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APPLICATION NUMBER:

210132Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA or BLA Number	210132
Link to EDR	\\CDSESUB1\evsprod\NDA210132\210132.enx
Submission Date	December 28, 2017 (SDN001), March 29, 2018 (SDN004), May 31, 2018 (SDN008), July 12, 2018 (SDN011), August 6, 2018 (SDN015), August 29, 2018 (SDN019)
Submission Type	Standard
Brand Name	BIJUVA™
Generic Name	Estradiol/progesterone
Dosage Form and Strength	Capsules, (b) (4) 1 mg/100 mg
Route of Administration	Oral administration
Proposed Indication	Treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus
Applicant	TherapeuticsMD Inc.
Associated IND	IND114477
OCP Review Team	Peng Zou, PhD; Doanh Tran, PhD
OCP Final Signatory	Doanh Tran, PhD

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1. EXECUTIVE SUMMARY

Vasomotor symptoms (VMS) such as hot flashes, flushing, and sweating are associated with hormonal changes at the time of menopause. TX-001HR (Brand name: BIJUVA™) is a fixed-dose combination product consisting of a softgel formulation containing solubilized estradiol (E2) with micronized progesterone (P) indicated for the treatment of moderate to severe vasomotor symptoms (VMS)

associated with menopause in women with a uterus. The Applicant conducted five Phase 1 studies and one Phase 3 study to support safety and efficacy of TX-001HR.

1.1 Recommendations

The Office of Clinical Pharmacology Division of Clinical Pharmacology-3 has reviewed the information contained in NDA 210450 and recommend approval of this NDA. The key review issues with specific recommendations/comments are summarized in the table below:

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	A dose-dependent increase in E2 and P plasma concentrations was observed in the pivotal Phase 3 trial. Consistent concentrations of E2 and P were maintained over 12 months for each treatment arm, which provided supportive evidence of effectiveness of TX-001HR.
General dosing instructions	One BIJUVA™ capsule (1 mg E2/100 mg P) should be taken orally each evening with food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The review team believes that the dosing (b) (4) inappropriate for Black patients and pharmacokinetics (PK)-based dose adjustment is not expected address the efficacy issue in Black population.
Labeling	Refer to Section 2.4 for the review team's recommendations.
Bridge between the to-be-marketed and clinical trial formulations	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 P] using in vitro dissolution data and CMC data. No clinical bioequivalence (BE) study is required. A cross-study comparison between Phase 1 Study 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 P.
Other (Bridging to listed drug Prometrium)	The Applicant conducted a BE study using Estrace 2 mg and Prometrium 200 mg as reference drugs and (b) (4) 2 mg E2/200 mg P as test drug. The results of the BE study showed that the (b) (4) 2 mg E2/200 mg P product had similar exposure to progesterone compared to the reference drug Prometrium 200 mg. Considering the composition of (b) (4) 2 mg E2/200 mg P and Catalent 1 mg E2/100 mg P is quantitatively proportional, there is no change in manufacturing process and the proposed highest clinical dose contains only 100 mg P (i.e., half the dose in the BE study), the review team believes that the proposed Catalent 1 mg E2/100 mg P product will result in exposure less than or equal to that of Prometrium 200 mg. Therefore, Study 459 successfully bridged TX-001HR 1 mg E2/100 mg P formulation to Prometrium 200 mg for purpose of bridging to the safety findings of Prometrium 200 mg.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

(b) (4) The Applicant proposed that one TX-001HR capsule be taken orally each evening with food. The PK profiles of E2 and P following a single dose of TX-001HR are shown in Figure 1.

Figure 1. Plasma Concentration-Time Profiles of Estradiol (A) and Progesterone (B) in Healthy Postmenopausal Female Subjects After Oral Administration of a Single Dose of TX-001HR 1 mg Estradiol/100 mg Progesterone (N = 20) (b) (4)



Absorption: After oral administration of multi-dose TX-001HR, the steady-state C_{max} of E2 and P 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 hour. Food ingestion did not affect systemic exposure of estrone (E1). A high-fat meal increased AUC_{0-t} and C_{max} of single-dose P by 79% and 162%, respectively.

Distribution: The plasma protein binding of E2 and P was not assessed. The Applicant relies on general knowledge regarding distribution of E2 and P.

Metabolism and Excretion: Steady-state PK of E2, E1 and P was achieved within 7 days. The PK was variable and differed slightly between the 2 doses. For the 1 mg E2/100 mg P dose, the mean effective half-lives of E2 and E1 were 26 and 22 hours, respectively. The mean elimination half-life of P was 10 hours. The baseline-adjusted AUC of E2, E1 and P on Day 7 increased by 93%, 91% and 28%, respectively, compared to the AUC on Day 1. (b) (4)

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed TX-001HR dose is (b) (4) 1 mg E2/100 mg P, to be taken orally each evening with food. (b) (4)

Patients would be reevaluated periodically as clinically appropriate to determine if treatment is still necessary. The division of bone, reproductive and urologic products (DBRUP) recommended approval of the 1 mg E2/100 mg P dose (b) (4).

2.2.2 Therapeutic individualization

The Applicant did not conduct a population PK analysis to assess the effect of intrinsic factors (e.g. race and body weight) on the PK of E2 and P. Subgroup analysis for efficacy showed that both 0.5 mg E2/100 mg P and 1 mg E2/100 mg P dose regimens failed to meet pre-specified co-primary endpoints in Black population (reductions in the frequency and severity of moderate to severe VMS at Weeks 4 and 12 compared to placebo). For the 0.5 mg E2/100 mg P treatment, this reviewer found no consistent difference in the plasma concentrations of E2, E1 and P between White and Black subjects at different visits in the pivotal Phase 3 trial. For the 1mg E2/100 mg P treatment, however, the median plasma concentrations of E2 and E1 in White subjects were consistently 15 - 40% higher than that in Black subjects. The median plasma concentrations of E2 and E1 in Black subjects treated with 1 mg E2/100 mg P in the Phase 3 trial were 13 – 65% higher than that in White subjects treated with 0.5 mg E2/100 mg P. Statistically significant improvements in both co-primary endpoints were observed in White subjects treated with 0.5 mg E2/100 mg P but not in Black subjects treated with 1 mg E2/100 mg P. The findings indicated that the race-dependent efficacy cannot be fully explained by the difference in PK. Overall, the review team believes that the current dosing regimens are inappropriate for Black patients and PK-based dose adjustment is not expected to address the efficacy issue in Black population.

2.3 Outstanding Issues

- [REDACTED] (b) (4)
Although the concentrations of E2 and E1 in White subjects were consistently 15 - 40% higher than that in Black subjects, PK-based dose adjustment is not expected to address the efficacy issue in Black population.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following Labeling recommendation and comments:

Section 12.1: We recommend revising the mechanism of action for P.

Section 12.3: [REDACTED] (b) (4)

Section 12.3, food effect: The increases in C_{max} and AUC of P under fed conditions were revised from (b) (4)% to 162% and from (b) (4)% to 79%, respectively.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

E2 and P are endogenous steroid hormones involved in female menstrual cycle and pregnancy. As medications, they are used as menopausal hormone therapy. The TX-001HR clinical studies for treatment of VMS were conducted under IND 114477. The pre-NDA meeting with the FDA was held on August 28, 2017.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Vasomotor symptoms are believed to be related to hormonal changes in postmenopausal women. Circulating estrogens modulate pituitary secretion of gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women and thus reduce the frequency and severity of VMS. Concomitant use of a progestin and estrogen is expected to reduce the incidence of endometrial hyperplasia induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.
Active Moieties	E2 and P
General Information	
Bioanalysis	LC-MS/MS and GC-MS/MS methods were used to measure E2 and its metabolite E1 in plasma and serum. LC-MS/MS methods were used to determine P in plasma and serum.
Healthy vs. Patients	No dedicated comparative PK study between healthy subjects and patients was conducted.
Drug exposure at steady state (Mean ± SD)	1 mg E2/100 mg P, baseline-adjusted AUC_{0-24} : 772 ± 384 pg*h/mL (E2), 4594 ± 2138 pg*h/mL (E1), 18 ± 16 ng*h/mL (P) [REDACTED] (b) (4)

Range of effective dose or exposure	(b) (4) 1 mg E2/100 mg P			
Maximally tolerated dose or exposure	Maximally tolerated dose was not established.			
Dose Proportionality	Dose-dependent increase of AUC τ and C $_{\max}$ of E2 was observed			(b) (4)
Accumulation	For the 1 mg E2/100 mg P dose, the baseline-adjusted AUC of E2, E1 and P on Day 7 increased by 93%, 91% and 28%, respectively, compared to the AUC on Day 1. (b) (4)			
Variability	Inter-subject variability on Day 1 (Study 16-01, fed conditions) 1 mg E2/100 mg P: E2 C $_{\max}$ 94%, AUC 39%; E1 C $_{\max}$ 43%, AUC 36%; P C $_{\max}$ 96%, AUC 70% (b) (4)			
Absorption				
Bioavailability	The absolute bioavailability in humans has not been established.			
T $_{\max}$ (Mean $\pm$ SD)	1 mg E2/100 mg P (fed): E2 10 $\pm$ 7 hours; E1 11 $\pm$ 6 hours; P 2.2 $\pm$ 1.5 hours (b) (4)			
Food effect (Fed/fasted) [90% CI]	1 mg E2/100 mg P	AUC $_{0-t}$	C $_{\max}$	T $_{\max}$
	E2 (N = 23)	105% [96% - 115%]	46% [37% - 57%]	815% [486% - 1367%]
	P (N =24)	179% [130 – 245%]	262% [184 – 374%]	111% [79 – 156%]
Distribution				
Volume of Distribution	P is approximately 96% to 99% bound to serum proteins, primarily to serum albumin (50% to 54%) and transcortin (43% to 48%).			
Elimination				
Terminal Elimination half-life (Mean $\pm$ SD)	1 mg E2/100 mg P (fed): E2 26 $\pm$ 15 hours*; E1 22 $\pm$ 8 hours*; P 10 $\pm$ 3 hours (b) (4)			
Metabolism				
Primary metabolic pathway(s)	E2 is converted reversibly to E1 in liver, and both can be converted to estriol, the major urinary metabolite. Estrogens also undergo sulfate and glucuronide conjugation in the liver. P is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites.			
Excretion				
Primary excretion pathways	E2, E1, and estriol are excreted in urine along with glucuronide and sulfate conjugates. The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. P metabolites are eliminated mainly by kidneys.			

