Action:	*Approval of the 1 mg estradiol and 100 mg progesterone dosage strength*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Theresa Van Der Vlugt
Statistical Review	Jia Guo, Mahboob Sobhan
Pharmacology Toxicology Review	Frederic Moulin, Kimberly Hatfield
OPQ Review	Soumya Mitra, Zhengfang Ge, Jingbo Xiao, Denise Miller, Sandra Suarez, Thao Vu, Florence Aisida, Mark Seggel
Clinical Pharmacology Review	Peng Zou, Doan (Donny) Tran
OPDP	Lynn Panholzer, Matthew Falter
DMPP	Kelly Jackson, Lynn Panholzer, LaShawn Griffiths, Sharon Wiliams
OSI	Cheryl Grandinetti
CDTL Review	Shelley S. Slaughter
OSE/DMEPA	Denise Baugh, Celeste Karpow, Lolita White
Project Management	Kimberly Shiley, Margaret Kober

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Benefit-Risk Integrated Assessment

The Cross-Discipline Team Leader (CDTL) (Dr. Shelley Slaughter) and I differ in the final recommended regulatory action for this NDA. I recommend approval of the higher dosage strength of 1 mg estradiol/100 mg micronized progesterone (approved tradename Bijuva), whereas Dr. Slaughter does not recommend approval of any dosage strength. This memo focuses on the efficacy findings, which are the basis of the differences in opinion.

Moderate to severe vasomotor symptoms (VMS) due to menopause can significantly reduce a woman's quality of life and interferes with her daily activities. Currently, estrogen-containing treatment is considered the most effective treatment for VMS. In women with a uterus, a progestogen, either synthetic (progestin) or progesterone, is added to the treatment regimen to protect the endometrium from the proliferative effects of estrogen. The Applicant sought approval (b) (4) of TX-001HR, formulated as a fixed dose combination of estradiol (E2) and micronized progesterone (P), for the treatment of moderate to severe VMS in women with a uterus. The (b) (4) dosage strength contains 1 mg E2/100 mg P (b) (4) . TX-001HR is the first combined estrogen/progestogen product that contains progesterone instead of a progestin. Unlike the approved micronized progesterone monotherapy, TX-001HR does not contain peanut oil, and is appropriate for women with peanut allergy who choose progesterone for endometrial protection.

A single randomized, double-blind, placebo-controlled safety and efficacy trial demonstrated that TX-001HR 1 mg E2/100 mg P oral capsule, hereafter referred to as its approved tradename Bijuva, is safe and effective for its intended use. In the 12-week efficacy phase of the trial, compared to placebo, Bijuva resulted in statistical significant reduction in the frequency and severity of VMS at Weeks 4 and 12, and clinically meaningful reduction of the frequency of VMS (reduction of at least 14 moderate to severe VMS episodes per week above placebo) starting at Week 5 that is maintained through Week 12. Although the standard threshold of "success" is achievement of clinically meaningful reduction in VMS frequency by Week 4, a slight delay to Week 5 is acceptable, given Bijuva's formulation of containing progesterone that could be used by women with peanut allergy. (b) (4) Subgroup analysis by race suggested lack of improvement in VMS frequency at Weeks 4 and 12 and severity at Week 4, but statistically significant improvement in severity was seen at Week 12, in self-identified Black/African American women. Findings from a subgroup analysis from a single trial, however, do not confirm the lack of efficacy in these women. I recommend approval of Bijuva, regardless of race, with labeling reflecting the race subgroup analysis.

The safety findings of Bijuva are consistent with the known safety profile of the drug class. The upper bound of a single-sided 95% confidence interval rate of endometrial hyperplasia with Bijuva (2%) was within the acceptable range (upper limit of < 4%) for a hormone therapy (HT) product.

1. Background

TherapeuticsMD, Inc. submitted this 505(b)(2) new drug application (NDA) for a fixed dose combination of estradiol and progesterone oral capsule (referred to as TX-001HR) for treatment of moderate and severe VMS symptoms due to menopause in a woman with a uterus. The Applicant seeks marketingapproval of the dosage strength of TX-001HR 1 mg estradiol/100 mg progesterone (b) (4).