* Effective t_{1/2}. Calculated as $24 \cdot \ln(2) / \ln(\text{accumulation ratio} / (\text{accumulation ratio} - 1))$ for subjects with accumulation ratio >1.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

In the pivotal Phase 3 trial (Study TXC12-05), blood was collected from the safety population to assess serum levels of E2, E1, and P 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 P were assessed at Screening and Visits 4 and 7 (Week 12 and Month 12, respectively). A dose-dependent increase in E2 concentrations (**Table 1**) and P concentrations (**Table 2**) was observed. Consistent concentrations of E2 and P maintained over 12 months for each treatment arm, which provided supportive evidence of effectiveness of TX-001HR.

Table 1. Baseline-Unadjusted Estradiol Concentrations for TX-001HR (Study TXC12-05)

E2 Concentration (pg/mL)	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)
Screening (n)	415	423	421	421	150
Mean (SD)	6.28 (6.62)	6.45 (7.24)	5.75 (6.06)	6.29 (6.25)	5.63 (4.32)
Median	4.6	4.5	4.2	4.5	4.0
Week 4 (n)	382	394	405	402	130
Mean (SD)	42.49 (36.51)	23.03 (23.91)	24.88 (25.43)	18.50 (33.34)	8.27 (22.50)
Median	34.5	18.6	18.7	12.2	3.8
Week 12 (n)	352	365	374	371	117
Mean (SD)	44.46 (39.11)	26.52 (27.32)	26.75 (31.05)	16.59 (19.26)	8.54 (23.22)
Median	36.0	20.4	20.1	12.3	3.9
Month 6 (n)	315	333	338	323	102
Mean (SD)	45.58 (49.03)	24.23 (22.05)	24.16 (16.53)	16.61 (16.96)	5.35 (4.68)
Median	35.9	20.2	20.9	13.2	4.2
Month 9 (n)	292	318	320	296	95
Mean (SD)	44.46 (35.67)	27.37 (35.27)	24.56 (20.40)	15.06 (13.55)	7.99 (15.18)
Median	36.0	20.5	20.3	12.6	4.1
Month 12 (n)	282	301	311	280	91
Mean (SD)	42.29 (41.21)	24.60 (26.44)	23.66 (18.65)	15.23 (20.08)	5.73 (7.28)
Median	35.2	20.4	20.1	12.2	4.1

Table 2. Baseline-Unadjusted Progesterone Concentrations for TX-001HR (Study TXC12-05)

P Concentration (ng/mL)	1 mg E2/ 100 mg P (N=415)	0.5 mg E2/ 100 mg P (N=424)	0.5 mg E2/ 50 mg P (N=421)	0.25 mg E2/ 50 mg P (N=424)	Placebo (N=151)
Screening (n)	415	422	420	419	150
Mean (SD)	0.056 (0.024)	0.065 (0.150)	0.057 (0.052)	0.056 (0.023)	0.053 (0.011)
Median	0.050	0.050	0.050	0.050	0.050
Week 12 (n)	351	366	374	373	117
Mean (SD)	0.452 (0.622)	0.548 (1.884)	0.229 (0.619)	0.247 (0.441)	0.057 (0.031)
Median	0.284	0.250	0.123	0.132	0.050
Month 12 (n)	283	301	311	280	91
Mean (SD)	0.534 (1.375)	0.387 (0.781)	0.181 (0.243)	0.219 (0.678)	0.056 (0.020)
Median	0.263	0.232	0.119	0.115	0.050

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

(b) (4) TX-001HR (1 mg E2/100 mg P, to be taken orally each evening with food) is appropriate for the treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.

Four doses of E2/P were evaluated in the pivotal Phase 3 trial: 1 mg E2/100 mg P, 0.5 mg E2/100 mg P, 0.5 mg E2/50 mg P, and 0.25 mg E2/50 mg P. For the general patient population, the 1 mg E2/100 mg P dose demonstrated statistically significant and clinically meaningful reductions in the frequency and severity of moderate to severe VMS at Weeks 4 and 12 (pre-specified co-primary endpoints) (**Figure 2** and **Figure 3**). Per the clinical reviewer, Dr. Theresa Van Der Vlugt, the 0.5 mg E2/100 mg P dose demonstrated statistically significant reductions in the frequency and severity of moderate to severe VMS at Week 4 and Week 12 but did not show a clinically meaningful reduction in the frequency of moderate to severe VMS until Week 9. The 0.5 mg E2/50 mg P dose failed to demonstrate a statistically significant reduction in the frequency of moderate and severe VMS at Week 4 compared to placebo. Both lower doses (0.5 mg E2/50 mg P and 0.25 mg E2/50 mg P) failed to demonstrate a statistically significant reduction in the severity of VMS at Week 4 compared to placebo. The 0.25 mg E2/50 mg P dose also did not show a statistically significant difference from placebo in reducing the severity of moderate to severe VMS at Week 12. Refer to Medical Officer Review for detailed efficacy assessment.

According to the Applicant, among 178 postmenopausal women received TX-001HR in five Phase 1 studies and 1835 subjects received at least one capsule of TX-001HR in Phase 3 trial, no cases of endometrial hyperplasia or malignancy were observed. A total of 47 treatment emergent severe adverse events (TESAEs) were reported for 40 subjects during the study. The percentage of subjects with TESAEs in the active treatment groups ranged from 1.9% to 3.1% compared to 1.3% in placebo. Refer to Medical Officer Review for detailed safety assessment.

Figure 2. Mean Reduction in Number of Weekly Moderate and Severe VMS from Week 1 Through Week 12 (MITT-VMS Population)

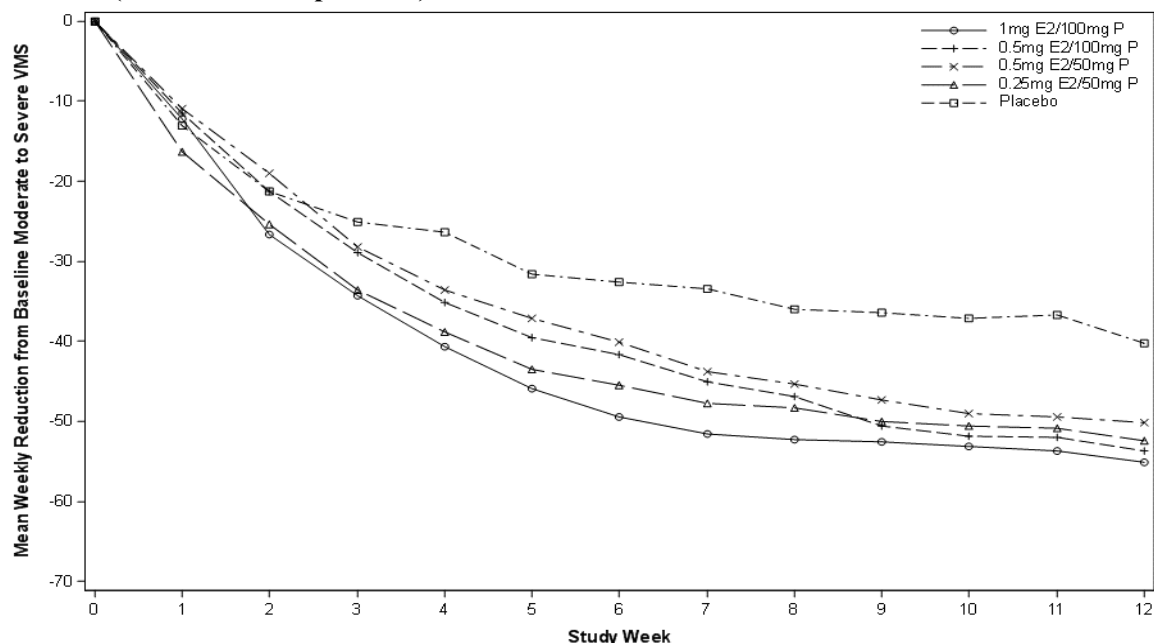
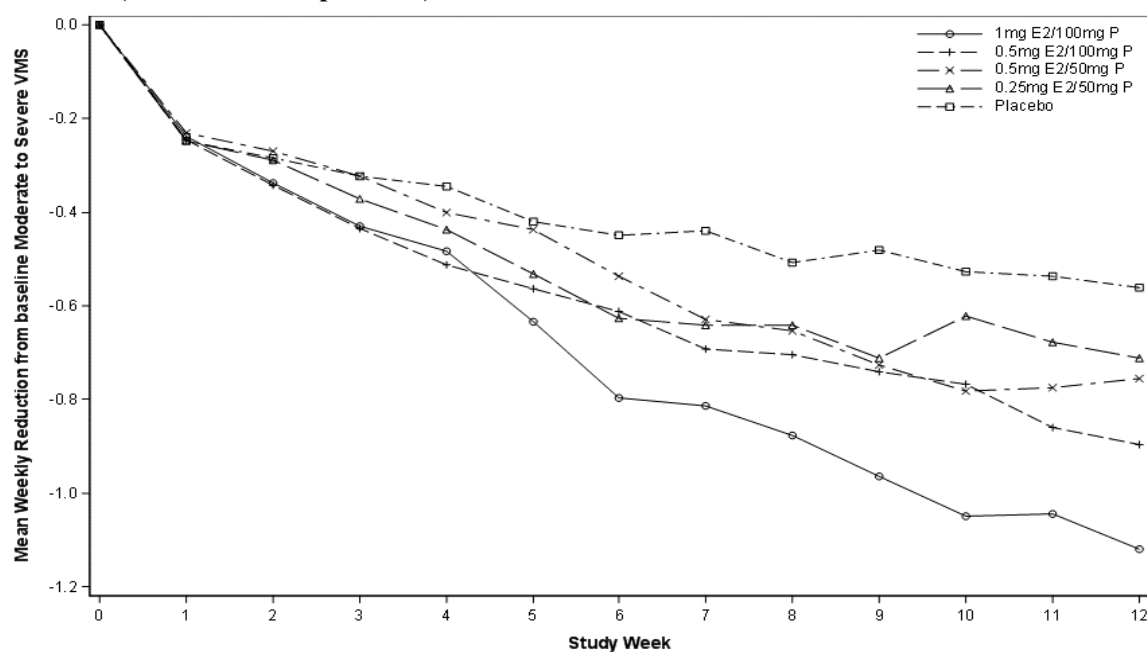


Figure 3. Mean Reduction in Severity of Weekly Moderate and Severe VMS from Week 1 Through Week 12 (MITT-VMS Population)



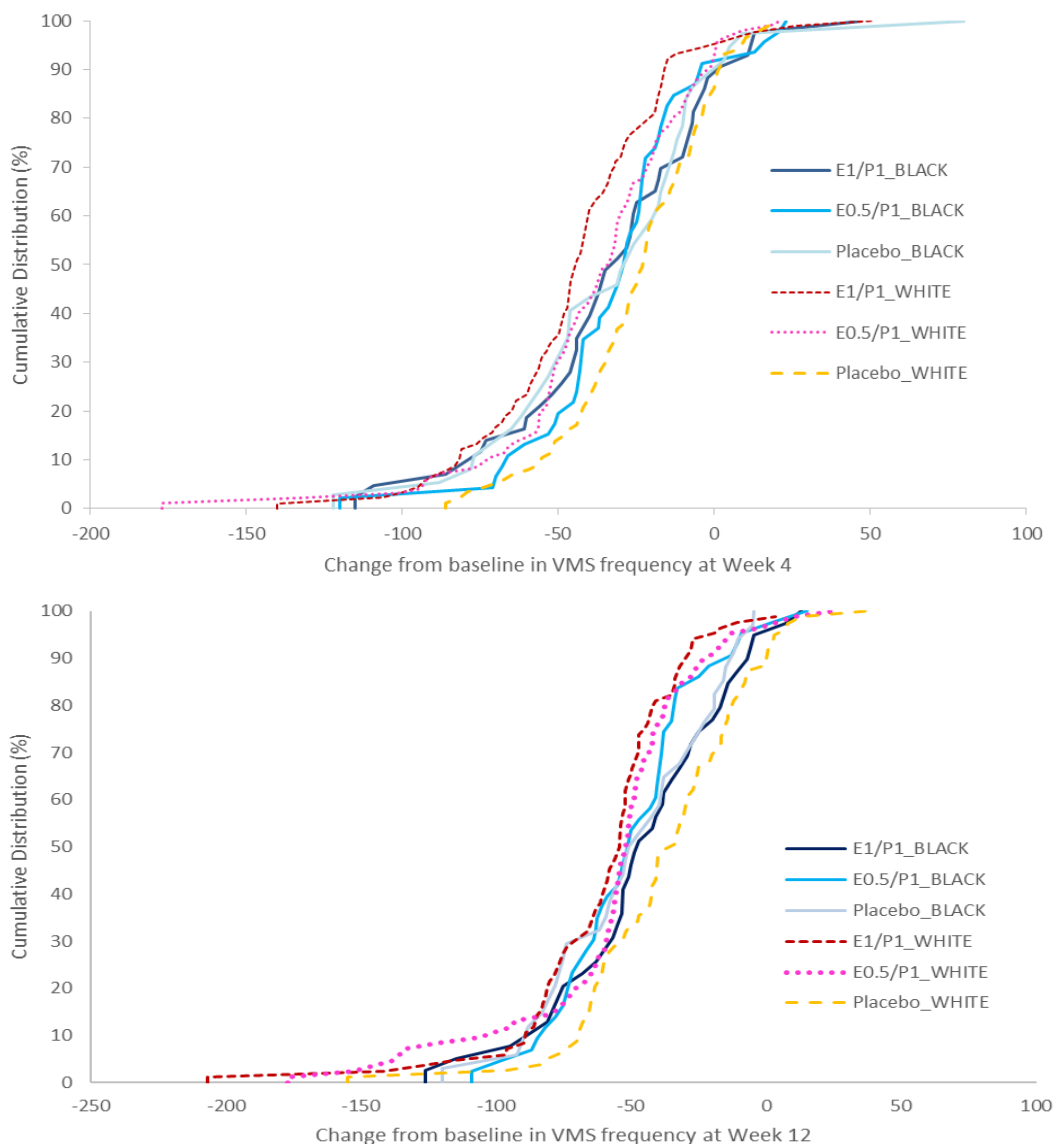
3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

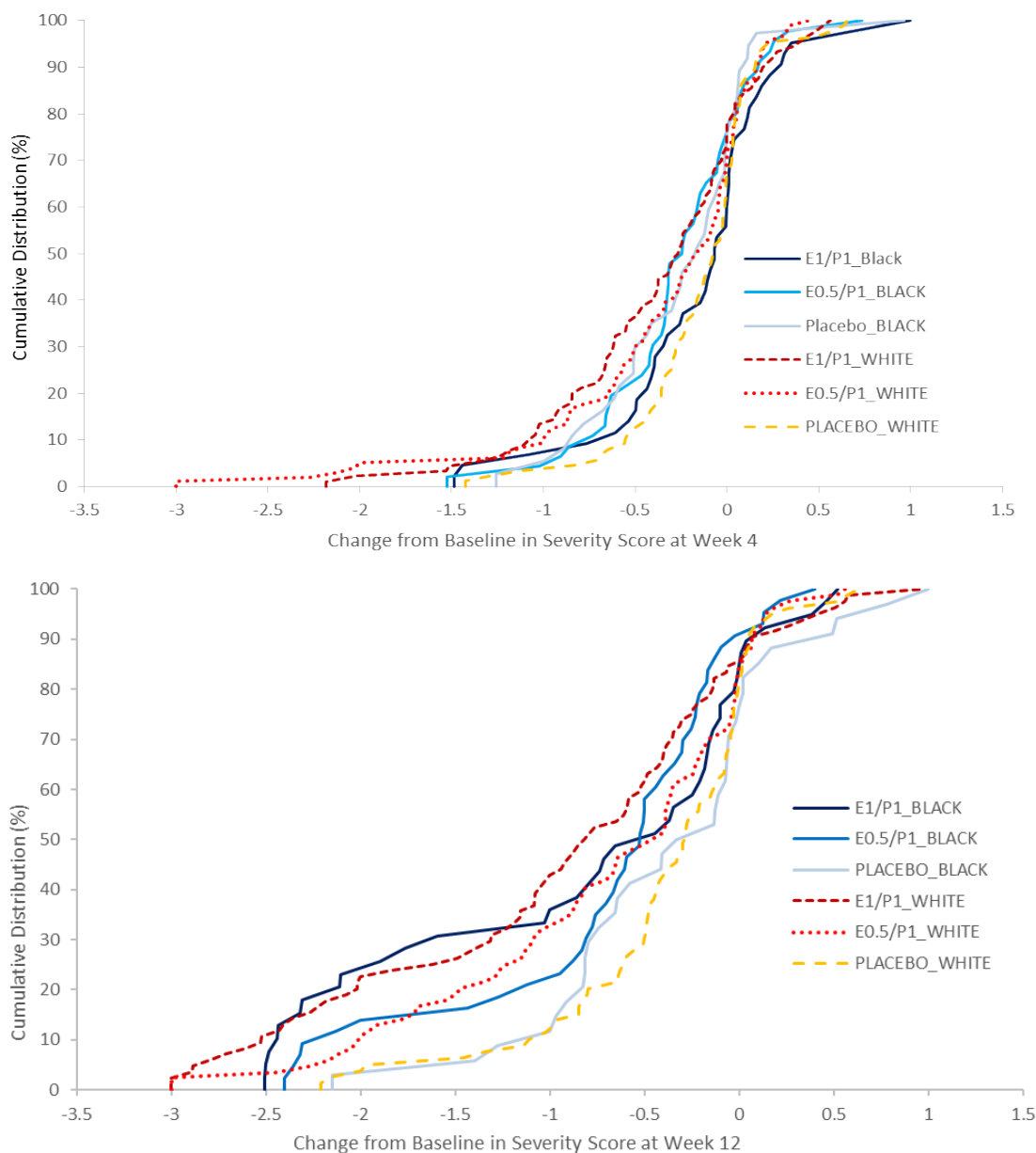
Race:

Yes, an alternative management strategy is required for Black population.

The Applicant did not conduct a population PK analysis to assess the effect of intrinsic factors on the PK of E2 and P. The Applicant's subgroup analysis for efficacy showed that statistically significant improvements in both co-primary endpoints were observed for 1 mg E2/100 mg P and 0.5 mg E2/100 mg P doses and at all time points in the White population, but no significant differences were noted in the Black population except for the change from baseline in the severity score of VMS at Week 12 (**Figure 4**).

Figure 4. Cumulative Distribution Function Curves for the Co-Primary Efficacy Endpoints
(Prepared by Statistical reviewer, Dr. Jia Guo)





In its response to the FDA's Statistical Information Request dated June 28, 2018, the Applicant provided multiple factors in Black subjects which might contribute to the differences in efficacy between races: a) higher placebo response rate, b) lower compliance rate with study drug and diary completion (Black 73% vs. White 78%), c) higher body mass index (BMI) (Black 27.9 kg/m² vs. White 26.1 kg/m²), d) more current smokers (Black 34.2% vs. White 18.9%), e) less alcohol use (Black 50.7% vs. White 63.2%), f) higher baseline E2 concentrations (Black 6.6 pg/mL vs. White 5.5 pg/mL). Among these factors, lower compliance rate with study drug, higher BMI and smoking may potentially cause a lower exposure to E2 in Black subjects. It was reported that obese women had a lower exposure to ethinyl estradiol than normal weight women¹. Smoking is known to induce CYP1A2 which contributes to the metabolism of E2².

¹ Westhoff C. et al., Contraception. 2010 June ; 81(6): 474–480

² Zevin S. Clin Pharmacokinet. 1999 Jun;36(6):425-38.

The review team evaluated the effect of race on the PK of E2 and P in Study 16-01 (single- and multi-dose PK) and Study 17-02 (food effect). No consistent difference in PK was observed between White and Black populations in the two studies. It is worthy to note the sample size of Black subjects was small ($N \leq 6$) in both studies.