Pharmacologic treatment options for moderate to severe VMS in women with a uterus include combined hormone therapy (HT) of estrogen plus progestogen (for endometrial protection from the proliferative effect of estrogen). As shown in Table 1, all currently approved combined HTs contain a progestin as the progestogen component.

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

Oral Estrogen Plus Progestin Products	Available Dosage Strengths
Activella® (estradiol [E2] plus norethindrone acetate [NETA])	0.5 mg E2 plus 0.1 mg NETA taken daily or 1 mg E2 plus 0.5 mg NETA taken daily
Angeliq® (drospirenone [DRSP] plus E2	0.25 mg DRSP plus 0.5 mg E2 or 0.5 mg DRSP plus 1 mg E2 taken daily
femhrt® (NETA plus ethinyl estradiol [EE])	0.5 mg NETA plus 2.5 mg EE taken daily
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE taken daily for 14 days, then 0.625 mg CE plus 0.5 mg MPA taken daily for days 15-28
Prempro® (CE plus MPA)	0.3 mg or 0.45 mg CE plus 1.5 mg MPA taken daily or 0.625 mg CE plus 2.5 mg or 5.0 mg MPS taken daily
Transdermal Estrogen Plus Progestin Products	Available Dosage Strengths
ClimaraPro® (E2 plus levonorgestrel)	0.045 mg E2 plus 0.015 mg levonorgestrel; patch applied weekly
CombiPatch® (E2 plus NETA)	Release of 0.05 mg E2 plus 0.14 mg NETA; patch applied twice weekly or 0.05 mg E2 plus 0.25 mg NETA; patch applied twice weekly

Source: Medical Officer Review (October 26, 2018), Table 1

Micronized progesterone (100, 200 mg) is approved under the tradename Prometrium as monotherapy for endometrial protection in women with a uterus using estrogen-only treatment. This product contains peanut oil and is contraindicated in women with peanut allergy.

The Applicant has developed TX-001HR as the first combined HT that contains micronized progesterone as the progestogen component and the product is peanut-free.

2. Product Quality

Recommends approval from a product quality perspective (see consolidated ONDQA Review by Dr. Mark Seggel, dated October 24, 2018). The team recommends a postmarketing commitment of in vitro studies to establish the appropriate dissolution method (s) and acceptance criteria. This will be conveyed in the approval letter.

Director's comment: I concur with ONDQA's recommendation of approval.

3. Nonclinical Pharmacology/Toxicology

Recommends approval from a pharmacology/toxicology perspective (see Pharmacology Toxicology review by Dr. Frederic Moulin, dated September 10, 2018).

The Applicant relied on the well-established safety of estradiol and progesterone. Select literature publications on estradiol and the Agency's previous finding of preclinical safety for Prometrium (progesterone, USP) support the nonclinical section of the NDA. The Applicant did not, and was not required to, conduct nonclinical studies for TX-001HR.

Director's comment: I concur with the pharmacology/toxicology team's recommendation of approval.

4. Clinical Pharmacology

Recommends the approval of the 1 mg/100 mg dosage strength from a clinical pharmacology perspective (see Clinical Pharmacology review by Dr. Peng Zou, dated September 7, 2018). Pertinent clinical pharmacology conclusions include:

- (b) (4) not appropriate for self-identified Black/African American women. Pharmacokinetics (PK)-based dose adjustment is not expected address the efficacy issue this population.
- Per the Biopharmaceutical reviewer, the to-be-marketed formulation (Catalent 1 mg E2/100 mg P) is adequately bridged to the Phase 3 trial formulation [(b) (4) 1 mg E2/100 mg P] using in vitro dissolution data and CMC data. No BE study was required.
- There has been adequate bridging between TX-001HR 1 mg estradiol/100 mg micronized progesterone and the safety findings of Prometrium (micronized progesterone) 200 mg.

Director's comment: I concur with the clinical pharmacology team's recommendation of approval of the 1 mg estradiol/100 mg progesterone dosage strength. Refer to Section 6 for my discussion on the race subgroup analysis.

5. Clinical Microbiology

Recommends approval from a microbiology perspective (ONDQA's consolidated review dated October 24, 2018).