Sparse PK samples were collected in the Phase 3 trial. The baseline-unadjusted plasma concentrations of E2, E1 and P at the (relatively) flat regions of concentration-time curves (between 6 – 16 hours post dose for E2 and E1 and between 10 – 24 hours post dose for P) were collected by the reviewer and compared between White and Black subjects (**Table 3**, **Table 4** and **Table 5**). For the 0.5 mg E2/100 mg P dose, no consistent difference in the plasma concentrations of E2, E1 and P was observed between White and Black subjects at different visits. For the 1mg E2/100 mg P dose, no consistent difference in P concentrations was detected between White and Black subjects. However, the median concentrations of E2 and E1 in White subjects were consistently 15 - 40% higher than that in Black subjects.

Table 3. A Comparison of Plasma Concentrations of Unadjusted Estradiol between White and Black Subjects (Study TXC12-05)

Dose	E2 0.5 mg/P 100 mg		E2 1 mg/P 100 mg	
	Visit 2, Week4			
	White (N = 185)	Black (N = 80)	White (N = 181)	Black (N = 76)
Mean ± SD (pg/mL)	22.8 ± 12.6	25.2 ± 31.6	45.8 ± 38.1	35.8 ± 31.4
Median (pg/mL)	21.1	17.1	36.9	29.6
	Visit 4, Week 12			
	White (N = 197)	Black (N = 76)	White (N = 197)	Black (N = 77)
Mean ± SD (pg/mL)	26.7 ± 26.6	27.3 ± 21.0	48.9 ± 41.8	35.4 ± 27.5
Median (pg/mL)	21.3	21.8	39.0	29.4
	Visit 5, Month 6			
	White (N = 178)	Black (N = 71)	White (N = 169)	Black (N = 66)
Mean ± SD (pg/mL)	24.3 ± 17.0	28.2 ± 27.1	50.3 ± 51.6	36.5 ± 27.0
Median (pg/mL)	21.4	22.2	40.0	28.1
	Visit 6, Month 9			
	White (N = 167)	Black (N = 67)	White (N = 172)	Black (N = 62)
Mean ± SD (pg/mL)	29.6 ± 43.1	25.8 ± 25.9	45.2 ± 32.3	43.5 ± 43.3
Median (pg/mL)	21.5	20.1	39.8	30
	Visit 7, Month 12			
	White (N = 165)	Black (N = 55)	White (N = 144)	Black (N = 50)
Mean ± SD (pg/mL)	25.9 ± 22.4	31.3 ± 41.7	48.5 ± 33.4	34.9 ± 27.9
Median (pg/mL)	22.4	21.5	42.6	29.9

Table 4. A Comparison of Plasma Concentrations of Unadjusted Estrone between White and Black Subjects (Study TXC12-05)

Dose	E2 0.5 mg/P 100 mg		E2 1 mg/P 100 mg	
	Visit 2, Week4			
Race	White (N = 188)	Black (N = 83)	White (N = 185)	Black (N = 72)
Mean ± SD (pg/mL)	125.4 ± 74.2	108.7 ± 77.3	240.3 ± 164.7	175.8 ± 140.1
Median (pg/mL)	121.5	95.0	212.0	137.0
	Visit 4, Week 12			
Race	White (N = 201)	Black (N = 77)	White (N = 202)	Black (N = 73)
Mean ± SD (pg/mL)	135.3 ± 80.5	129.0 ± 91.1	257.4 ± 185.0	178.7 ± 144.1
Median (pg/mL)	127.0	120.0	228.5	148.0
	Visit 5, Month 6			

Race	White (N = 182)	Black (N = 72)	White (N = 172)	Black (N = 64)
Mean ± SD (pg/mL)	135.0 ± 78.7	138.2 ± 136.3	261.8 ± 176.6	194.6 ± 150.2
Median (pg/mL)	124.5	119.5	232.5	161.0
Visit 6, Month 9				
Race	White (N = 171)	Black (N = 70)	White (N = 175)	Black (N = 60)
Mean ± SD (pg/mL)	136.4 ± 88.5	112.5 ± 102.3	258.2 ± 163.9	224.9 ± 253.6
Median (pg/mL)	129.0	95.6	227.0	173.0
Visit 7, Month 12				
Race	White (N = 167)	Black (N = 59)	White (N = 145)	Black (N = 48)
Mean ± SD (pg/mL)	132.2 ± 68.6	121.1 ± 89.9	274.1 ± 197.2	195.9 ± 168.8
Median (pg/mL)	127.0	109.0	242.0	145.0

Table 5. A Comparison of Plasma Concentrations of Unadjusted Progesterone between White and Black Subjects (Study TXC12-05)

Dose	E2 0.5 mg/P 100 mg		E2 1 mg/P 100 mg	
	Visit 4, Week 12			
Race	White (N = 195)	Black (N = 85)	White (N = 201)	Black (N = 75)
Mean ± SD (pg/mL)	495 ± 2142	740 ± 1928	501 ± 731	427 ± 401
Median (pg/mL)	236	303	299	327
	Visit 7, Month 12			
Race	White (N = 164)	Black (N = 53)	White (N = 140)	Black (N = 44)
Mean ± SD (pg/mL)	409 ± 841	387 ± 410	554 ± 1603	820 ± 1424
Median (pg/mL)	258	269	302	323

It is worthy to note that the median plasma concentrations of E2 and E1 in Black subjects treated with 1 mg E2/100 mg P were 13 – 65% higher than that in White subjects treated with 0.5 mg E2/100 mg P. Statistically significant improvements in both co-primary endpoints were observed in White subjects treated with 0.5 mg E2/100 mg P but not in Black subjects treated with 1 mg E2/100 mg P. The findings indicated that the race-dependent efficacy cannot be fully explained by the difference in PK. Overall, the review team believes that current dosing regimens are inappropriate for Black patients and PK-based dose adjustment is not expected to address the efficacy issue in the Black population.

Body Mass Index (BMI):

The Applicant's subgroup analysis for efficacy showed that BMI affected the efficacy of 1 mg E2/100 mg P dose but not the 0.5 mg E2/100 mg P dose. For 1 mg E2/100 mg P dose, according to the Applicant's analysis, statistically significant reductions in the frequency of VMS was observed for the lower and middle BMI tertiles (< 25 kg/m² and 25 to <30 kg/m²) for Week 4 and for all tertiles at Week 12. Statistically significant reductions in the severity of VMS was observed in the lowest BMI tertile for Weeks 4 and 12 and at Week 12 only for the middle and higher tertiles (≥ 30 kg/m²). For the 0.5 mg E2/100 mg P dose, frequency and severity of VMS were significantly reduced at Week 4 for the highest BMI group only and for the lowest and highest BMI groups at Week 12. The Applicant did not assess the effect of BMI or body weight on the PK of E2 and P. Since inconsistent effect of BMI on efficacy was observed across dose regimens and the high dose (1 mg E2/100 mg P, the only effective dose in general population) showed statistically significant reductions in the frequency and severity of VMS for all BMI tertiles at Week 12, the review team does not recommend BMI- or body weight- based dose adjustment.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Drug-Drug Interactions:

No drug-drug interaction study report was submitted in this NDA. The Applicant relies on general knowledge regarding drug interactions with E2 and P.

Food Effects:

Yes, there is clinically relevant food-drug interaction. Per the Agency's request, the Applicant conducted a dedicated single-dose food effect study (Study TXC17-02) with the Catalent 1 mg E2/100 mg P formulation (Refer to individual study review in Appendix 4.2.2). Subject (b) (6) was excluded from E2 relative BA analysis due to her high baseline level of E2 in study period 2 (111 pg/mL). Both the Applicant's and the reviewer's analyses consistently showed that a high fat meal did not affect the AUC of E2 but reduced C_{max} by 54% and prolonged T_{max} from 1.2 hour to 10 hours (**Table 6**). Food intake had no effect on the pharmacokinetics of E1 (**Table 7**). Subject (b) (6) was excluded from the Applicant's P relative BA analysis but included in the reviewer's analysis. The reviewer's analysis showed that a high fat meal increased C_{max} and AUC_{0-t} of P by 162% and 79% (**Table 8**), respectively, which were slightly lower than the Applicant's results (C_{max} 171% and AUC_{0-t} 82%, data not shown).

Table 6. The Effect of Food Intake on the Baseline-Adjusted Pharmacokinetics of Estradiol in Catalent 1 mg/100 mg Capsule (Study TXC17-02, Subject (b) (6) was excluded, Reviewer's Analysis)

Parameters	Geometric Mean		Geometric Mean Ratio (GMR) Fed/Fasting (%)	90% CI for GMR (%)
	Fed	Fasting		
AUC0-t (pg*h/mL)	957.91	913.51	104.86	95.76 – 114.82
AUCinf (pg*h/mL)	1185.25	1158.34	102.32	91.43 – 114.52
Cmax (pg/mL)	27.65	60.23	45.90	36.85 – 57.18
Tmax (h)	9.86	1.21	814.81	485.79 – 1366.66

Table 7. The Effect of Food Intake on the Baseline-Adjusted Pharmacokinetics of Estrone in Catalent 1 mg/100 mg Capsule (Study TXC17-02, Reviewer's Analysis)

Parameters	Geometric Mean		Geometric Mean Ratio (GMR) Fed/Fasting (%)	90% CI for GMR (%)
	Fed	Fasting		
AUC0-t (pg*h/mL)	3297.12	2934.42	112.36	103.78 – 121.65
AUCinf (pg*h/mL)	3654.10	3193.76	114.41	105.81 – 123.71
Cmax (pg/mL)	131.93	139.61	94.50	87.03 – 102.60
Tmax (h)	6.85	6.51	105.22	88.17 – 125.58

Table 8. The Effect of Food Intake on the Baseline-Adjusted Pharmacokinetics of Progesterone in Catalent 1 mg/100 mg Capsule (Study TXC17-02, Reviewer's Analysis)

Parameters	Geometric Mean		Geometric Mean Ratio (GMR) Fed/Fasting (%)	90% CI for GMR (%)
	Fed	Fasting		
AUC0-t (ng*h/mL)	6.88	3.86	178.51	129.81 – 245.49
AUCinf (ng*h/mL)	6.98	5.05	138.39	80.68 – 237.38
Cmax (ng/mL)	2.63	1.00	261.86	183.50 – 373.70
Tmax (h)	2.25	2.02	111.24	79.18 – 156.28

3.3.5 Does pharmacokinetic data bridge the proposed to-be-marketed product to listed drug(s) or Phase 3 trial formulation?

Bridging to listed drug Prometrium:

Yes, bioequivalence (BE) Study 459 successfully bridged the proposed to-be-marketed (TBM) product to the FDA's finding of nonclinical safety for the listed drug Prometrium 200 mg.

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 P, the Applicant relied upon the FDA's finding of nonclinical safety for Prometrium® (progesterone capsules USP, NDA 019781) as the reference drug using Study 459 as the primary bridge to FDA's finding of safety. To bridge to the nonclinical safety findings of Prometrium, the Applicant needs to demonstrate that the P exposure of TX-001HR 1 mg E2/100 mg P capsule administered under fed conditions is less than or comparable to the listed drug (Prometrium 200 mg strength).

Study 459 was conducted under fed conditions to assess the relative bioavailability (BA) between TX-001HR 2 mg E2/200 mg P capsule (Test product) and Prometrium 200 mg/Estrace 2mg (Reference product). Due to the large intra-subject variability in the PK of P (CV > 29.4%), a reference-scaled BE method was used for statistical analysis. As shown in **Table 9**, both the Applicant's and the reviewer's analysis showed that the baseline-adjusted AUC of P met the standard BE criteria. Inconsistent with the Applicant's analysis, the reviewer's analysis showed that baseline-adjusted C_{max} met BE criteria. The review team concluded that under fed conditions, the TX-001HR 2 mg E2/200 mg P capsule manufactured at (b) (4) was bioequivalent to Prometrium 200 mg capsule (Refer to individual study review in Appendix 4.2.1 for more details).

Table 9. Point Estimate and 95% Upper Confidence Bound of Test Product (TX-001HR 2 mg E2/200 mg P) versus the Averaged Reference Products (Prometrium 200 mg and Estrace 2mg) for Baseline-adjusted Progesterone

PK Parameters	N	Point Estimate %	95% Upper Confidence Bound	Within-subject SD (S _{WR})	Bioequivalent
Applicant's Results					
C_{max} (ng/mL)	62	115.9	0.0799	0.3881	No
AUC_{0-t} (ng*h/mL)	62	105.5	-0.1006	0.6305	Yes
Reviewer's Results					
C_{max} (ng/mL)	62	115.9	-0.7850	1.179	Yes
AUC_{0-t} (ng*h/mL)	62	105.5	-0.5429	0.956	Yes

During drug development, the manufacturing site was changed from (b) (4) to Catalent Pharma Solutions LLC (Catalent). The drug products used in Study 459 (2 mg E2/200 mg P) and pivotal Phase 3 Study TXC12-05 (all the four strengths) were manufactured at (b) (4). The drug products used in Study TXC17-02 (1 mg E2/100 mg P) and Study TXC16-01 (0.5 mg E2/100 mg P and 1 mg E2/100 mg P) were manufactured at Catalent. The TBM formulations will also be manufactured at Catalent. At the pre-NDA meeting, both FDA and the Applicant agreed to bridge the manufacturing site change and formulation change with comparative in vitro dissolution data. However, the dissolution method submitted in the NDA was not accepted by the biopharmaceutical review team because the method was not sensitive to formulation variations.

This reviewer conducted a cross-study comparison of the PK of P for the Applicant's formulations and the reference product Prometrium (Refer to Appendix 4.4). A large variability in the C_{max} and AUC_{0-t} of P administered under fed conditions between Study 459 and Study TXC17-02 was observed. For example, the geometric mean AUC_{0-t} of P (63.37 ng*h/mL) observed in Study 459 was 9.2-fold higher than that observed in Study TXC17-02 (6.88 ng*h/mL) (**Table 10**), while the dose was only 2-fold higher in Study 459. In the response to FDA's information request dated July 30, 2018, the Applicant explained that cross-study comparison is difficult given the significant differences in: a) meal components in the fed studies (Study 459's vegetable oil vs. Study TXC17-02's butter), b) sample size (N = 64 vs. N = 24) and demographics (India vs. US), c) dosage (2 mg E2/200 mg P vs. 1 mg E2/100 mg P) and d) bioanalytical assays. The Applicant also explained that the abnormally high AUC and C_{max} of P and the high variability in Study 459 might contribute to the large cross-study variability (Refer to Appendix 4.4 for the Applicant's response).

Table 10. Cross-study Comparison of Pharmacokinetics of Progesterone for various formulations

Products (Study No.)	Fasting/ Fed	Geometric Mean C_{max} (ng/mL)	Geometric Mean AUC_{0-t} (ng*h/mL)
(b) (4) 200 mg (351)	Fasting	2.28	8.36
Prometrium 200 mg (351)		2.96	10.89
(b) (4) 200 mg (352)	Fed	47.04	107.57
Prometrium 200 mg (352)		42.99	97.81
(b) (4) 200 mg (459)	Fed	35.11	63.37
Prometrium 200 mg (459)		23.26	60.01
Catalent 100 mg (17-02)	Fasting	1.00	3.86
	Fed	2.63	6.88

Considering the large cross-study variability in the PK of P, it is difficult to do a cross-study comparison of PK between the (b) (4) 2 mg E2/200 mg P used in Study 459 and the Catalent 1 mg E2/100 mg P used in Study 17-02 and Study 16-01. However, since the composition of (b) (4) 2 mg E2/200 mg P and Catalent 1 mg E2/100 mg P is quantitatively proportional and the manufacturing process is not changed, the manufacturing site change is not expected to dramatically affect the PK of TX-001HR. The Catalent 1 mg E2/100 mg P (i.e. containing 100 mg P) is not expected to have a higher exposure to P than (b) (4) 2 mg E2/200 mg P or Prometrium 200 mg. The review team concluded that Study 459 successfully bridged TX-001HR 1 mg E2/100 mg P formulation to the non-clinical safety of Prometrium 200 mg.

Bridging to the Phase 3 trial formulation:

The TBM formulation (Catalent 1 mg E2/100 mg P) was bridged to the Phase 3 trial formulation (b) (4) 1 mg E2/100 mg P) using in vitro dissolution data and CMC data. No clinical BE study is required. Per biopharmaceutical reviewer, Dr. Sandra Suarez's request, this reviewer did a cross-study PK comparison between Phase 1 Study TXC16-01 (Catalent 1 mg E2/100 mg P) and Phase 3 Study TXC12-05 (b) (4) 1 mg E2/100 mg P). In Study TXC12-05, PK samples of E2 and E1 were sparsely collected at Screening and Visits 2 (Week 4), 4 (Week 12), 5 (Month 6), 6 (Month 9), and 7 (Month 12/End of Treatment). PK samples of P were sparsely collected at Screening and Visits 4 (Week 12) and 7 (Month 12/End of Treatment). Only one blood sample was collected at each Visit. More than 95% of PK samples were collected between 6 – 24 hours postdose. As shown in **Figure 5**, the PK profiles of E2 were flat, indicating the average E2 concentrations of PK samples collected between 6 – 24 hours postdose might reflect steady-state E2 average concentrations. However, there was a rapid post-peak decline in the PK profiles of P. The average P concentration of PK samples collected between 6 – 24 hours postdose is expected to underestimate steady-state P average concentrations. As shown in **Table 11**, the cross-study

comparison did not detect a dramatic difference in the plasma concentrations of E2 or P between Catalent 1 mg E2/100 mg P product and (b) (4) 1 mg E2/100 mg P product. This information, including the above caveat regarding P concentrations, was shared with Dr. Sandra Suarez.

Table 11. Cross-study Comparison of Pharmacokinetics of Estradiol and Progesterone between Study TXC16-01 and Study TXC12-05

Unadjusted Plasma Concentrations of Estradiol and Progesterone (Mean ± SD)		
(b) (4) 1mg Estradiol/100 mg Progesterone		
	Estradiol (pg/mL)	Progesterone (ng/mL)
Study TXC 16-01		
Day 7	38.07 ± 14.17	0.77 ± 0.64
Study TXC 12-05		
Screening	6.28	0.056
Week 4	42.49 ± 36.51	N.A.
Week 12	44.46 ± 39.11	0.45 ± 0.62
Month 6	45.58 ± 49.03	N.A.
Month 9	44.46 ± 35.67	N.A.
Month 12	42.29 ± 41.21	0.53 ± 1.38



Source: Applicant's drug label

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Assays for E2 and E1:

Two LC-MS/MS methods and one GC-MS method were developed and validated in three analytical labs for quantitative analysis of E2 and E1 in human plasma or serum. The validation reports for each method and analytical study reports for each PK study were submitted. The methods were validated for linearity of standard curve, accuracy and precision, selectivity, matrix effect, long-term and freeze-thaw stability and the results met requirements (**Table 12**). The established long-term storage stability covered the corresponding study period and sample analysis period. The method validation for E2 and E1 is acceptable.