Director's comment: I concur with the clinical microbiology's team recommendation of approval.

6. Clinical/Statistical-Efficacy

The clinical reviewer and statistical team recommend approval of the 1 mg/100 mg dosage strength (see Clinical Review by Dr. Theresa van der Vlugt, dated October 26, 2018, and the Statistical Review by Dr. Jia Guo, dated October 16, 2018). The CDTL does not recommend approval of any dosage strength based on deficiencies in efficacy (see CDTL summary review by Dr. Shelley Slaughter, dated October 28, 2018). My discussion focuses on the efficacy findings of interest: (1) the delay in time of onset of clinically meaningful reduction in VMS frequency and (2) subgroup analysis by race.

The Applicant conducted a single randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of TX-001HR in postmenopausal women between 40 and 65 years old with an intact uterus experiencing moderate to severe VMS associated with menopause (Study TXC12-05). (b) (4) The Division has generally accepted data from a single adequate and well-controlled clinical trial as potentially adequate to support the safety and effectiveness of an estrogen/progestin drug product for the indication of treatment of moderate to severe vasomotor symptoms.

Study TXC12-05 enrolled a total of 1845 patients. Seven hundred fifty six (756) patients who experienced a minimum daily frequency of ≥ 7 (or ≥ 50 per week) moderate to severe hot flushes participated in the VMS efficacy substudy during the first 12 weeks of treatment, and then continued participation on the same treatment for an additional nine months for endometrial safety evaluation. Patients in the VMS efficacy substudy were randomized in a 1:1:1:1:1 allocation ratio to one of the following:

- Treatment 1: Combined 1 mg E2/100 mg P (1 mg/100 mg dosage strength)
- Treatment 2: Combined 0.5 mg E2/100 mg P (0.5 mg/100 mg)
- Treatment 3: Combined 0.5 mg E2/50 mg P (0.5 mg/50 mg)
- Treatment 4: Combined 0.25 mg E2/50 mg P (0.25 mg/50 mg)
- Treatment 5: Placebo.

The Applicant evaluated the efficacy of TX-001HR in the VMS substudy using the standard 4 co-primary efficacy endpoints, recorded using daily dairies:

- Mean change in frequency of moderate to severe vasomotor symptoms from Baseline to Week 4 in an active treatment group compared with placebo;
- Mean change in frequency of moderate to severe vasomotor symptoms from Baseline to Week 12 in an active treatment group compared with placebo;
- Mean change in severity of moderate to severe vasomotor symptoms at Baseline to Week 4 in an active treatment group compared with placebo;
- Mean change in severity of moderate to severe vasomotor symptoms at Baseline to Week 12 in an active treatment group compared with placebo.

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

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

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

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

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

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

The assessments were consistent with recommendations in the Agency's 2003 draft Guidance for Industry titled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (hereafter referred to as the draft HT Clinical Trial Guidance).

The MITT-VMS population was the primary population for efficacy assessment. The MITT population included all randomized patients with valid baseline hot flush diary data who received at least one dose of randomized treatment, and who had at least one day of on-treatment daily diary data. For each co-primary endpoint, a Mixed Model Repeated Measures (MMRM) analysis was applied to the 12 weekly change scores.

A gatekeeping (hierarchal) testing procedure was used to control the overall type I error for the four combination doses and the co-primary efficacy endpoints. The testing started by examining the highest dose (1 mg/100 mg) for each of the co-primary endpoints at 0.05 level, 2-sided. If the four p-values for the co-primaries were significant ($p \leq 0.05$) then the hypothesis testing would continue to the next dose (0.5 mg/100 mg) for each of the co-primaries, as described above. If at any point the hypothesis testing yielded a non-significant result, the testing would be stopped. The four co-primary efficacy endpoints were analyzed using MMRM models as pre-specified in the protocol.

RESULTS

Overall, 71% (517 of 726 patients in the MITT-VMS population) completed the trial. The mean age of patients was 55 years, with a median of 4.6 years since menopause, and approximately 67% of patients were White and 31% Black/African-American.