Table 12. Method Validation Parameters for Estradiol and Estrone

Method	(b) (4)		
Study(s)	351, 352, and 459	TXC17-02	TXC12-05 and TXC16-01
Analytical Lab	(b) (4)		
Methodology	UPLC-MS/MS	LC-MS/MS	GC-MS/MS
Biological matrix	Plasma	Plasma	Serum
Anticoagulant	K ₂ EDTA	K ₃ EDTA	NA
Extraction method	Solid phase, derivatization, & liquid-liquid	Liquid-liquid & derivatization	Solid phase
Calibration curve range	E2: 5.0380-1003.9980 pg/mL E1: 25.2600-5034.4000 pg/mL	E2: 5.00-500 pg/mL E1: 5.00-500 pg/mL	E2: 2.00-500 pg/mL E1: 5.00-1000 pg/mL
Analyte(s) of interest	Estradiol & estrone	Estradiol & estrone	Estradiol & estrone
Internal standard	d ₄ -estradiol	d ₃ -estradiol & d ₄ -estrone	d ₄ -estradiol & d ₄ -estrone
Inter-run accuracy for each QC	E2: LQC (18.9366 pg/mL): -0.77% bias MQC (382.3806 pg/mL): -5.58% bias HQC (760.1796 pg/mL): -6.83% bias E1: LQC (97.3503 pg/mL): 4.59% bias MQC (1912.2993 pg/mL): -6.21% bias HQC (3805.0593 pg/mL): -7.02% bias	E2: LQC (15.0 pg/mL): 2.88% bias MQC (100 pg/mL): -0.37% bias HQC (400 pg/mL): -3.08% bias E1: LQC (15.0 pg/mL): -0.78% bias MQC (100 pg/mL): -3.93% bias HQC (400 pg/mL): -1.92% bias	E2: LQC (6.52 pg/mL): -3.37% bias MQC (51.1 pg/mL): 0.00% bias HQC (441 pg/mL): 1.36% bias E1: LQC (17.1 pg/mL): 3.51% bias MQC (120 pg/mL): 2.50% bias HQC (865 pg/mL): 4.62% bias
Inter-run precision for each QC	E2: LQC (18.9366 pg/mL): 8.10% CV MQC (382.3806 pg/mL): 3.26% CV HQC (760.1796 pg/mL): 3.74% CV E1: LQC (97.3503 pg/mL): 6.31% CV MQC (1912.2993 pg/mL): 4.14% CV HQC (3805.0593 pg/mL): 6.04% CV	E2: LQC (15 pg/mL): 5.9% CV MQC (100 pg/mL): 3.0% CV HQC (400 pg/mL): 1.4% CV E1: LQC (15 pg/mL): 5.9% CV MQC (100 pg/mL): 2.8% CV HQC (400 pg/mL): 3.5% CV	E2: LQC (6.52 pg/mL): 8.46% CV MQC (51.1 pg/mL): 3.51% CV HQC (441 pg/mL): 4.92% CV E1: LQC (17.1 pg/mL): 6.78% CV MQC (120 pg/mL): 5.37% CV HQC (865 pg/mL): 6.82% CV
Long-term stability	232 days at -20°C & -70°C ^a	237 days at -20°C & -70°C	1056 days at -20°C & 368 days at -80°C
Freeze-thaw stability	Demonstrated for 4 cycles at -30°C and -70°C	Demonstrated for 5 cycles at -20°C	Demonstrated for 8 cycles at -20°C
Incurred sample reanalysis	Study 351: Not done Study 352: Not done Study 459: Not done	Study TXC17-02: E2: 97.7% passed E1: 90.8% passed % analyzed: ~10%	Study TXC12-05: E2: 89.4% passed E1: 85.1% passed % analyzed: ~6% Study TXC16-01: E2: 84.7% passed E1: 94.6% passed % analyzed: ~10%
Time from first sample drawn to last sample analyzed (including ISR)	Study 351: 67 days Study 352: 61 days Study 459: 54 days	Study TXC17-02: 36 days	Study TXC12-05: 1052 days Study TXC16-01: 56 days
Storage temperature at each site	Collection site: -30°C Analytical site: -70°C	Collection site: -20°C Analytical site: -20°C	Collection site: -20°C Analytical site: -20°C

Assays for Progesterone:

Three LC-MS/MS methods were developed and validated in three analytical labs for quantitative determination of P in human plasma or serum. The validation reports for each method and analytical study reports for each PK study were submitted. The methods were validated for linearity of standard curve, accuracy and precision, selectivity, matrix effect, long-term and freeze-thaw stability and the results met requirements (Table 13).

Table 13. Method Validation Parameters for Progesterone

Method	(b) (4)		
Study(s)	351, 352, and 459	TXC17-02	TXC12-05 and TXC16-01
Analytical Lab	(b) (4)		
Methodology	UPLC-MS/MS	LC-MS/MS	LC-MS/MS
Biological matrix	Plasma	Plasma	Serum
Anticoagulant(s)	K ₂ EDTA	K ₃ EDTA	NA
Extraction method	Solid phase	Liquid-liquid	Liquid-liquid
Calibration curve range	0.4031-122.5172 ng/mL	0.100-50.0 ng/mL	50.0-50,000 pg/mL
Analyte of interest	Progesterone	Progesterone	Progesterone
Internal standard	19-Norethindrone	d ₉ -Progesterone	d ₄ -Progesterone
Validation Report No.	(b) (4)		
Inter-run accuracy for each QC	LQC (1.1465 ng/mL): -8.26% bias MQC (45.8592 ng/mL): -4.26% bias HQC (91.7185 ng/mL): -0.38% bias	LQC (0.330 ng/mL): 0.3% bias MQC (4.00 ng/mL): 2.5% bias HQC (40.0 ng/mL): 1.8% bias	LQC (150 pg/mL): 0.00% bias MQC (2400 pg/mL): 2.08% bias HQC (37500 pg/mL): 3.20% bias
Inter-run precision for each QC	LQC (1.1465 ng/mL): 6.92% CV MQC (45.8592 ng/mL): 3.42% CV HQC (91.7185 ng/mL): 3.56% CV	LQC (0.330 ng/mL): 7.3% CV MQC (4.00 ng/mL): 2.7% CV HQC (40.0 ng/mL): 3.6% CV	LQC (150 pg/mL): 5.42% CV MQC (2400 pg/mL): 4.65% CV HQC (37500 pg/mL): 2.97% CV
Long-term stability	146 days at -20°C & -70°C	111 days at -20°C 131 days at -70°C	839 days at -20°C 512 days at -80°C
Freeze-thaw stability	Demonstrated for 4 cycles at -30°C and -70°C	Demonstrated for 5 cycles at -20°C	Demonstrated for 6 cycles at -20°C 5 cycles at -80°C
Incurred sample reanalysis (ISR)	Study 351: Not done Study 352: Not done Study 459: 83.18% passed % analyzed: ~10%	Study TXC17-02: 82.8% passed % analyzed: ~10%	Study TXC12-05: 77.2% passed % analyzed: ~6% Study TXC16-01: 95.5% passed % analyzed: ~10%
Time from first sample drawn to last sample analyzed (including ISR)	Study 351: 35 days Study 352: 43 days Study 459: 51 days	Study TXC17-02: 35 days	Study TXC12-05: 1059 days Study TXC16-01: 32 days
Storage temperature at each site	Collection site: -30°C Analytical site: -70°C	Collection site: -20°C Analytical site: -20°C	Collection site: -20°C Analytical site: -20°C

Reviewer's Comments:

- The reviewer noted that the established long-term storage stability (839 days at -20°C) for Method (b) (4) did not cover the study period of Phase 3 trial (Study TXC12-05, 1059 days).

On August 24, 2018, an Information Request (IR) was sent to the Applicant. The Applicant was requested to confirm that all PK samples collected from Phase 3 trial were analyzed within 839 days post-collection. Otherwise, the Applicant is requested to provide additional long-term storage stability data up to 1059 days. On August 29, 2018, the Applicant provided a complete response to the IR. As shown in **Table 14**, only 10 among 351 PK samples from 1 mg E2/100 mg P group at Week 12 Visit were analyzed beyond 839 days and 11 among 366 samples from 0.5 mg E/100 mg P group at Week 12 were analyzed beyond 839 days. There were no samples at Month 12 that were analyzed beyond the long-term stability of 839 days. As shown in **Table 15**, the mean P concentrations at Screening and at Week 12 were not different when all samples were included in the analysis compared to when samples analyzed > 839 days after collection were removed from the analysis. The data showed that the samples analyzed > 839 days after collection did not significantly impact the overall P concentrations at Screening and Week 12.

Table 14. Samples Per Dosage Group Analyzed Beyond 839 Days

Visit	1 mg E2/ 100 mg P (N = 415)	0.5 mg E2/ 100 mg P (N = 424)	0.5 mg E2/ 50 mg P (N = 421)	0.25 mg E2/ 50 mg P (N = 424)	Placebo (N = 151)
Screening	45/415	33/422	47/420	45/419	14/150
Week 12	10/351	11/366	12/374	15/373	3/117
Month 12	0/283	0/301	0/311	0/280	0/91

Table 15. Serum Concentration of Progesterone with All Samples Analyzed and Samples Analyzed Greater than 839 Days Removed

Progesterone (pg/mL)	1 mg E2/ 100 mg P (N = 415)	0.5 mg E2/ 100 mg P (N = 424)	0.5 mg E2/ 50 mg P (N = 421)	0.25 mg E2/ 50 mg P (N = 424)	Placebo (N = 151)
Screening - All Samples	415	422	420	419	150
Mean (SD)	55.86 (24.393)	65.35 (150.258)	57.43 (52.544)	55.99 (22.564)	53.38 (11.325)
Screening - Samples Removed	370	389	373	374	136
Mean (SD)	56.27 (25.438)	66.43 (156.454)	54.87 (19.707)	56.46 (23.736)	53.63 (11.841)
Week 12 – All Samples	351	366	374	373	117
Mean (SD)	451.68 (621.921)	547.83 (1884.845)	228.52 (618.660)	247.17 (441.289)	57.32 (30.769)
Week 12 – Samples Removed	341	355	362	358	114
Mean (SD)	456.24 (629.898)	557.04 (1912.915)	226.62 (624.818)	242.91 (438.571)	57.52 (31.151)

4.2 BA/BE Assessments

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 submitted nonclinical published literature for E2. For P, the Applicant relied upon the FDA's findings of nonclinical safety for Prometrium® (progesterone capsules USP, NDA 019781) and conducted three BA/BE studies (Study 351, 352 and 459) in healthy postmenopausal female subjects (**Table 16**) to bridge (b) (4) 2 mg E2/200 mg P formulation to the reference products (Estrace 2 mg plus Prometrium 200 mg). Due to the large variability in the PK of E2 and P and the small study sample size of Study 351 and Study 352, the Applicant relied on Study 459 for formulation bridging.

Table 16. Tabular Summary of Clinical Studies

Study (Country)	Phase	Product Batch No.	Dose (E2/P)	Description
351 (India)	1	(b) (4) PN0082-01	2 mg/200 mg	24 subjects fasted, single dose, comparative BA, crossover with reference (Estrace, Prometrium)
352 (India)	1	(b) (4) PN0082-01	2 mg/200 mg	24 subjects fed high fat, single dose, comparative BA, crossover with reference (Estrace, Prometrium)
459 (India)	1	(b) (4) PN0082-01	2 mg/200 mg	66 subjects fed high-fat, single dose, 3-way crossover, reference-replicated, reference-scaled BE (Estrace, Prometrium)
TXC17-02 (USA)	1	Catalent 3012843	1 mg/100 mg	24 subjects, single dose, two-treatment (fed and fasting), crossover, food effect
TXC16-01 (USA)	1	Catalent 3012843, 3003611	1 mg/100 mg 0.5 mg/100 mg	40 subjects fed moderate-fat, 1 and 7 daily doses, parallel group (20 subjects), PK
TXC12-05 (USA)	3	(b) (4) PN0082-02,04,05,06,07,08,10,11,13,15,16,17,18,19,20,22,23,24,25,26,27,30,31,32,33,34,39	1 mg/100 mg 0.5 mg/100 mg 0.5 mg/50 mg 0.25 mg/50 mg	> 280 subjects/dose, single point > 8 hr after dose, dose taken "at bedtime with food" and sample collected "next morning" as part of the long-term safety and efficacy study

4.2.1 Study 459

Title: An open-label, balanced, randomized, single-dose, two-treatment, three-period, three- sequence, crossover, partial-replicate, reference-scaled oral bioequivalence study of combined P 200 mg/E2 2 mg capsules of TherapeuticsMD Inc, Florida and Prometrium® (progesterone) soft gel capsule 200 mg of Catalent Pharma Solutions, St. Petersburg, FL 33716 & Estrace® (estradiol, USP) tablets 2 mg of Teva Pharmaceuticals, USA in normal healthy, adult human post-menopausal female subjects under fed conditions.

Study design: Sixty-six healthy postmenopausal women were housed in the clinical facility for at least 11 hours before dosing until after the 24-hour postdose blood draw in each period. All subjects received the Test product during one period and the Reference products during two periods, with a 14-day washout period between dosing periods. A randomization schedule determined the order in which each

subject received the products. Plasma levels of E2, P, and unconjugated and total E1 were evaluated under fed conditions. For each period, after an overnight-fast of at least 10 hours, a high-fat, high-calorie breakfast was served 30 minutes prior to administration of investigational products.

A total of 24 blood samples (8-mL or 10-mL, depending on time of sample) were collected during each period at specified time points: -1, -0.5, 0, 0.25, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36 and 48 hours. Blood samples were processed to plasma and analyzed for their content of unconjugated E2 and E1 simultaneously using an LC-MS/MS method, unconjugated P, and total E1 using separate LC-MS/MS methods. Analysis was performed at (b) (4).

For subjects completing all three periods, PK parameters for baseline-adjusted and baseline-unadjusted levels of unconjugated E2, E1, and P, and total E1 were determined by performing a non-compartmental analysis. The reference scaled-average bioequivalence (RSABE) method for highly variable drugs was used to compare TX-001HR with the Reference products in cases where the within-subject CV for the reference product was 30% or more. The unscaled average BE method was used to evaluate BE in cases where the within-subject CV was less than 30%.

Results:

Table 17. Reference Scaled Bioequivalence Analysis of Test Product (TX-001HR 2 mg E2/200 mg P) versus Reference Products (Prometrium 200 mg and Estrace 2mg) for Baseline-adjusted Progesterone

PK Parameters	N	Point Estimate %	95% Upper Confidence Bound	Within-subject SD (S_{WR})	Bioequivalent
Applicant's Results					
Cmax (ng/mL)	62	115.9	0.0799	0.3881	No
AUC0-t (ng*h/mL)	62	105.5	-0.1006	0.6305	Yes
Reviewer's Results					
Cmax (ng/mL)	62	115.9	-0.7850	1.179	Yes
AUC0-t (ng*h/mL)	62	105.5	-0.5429	0.956	Yes

Table 18. Reference Scaled Bioequivalence Analysis of Test Product (TX-001HR 2 mg E2/200 mg P) versus Reference Products (Prometrium 200 mg and Estrace 2mg) for Baseline-adjusted Estradiol

PK Parameters	N	Excluded Subjects	Point Estimate %	95% Upper Confidence Bound	Within-subject SD (S_{WR})	Bioequivalent
Applicant's Results						
Cmax (pg/mL)	62	None	88.24	-0.0310	0.4310	Yes
AUC0-t (pg*h/mL)	62		93.14	-0.1360	0.7283	Yes
Reviewer's Results						
Cmax (pg/mL)	62	None	88.24	-0.0402	0.344	Yes
AUC0-t (pg*h/mL)	62		93.14	-0.0914	0.411	Yes

Table 19. Reference Scaled Bioequivalence Analysis of Test Product (TX-001HR 2 mg E2/200 mg P) versus Reference Products (Prometrium 200 mg and Estrace 2mg) for Baseline-adjusted Total Estrone

PK Parameters	N	Point Estimate %	95% Upper Confidence Bound	Within-subject SD (SWR)	Bioequivalent
Applicant's Results					
C _{max} (ng/mL)	62	174.6	0.3566	0.3269	No
Reviewer's Results					
C _{max} (ng/mL)	62	174.6	0.348	0.3351	No

Table 20. Average Bioequivalence Analysis of Test Product (TX-001HR 2 mg E2/200 mg P) versus Reference Products (Prometrium 200 mg and Estrace 2mg) for Baseline-adjusted Total Estrone

PK Parameters	N	Geometric Mean		T/R Ratio %	90% CIs (%)	Within-subject SD (SWR)	Bioequivalent
		Test	Reference				
Applicant's Results							
AUC _{0-t} (ng*h/mL)	62	180.01	171.8	104.8	96.36 – 114.0	0.0453	Yes
Reviewer's Results							
AUC _{0-t} (ng*h/mL)	62	180.3	171.4	105.2	92.49 – 119.70	0.290	Yes

Table 21. Reference Scaled Bioequivalence Analysis of Test Product (TX-001HR 2 mg E2/200 mg P) versus Reference Products (Prometrium 200 mg and Estrace 2mg) for Baseline-adjusted Unconjugated Estrone

PK Parameters	N	Point Estimate %	95% Upper Confidence Bound	Within-subject SD (SWR)	Bioequivalent
Applicant's Results					
AUC _{0-t} (pg*h/mL)	62	88.50	-0.0206	0.3702	Yes

Table 22. Average Bioequivalence Analysis of Test Product (TX-001HR 2 mg E2/200 mg P) versus Reference Products (Prometrium 200 mg and Estrace 2mg) for Baseline-adjusted Unconjugated Estrone

PK Parameters	N	Geometric Mean		T/R Ratio %	90% CIs (%)	Within-subject SD (SWR)	Bioequivalent
		Test	Reference				
Applicant's Results							
C _{max} (pg/mL)	62	375.8	406.9	92.35	86.57 – 98.52	0.2896	Yes
Reviewer's Results							
C _{max} (pg/mL)	62	375.9	406.7	92.42	86.58 – 98.66	0.256	Yes
AUC _{0-t} (pg*h/mL)	62	7287.7	8229.3	88.56	84.05 – 93.31	0.204	Yes

Discussion:

P: The same point estimates of the least squares means of C_{max} and AUC were observed between the Applicant's and the reviewer's analyses (Table 17). Both the Applicant's and the reviewer's RSABE analysis showed negative 95% upper confidence bounds of baseline-adjusted AUC_{0-t}. The Applicant's analysis showed the 95% upper confidence bounds for baseline-adjusted C_{max} > 0 while the reviewer's analysis showed the adjusted C_{max} met BE criteria. The reason for this inconsistency is unknown. The

reviewer concluded that the exposure of P in (b) (4) 2 mg E2/200 mg P was bioequivalent to that of Prometrium 200 mg under fed conditions.

E2: Although differences in intra-subject variability and 95% upper confidence bounds of baseline-adjusted PK parameters were observed between the Applicant's and the reviewer's results (**Table 18**), both analyses showed the same values of point estimates and BE conclusion. The reviewer concluded that the E2 of (b) (4) 2 mg E2/200 mg P was bioequivalent to that of Estrace 2 mg under fed conditions.

Total E1: Both the Applicant's and the reviewer's analyses consistently showed the AUC_{0-t} of baseline-adjusted total E1 met BE criteria but C_{max} did not (**Table 19** and **Table 20**). The C_{max} of baseline-adjusted total E1 for (b) (4) 2 mg E2/200 mg P was 74.6% higher than that for Estrace 2 mg. The reviewer is not concerned with the higher C_{max} of total E1 because the Applicant relied on nonclinical literature data instead of Study 459 to support the safety of E2 and E1 after TX-001HR administration. In addition, the highest proposed clinical dose of TX-001HR is 1 mg E2, which is one half of the reference Estrace product.

Unconjugated E1: Both the Applicant's and the reviewer's analyses (**Table 21** and **Table 22**) showed the unconjugated E1 for (b) (4) 2 mg E2/200 mg P was bioequivalent to that of Estrace 2 mg under fed conditions.