Tables 2 and 3 summarize the efficacy results for the two higher dose groups (1 mg/100 mg, 0.5 mg /100 mg). Unlike the lower two dose groups (0.5 mg/50 mg, 0.25 mg/50 mg, data not shown), both the 1 mg/100 mg and 0.5 mg/100 mg groups showed statistically significant decrease in the weekly moderate to severe VMS frequency and severity from baseline compared to placebo at Weeks 4 and 12. However, neither dose groups achieved the standard clinically meaningful reduction of at least14 episodes of moderate to severe VMS per week at Week 4. The higher dose group achieved this threshold starting at Week 5 that is maintained through Week 12; the lower dose group achieved this threshold starting at Week 9 that is maintained to Week 12 (see Table 25 of the Medical Officer's Review by Dr. Theresa van der Vlugt dated October 26, 2018, for weekly change in VMS frequency from Weeks 4 through 12).

Table 2 – VMS Frequency: Change from Baseline in the Mean Number of Weekly Moderate and Severe VMS at Week 4 and Week 12 (MITT-VMS Population)

	1 mg E2/ 100 mg P N=141)	0.5 mg E2/ 100 mg P (N=149)	Placebo (N=135)
Baseline Mean (SD)	74.4 (35.26)	72.1 (27.76)	72.4 (23.26)
Week 4 (n)	134	144	126
Mean (SD) change from Baseline	-40.6 (30.59)	-35.1 (29.14)	-26.4 (27.05)
LS Mean (SE) change from placebo	-12.81 (3.30)	-8.07 (3.25)	---
MMRM P-value vs placebo	< 0.001	0.013	---
Week 12 (n)	124	129	115
Mean (SD) change from Baseline	-55.1 (31.36)	-53.7 (31.93)	-40.2 (29.79)
LS Mean (SE) change from placebo	-16.58 (3.44)	-15.07 (3.39)	---
MMRM P-value vs placebo	< 0.001	< 0.001	---

Source: Statistics Review (October 16, 2018), Table 3 (adapted)

Table 3 – VMS Severity: Change from Baseline in the Mean Weekly Severity Scores of VMS at Week 4 and Week 12 (MITT-VMS Population)

	1 mg E2/ 100 mg P (N=141)	0.5 mg E2/ 100 mg P (N=149)	Placebo (N=135)
Baseline			
Mean (SD)	2.54 (0.320)	2.51 (0.249)	2.52 (0.246)
Week 4 (n)	134	144	126
Mean (SD) change from Baseline	-0.48 (0.547)	-0.51 (0.563)	-0.34 (0.386)
LS Mean (SE) change from placebo	-0.13 (0.061)	-0.17 (0.060)	---
MMRM P-value vs placebo	0.031	0.005	---
Week 12 (n)	124	129	115
Mean (SD) change from Baseline	-1.12 (0.963)	-0.90 (0.783)	-0.56 (0.603)

LS Mean (SE) change from placebo	-0.57 (0.100)	-0.39 (0.099)	---
MMRM P-value vs placebo	< 0.001	< 0.001	---

Source: Statistics Review (October 16, 2018), Table 4 (adapted)

Director's comment: Overall, both the 1 mg/100 mg and the 0.5 mg/100 mg dose groups demonstrated statistically significant reduction in frequency and severity of VMS at Weeks 4 and 12. Regarding clinically meaningful reduction in VMS frequency, defined as decrease of at least 14 episodes per week, the higher dosage strength met this threshold starting at Week 5 but the lower dose did not do so until Week 9.

For VMS frequency, the standard approach to approving HT is that drug treatment should result in statistically significant and clinically meaningful reduction in VMS frequency starting at Week 4 and maintained through Week 12. These expectations for approval were previously conveyed to the Applicant during drug development. Therefore, Dr. Slaughter does not recommend approval of any TX-HR001 dosage strength, including the 1 mg/100 mg dose, because none met all four of the pre-specified co-primary endpoints at Weeks 4 and 12. She stated that the requested dosage strength of the estrogen component is high, based on current standards. And at such dosage strength, the expectation is such product would meet all criteria starting at Week4 and to approve Bijuva would allow "drift in the expectations for approval." Dr. Slaughter does not believe that the fact that TX-001HR contains progesterone, instead of a progestin, and is free of peanut, offer any relative benefit compared to other approved products (see CDTL Review by Dr. Shelley Slaughter dated October 28, 2018).

I believe that TX-001HR provides a new therapeutic option for women who wish to use a combination HT product containing progesterone, and not a progestin. Although there is no direct comparison between a progestin and micronized progesterone to indicate one is better or worse than the other, some women may prefer the micronized progesterone over a progestin for various reasons; which may include better individual tolerability or the desire to use a progestogen that structurally mimics endogenous progesterone. This formulation also offers an option for women with peanut allergy who choose progesterone over a progestin and are not able to use the currently marketed micronized progesterone monotherapy because it contains peanut oil (Prometrium). For the 1 mg/100 mg dosage strength, I believe that a slight delay of one week (until Week 5) to see clinically meaningful reduction in VMS frequency is an acceptable tradeoff for a new treatment alternative for women in whom the TX-001HR formulation is the therapy of choice. Labeling will reflect the delay in time to achieving clinically meaningful reduction in VMS frequency seen in study TXC12-05, so prescribers could appropriately counsel patients. Regarding the estrogen dose of Bijuva being on the higher end of the available dosage strengths of estrogen, the estradiol 1 mg dose is still within the range of approved estradiol doses, not higher, and is in line with the standard conjugated estrogen 0.625 mg dosage strength. The clinical recommendation is for a woman to use the lowest effective dose to treat her VMS symptoms; in some women, especially those with severe symptoms, the lowest effective dose may be 1 mg estradiol. For the above reasons, I recommend the approval of the 1 mg/100 mg dosage strength. I acknowledge approving an HT product that does not provide clinically meaningful reduction in VMS frequency until Week 5 deviates from the approval standard of meeting such criterion at Week 4. However, when the

new product could offer something not currently available, some flexibility to the usual standards should be considered, as I have done in this case.

(b) (4)

[redacted]

Subgroup analysis:
Most patients in the safety and efficacy trial were White (~65%) or Black/African American (~31%), and therefore, subgroup analyses base on race were performed for these two racial groups. The analyses are shown only for the 1 mg/100 mg dose group, the dosage strength that I recommend for approval.

Table 4 shows similar VMS frequency at baseline for White and Black/African-American patients. However, compared to placebo, drug treatment showed no effect on frequency reduction in the Black/African-American patients, compared to the expected efficacy in White patients.

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

	1 mg E2/ 100 mg P (N=141)	Placebo (N=135)
Black/African-American		
Baseline (n)	45	41
Mean (SD)	75.4 (47.93)	74.6 (27.01)
Week 4 (n)	43	37
Mean (SD) change from Baseline	-32.5 (32.47)	-32.1 (34.94)
LS Mean (SE) change from placebo	-0.55 (6.60)	---
95% CI	(-13.57, 12.46)	
MMRM P-value vs placebo	0.933	---
Week 12 (n)	39	34
Mean (SD) change from Baseline	-45.3 (31.56)	-48.8 (29.27)
LS Mean (SE) change from placebo	0.24 (6.59)	---
95% CI	(-12.76, 13.23)	
MMRM P-value vs placebo	0.971	---
White		
Baseline (n)	95	91
Mean (SD)	73.8 (27.83)	71.9 (21.73)
Week 4 (n)	90	87
Mean (SD) change from Baseline	-44.0 (28.93)	-24.4 (22.81)
LS Mean (SE) change from placebo	-18.07 (3.74)	---
95% CI	(-25.43, -10.72)	
MMRM P-value vs placebo	< 0.001	---

Week 12 (n)	84	79
Mean (SD) change from Baseline	-59.4 (30.47)	-36.7 (29.66)
LS Mean (SE) change from placebo	-23.98 (3.96)	---
95%CI	(-31.76, -16.19)	
MMRM P-value vs placebo	< 0.001	---

Source: Statistics Review (October 16, 2018), Table 6 (adapted)

Baseline severity of moderate to severe VMS was similar across racial groups. At Week 4, compared to placebo, there was no treatment effect on severity reduction in Black/African American patients treated with 1mg /100 mg; and at Week 12, the treatment effect was statistically significant but smaller in Black/African American than White patients (see Table 5).

Table 5 – VMS Severity: Change from Baseline in the Severity of Weekly Moderate to Severe VMS at Week 4 and Week 12 by Race (MITT-VMS Population)

	1 mg E2/ 100 mg P (N=141)	Placebo (N=135)
Black/African-American		
Baseline (n)	45	41
Mean (SD)	2.52 (0.427)	2.52 (0.203)
Week 4 (n)	43	37
Mean (SD) change from Baseline	-0.35 (0.546)	-0.51 (0.427)
LS Mean (SE) change from placebo	0.14 (0.103)	---
95% CI	(-0.06, 0.34)	
MMRM P-value vs placebo	0.181	---
Week 12 (n)	39	34
Mean (SD) change from Baseline	-1.06 (0.991)	-0.63 (0.656)
LS Mean (SE) change from placebo	-0.38 (0.171)	---
95% CI	-0.71, -0.04	
MMRM P-value vs placebo	0.028	---
White		
Baseline (n)	95	91
Mean (SD)	2.56 (0.255)	2.52 (0.267)
Week 4 (n)	90	87
Mean (SD) change from Baseline	-0.54 (0.537)	-0.28 (0.347)
LS Mean (SE) change from placebo	-0.25 (0.075)	---
95% CI	(-0.39, -0.10)	
MMRM P-value vs placebo	0.001	---

Week 12 (n)	84	79
Mean (SD) change from Baseline	-1.13 (0.954)	-0.53 (0.579)
LS Mean (SE) change from placebo	-0.66 (0.125)	---
95% CI	(-0.90, -0.42)	
MMRM P-value vs placebo	< 0.001	---

Source: Statistics Review (October 16, 2018), Table 7 (adapted)

At FDA's request, the Applicant conducted additional exploratory analyses to investigate potential reasons for the disparity in efficacy between White and Black/African American patients. Analyses evaluating outliers, baseline demographics and subject characteristics, drug compliance, diary completion and study sites, did not account for the differences between these two racial groups.

Regarding baseline demographics and characteristics, the White and Black/African American groups differed in main four factors. Compared to White patients, Black/African-American patients had

1. higher average BMI (28 versus 26 kg/m^2),
2. higher prevalence of current smokers (34% versus 19%),
3. higher average baseline estradiol levels ((~6.6 versus 5.5 pg/mL), and
4. lower prevalence of current alcohol use (51% versus 63%).

Analyses adjusting for each of these four baseline factors showed that no single factor independently explained the differences in efficacy between these two racial groups. To explore the impact of multiple covariates on efficacy, the statistical reviewer used an analysis of covariance (ANCOVA) interaction model to assess the impact of the above four factors. The ANCOVA analysis indicated a significant interaction between treatment and race (see Table 6). After adjusting for the four factors, the treatment-race interaction remains at Week 12 (see Table 7). The statistical reviewer concluded that the differences in the four baseline factors did not account for the disparity in efficacy.

Table 6: Change from baseline in Weekly VMS frequency at Weeks 4 and 12- ANCOVA analysis

Subgroup		Week 4		Week 12	
		1 mg E2 / 100 mg P	Placebo	1 mg E2 / 100 mg P	Placebo
Black	LS mean (SE)	-34.3	-30.9	-48.3	-46.9
	95% CI	-42.0, -26.6	-39.2, -22.6	-55.6, -41.1	-54.6, -39.1
	LS mean Difference	-3.4		-1.4	
	95% CI	-14.7, 7.9		-12.1, 9.2	
White	LS mean (SE)	-43.3	-24.6	-58.2	-37.4
	95% CI	-48.7, -38.0	-30.0, -19.3	-63.1, -53.2	-42.5, -32.3
	LS mean Difference	-18.7		-20.7	
	95% CI	-26.2, -11.1		-27.9, -13.7	
P-value for Trt*Race		0.0274		0.0032	

Source: Statistics review (October 16, 2018), Table 8

Table 7: Change from baseline in Weekly VMS frequency at Weeks 4 and 12- ANCOVA adjusting for baseline characteristics ‡ analysis

		Week 4	Week 12

		1 mg E2 / 100 mg P	Placebo	1 mg E2 / 100 mg P	Placebo
Black	LS mean (SE)	-32.6	-30.0	-45.8	-46.8
	95% CI	-40.6, -25.4	-38.7, -21.3	-53.3, -38.3	-54.7, -38.9
	LS mean Difference	-2.5		1.0	
	95% CI	-14.4, 9.3		-9.9, 11.9	
White	LS mean (SE)	-39.0	-26.7	-52.0	-40.4
	95% CI	-45.9, -32.2	-33.7, -19.8	-58.4, -45.7	-47.0, -33.9
	LS mean Difference	-12.3		-11.6	
	95% CI	-22.0, -2.6		-20.6, -2.5	
P-value for Trt*Race		0.1970		0.0754	

Source: Statistics Review (October 16, 2018), Table 9
‡ the baseline characteristics include baseline BMI), current smoking status (Yes, No), alcohol use (Yes, No), and baseline estradiol concentration.

Director's comment: Study TXC12-05 enrolled a substantial proportion of self-identified Black/African-American women. Whereas previous trials have typically enrolled approximately 10-20% Black/African-American women, this trial enrolled ~31%. The subgroup analyses by race indicated a potential lack of efficacy in self-identified Black/African-American patients, except for statistically significant reduction in severity at Week 12. The dissimilarities between White and Black/African-American women in compliance, subject characteristics, and baseline demographics did not appear to account for the differences in efficacy. The reason for the discrepancy in efficacy between White and Black/African-American women is unknown.

The statistical review team opined that a subgroup analysis in one phase 3 trial does not establish that the drug is ineffective in Black/African-American patients, but the subgroup findings suggesting lack of efficacy in Black/African-American patients could be generally described in Section 14 of the prescribing information (see Addendum to Statistical Review, dated October 26, 2018). Also, the statistical reviewer concluded that the trial was not powered to demonstrate efficacy by subgroup of race.

I concur with assessment of the statistical review team. I do not believe that the subgroup findings confirm that the drug is ineffective as to preclude the use of TX-001HR in Black/African-American patients. Labeling, however, should summarize the subgroup findings to inform prescribers of the uncertainty of efficacy of TX-001HR 1 mg/100 mg in self-identified Black/African-American patients.

Overall, I believe that there is substantial evidence of efficacy for the 1 mg /100 mg dosage strength (b) (4) Although the subgroup analysis by race suggested uncertain efficacy in self-identified Black/African-American patients in the pivotal trial, the findings do not confirm the lack of efficacy in these women.

7. Safety

Refer to the CDTL summary review (by Dr. Shelley Slaughter, dated October 28, 2018) and the clinical reviewer memo (by Dr. Theresa van der Vlugt, dated October 26, 2018) for details. The safety profile of Bijuva is consistent with the drug class. The risk of endometrial hyperplasia based on endometrial biopsy results at one year was 0.36%, with the one-sided

upper bound of 95% CI of 2%; this was below the acceptable upper bound of a single-sided 95% confidence interval rate of endometrial hyperplasia ≤ 4%. As with all estrogen-containing products, labeling will include the findings of the WHI study and all other class warnings and precautions.

8. Advisory Committee Meeting

No Advisory Committee meeting was needed for this application.

9. Pediatrics

The Agency granted this NDA a full PREA waiver.

10. Other Relevant Regulatory Issues

See CDTL and Clinical Reviewer memos.

11. Labeling

Labeling negotiations have been successfully completed. The approved dosage strength of 1 mg/100 mg will receive the standard class indication of treatment of symptoms of moderate to severe VMS in postmenopausal women with a uterus. Section 14 will state the lack of treatment effect on reducing the frequency and severity of VMS in self-identified Black/African-American patients in study TXC12-05. Bijuva will have the standard class labeling for safety. Final revised labeling received on October 24, 2018, was acceptable.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Other Postmarketing Requirements and Commitments

None.

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/s/

CHRISTINE P NGUYEN
10/28/2018