Reviewer's Comments

- *Exclusion of subjects from BE analysis: In the Applicant's BE sensitivity analysis for E2, Subject (b) (6) were excluded because their pre-dose E2 concentration levels were found to be more than 5% of C_{max}. The Applicant also excluded Subject (b) (6) from the BE sensitivity analysis for total E1 because their pre-dose total E1 concentration levels were found to be more than 5% of C_{max}. According to the BE guidance for oral E2 valerate tablets developed by the Office of Generic Drugs³, only subjects with a **baseline-adjusted** pre-dose E2 concentration at time 0 hour greater than 5% of their C_{max} should be excluded from BE analysis. The reviewer checked the baseline-adjusted pre-dose E2 and E1 concentrations at 0 hour for all 62 subjects, none of them was greater than 5% of their C_{max}. Therefore, no subject was excluded from the reviewer's BE analysis.*
- *As shown in the tables below, no obvious or consistent study period effect on the AUC of P, E2, total E1, or unconjugated E1 was observed but a large inter-subject and inter-period variability in the AUC of P was observed.*

Baseline-adjusted progesterone AUC (ng*hr/mL):

	Period 1		Period 2		Period 3	
Formulation	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
Reference	137.2 ± 175.3	40	105.5 ± 121.3	42	114.7 ± 97.3	42
Test	111.0 ± 123.1	22	197.2 ± 239.0	20	53.0 ± 40.3	20

Baseline-adjusted E2 AUC (pg*hr/mL):

	Period 1		Period 2		Period 3	
Formulation	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
Reference	1460.0 ± 893.2	40	1719.7 ± 1026.8	42	1574.2 ± 883.4	42
Test	1360.2 ± 743.9	22	1459.1 ± 842.0	20	1410.8 ± 754.0	20

³ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM238053.pdf>

*Baseline-adjusted total E1 AUC (ng*hr/mL):*

	Period 1		Period 2		Period 3	
Formulation	<i>Mean ± SD</i>	<i>N</i>	<i>Mean ± SD</i>	<i>N</i>	<i>Mean ± SD</i>	<i>N</i>
Reference	174.6 ± 96.5	40	187.7 ± 70.6	42	206.6 ± 106.8	42
Test	178.4 ± 101.9	22	201.3 ± 83.0	20	222.8 ± 99.4	20

*Baseline-adjusted unconjugated E1 AUC (pg*hr/mL):*

	Period 1		Period 2		Period 3	
Formulation	<i>Mean ± SD</i>	<i>N</i>	<i>Mean ± SD</i>	<i>N</i>	<i>Mean ± SD</i>	<i>N</i>
Reference	8808.6 ± 4801.5	39	10300.7 ± 4597.4	42	9215.1 ± 4533.0	41
Test	8253.1 ± 4802.1	22	7712.4 ± 4097.5	20	9006.1 ± 3735.6	20

4.2.2 Study TXC17-02

Title: A Phase 1, open-label, randomized, balanced, single-dose, two-treatment (fed and fasting), crossover, single-center study to assess the effect of food on the bioavailability of TX-001HR (E2 and micronized P capsules) in healthy postmenopausal female subjects

Study design: Twenty-four subjects meeting the eligibility criteria, were enrolled. TX-001HR, 1 mg E2/100 mg P, was dosed under either fasting or fed conditions, in a 1:1 ratio, in the morning of Period 1, Day 1. The assigned meal condition was specified from a randomization table. Regardless of treatment, subjects fasted overnight, for at least 10 hours. For treatment under fasting conditions, a single dose of study drug was administered by the Investigator or a staff along with 240 mL of water within 5 minutes after the 0-hour PK blood draw. Subjects continued fasting until following the 4-hour blood draw when the subjects were served a moderate-fat meal. For treatment under fed conditions, a single dose of study drug was administered by the Investigator or a staff member approximately 30 minutes after beginning a standardized high-fat meal and within 5 minutes after the 0-hour PK blood draw on Day 1. Subjects were then fasted until after the 4-hour blood draw when the subjects were served a moderate-fat meal. Venous blood samples were obtained at the following times with respect to the Day 1 dose to assess E2, P, and E1 concentrations: -60, -30, and 0 minutes (the average of which represents baseline) and then 20, 40, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours after study drug administration. Following the collection of the 72-hour PK sample, the subjects were discharged from the research facility.

Following a minimum 14-day washout period between treatments, the subjects were again admitted to the research facility on Period 2, Day -1 for the alternative meal condition per the randomization schedule. Dosing and sample collection were the same as in Period 1. Following the collection of the 72-hour PK sample, the subjects were discharged from the study.

Results:

Applicant's Analyses:

Table 23. Applicant's Analysis of the effect of Food on the Pharmacokinetics of Baseline-Adjusted Estradiol (N = 23, Subject ^{(b) (6)} excluded)

Parameter	Adjusted Geometric Mean ^a		Adjusted GMR Fed/Fasting (%)	90% CI for Adjusted GMR (%)	Intra-Subject Variability ^b
	Fed	Fasting			
AUC _{0-t} (pg·h/mL)	959.32	916.99	104.6	(95.5, 114.6)	18.1
AUC _{0-∞} (pg·h/mL)	1144.57	1123.41	101.9	(90.8, 114.3)	20.7
C _{max} (pg/mL)	27.71	60.37	45.9	(36.6, 57.5)	46.7

Table 24. Applicant's Analysis of the effect of Food on the Pharmacokinetics of Baseline-Adjusted Progesterone (N = 23, Subject ^{(b) (6)} excluded)

Parameter	Adjusted Geometric Mean ^a		Adjusted GMR Fed/Fasting (%)	90% CI for Adjusted GMR (%)	Intra-Subject Variability ^b
	Fed	Fasting			
AUC _{0-t} (ng·h/mL)	6.45	3.54	182.2	(131.7, 251.9)	70.9
AUC _{0-∞} (ng·h/mL)	6.72	5.26	127.8	(49.6, 329.6)	57.7
C _{max} (ng/mL)	2.50	0.92	270.9	(188.2, 389.9)	82.0

Table 25. Applicant's Analysis of the effect of Food on the Pharmacokinetics of Baseline-Adjusted Unconjugated Estrone (N = 23, Subject ^{(b) (6)} excluded)

Parameter	Adjusted Geometric Mean ^a		Adjusted GMR Fed/Fasting (%)	90% CI for Adjusted GMR (%)	Intra-Subject Variability ^b
	Fed	Fasting			
AUC _{0-t} (pg·h/mL)	3320.51	2983.92	111.3	(102.6, 120.7)	16.0
AUC _{0-∞} (pg·h/mL)	3691.06	3227.13	114.4	(106.2, 123.2)	12.8
C _{max} (pg/mL)	135.25	143.06	94.5	(86.8, 103.0)	17.0

The Reviewer's Analyses:

Table 26. The Reviewer's Analysis of the effect of Food on the Pharmacokinetics of Baseline-Adjusted Estradiol (N = 23, Subject ^{(b) (6)} excluded)

Parameters	Geometric Mean		Geometric Mean Ratio (GMR) Fed/Fasting (%)	90% CI for GMR (%)
	Fed	Fasting		
AUC _{0-t} (pg·h/mL)	957.91	913.51	104.86	95.76 – 114.82
AUC _{inf} (pg·h/mL)	1185.25	1158.34	102.32	91.43 – 114.52
C _{max} (pg/mL)	27.65	60.23	45.90	36.85 – 57.18
T _{max} (h)	9.86	1.21	814.81	485.79 – 1366.66

Table 27. The Reviewer's Analysis of the effect of Food on the Pharmacokinetics of Baseline-Adjusted Estradiol (N = 24, No subject excluded)

Parameters	Geometric Mean		Geometric Mean Ratio (GMR) Fed/Fasting (%)	90% CI for GMR (%)
	Fed	Fasting		
AUC _{0-t} (pg·h/mL)	968.36	871.58	111.10	97.39 – 126.75

AUCinf (pg*h/mL)	1185.25	1158.34	102.32	91.43 – 114.52
Cmax (pg/mL)	27.64	61.92	44.64	36.00 – 55.37
Tmax (h)	10.23	1.15	892.25	531.45 – 1497.97

Table 28. The Reviewer's Analysis of the effect of Food on the Pharmacokinetics of Baseline-Adjusted Progesterone (N = 24, No subject excluded)

Parameters	Geometric Mean		Geometric Mean Ratio (GMR) Fed/Fasting (%)	90% CI for GMR (%)
	Fed	Fasting		
AUC0-t (ng*h/mL)	6.88	3.86	178.51	129.81 – 245.49
AUCinf (ng*h/mL)	6.98	5.05	138.39	80.68 – 237.38
Cmax (ng/mL)	2.63	1.00	261.86	183.50 – 373.70
Tmax (h)	2.25	2.02	111.24	79.18 – 156.28

Table 29. The Reviewer's Analysis of the effect of Food on the Pharmacokinetics of Baseline-Adjusted Unconjugated Estrone (N = 24, No subject excluded)

Parameters	Geometric Mean		Geometric Mean Ratio (GMR) Fed/Fasting (%)	90% CI for GMR (%)
	Fed	Fasting		
AUC0-t (pg*h/mL)	3297.12	2934.42	112.36	103.78 – 121.65
AUCinf (pg*h/mL)	3654.10	3193.76	114.41	105.81 – 123.71
Cmax (pg/mL)	131.93	139.61	94.50	87.03 – 102.60
Tmax (h)	6.85	6.51	105.22	88.17 – 125.58

Discussion:

Subject (b) (6) was found to have baseline levels of E2 (108 to 115 pg/mL) higher than the upper limit of the range generally accepted for postmenopausal women in Period 2. The Applicant excluded Subject (b) (6) from food effect analyses for E2, E1 and P. High baseline levels of E2 is not expected to alter the food effect results of P; Therefore, Subject (b) (6) was included in the reviewer's analysis for P.

E2: Both the Applicant's and the reviewer's analyses showed that food intake did not affect the AUC of E2 but reduced Cmax of E2 by 54% (Table 23 and Table 26.). Food intake extended the Tmax of E2 from 1 hour to 10 hours. The inclusion of Subject (b) (6) did not affect the conclusion (Table 27).

P: Subject (b) (6) was excluded from the Applicant's analysis for P but included in the reviewer's analysis. The reviewer's analysis showed that a high fat meal increased C_{max} and AUC_{0-t} of P by 162% and 79% respectively (Table 28), which were slightly lower than the Applicant's results (C_{max} 171% and AUC_{0-t} 82%).

Unconjugated E1: Both the Applicant's and the reviewer's analyses consistently showed that a high fat meal did not affect the PK of unconjugated E1.

Reviewer's comments:

- Among 24 subjects enrolled in Study TXC17-02, only five subjects had detectable pre-dose plasma P, indicating the 14-day wash out period was adequate to eliminate exogenous P. Among the five subjects, none of them had baseline-adjusted pre-dose concentrations of P at time 0 hour greater than 5% of their C_{max}. Except Subject (b) (6) no other subject had baseline-adjusted pre-dose concentrations of E2 at time 0 hour greater than 5% of her C_{max}.

- As shown in **Table 30** below, no obvious or consistent study period effect on the AUC of E2 or unconjugated E1 was observed. For subjects with a fed/fasting study sequence, it is unanticipated that the AUC of P measured under fasting conditions was higher than that measured under fed conditions, which was likely caused by the large inter-subject variability in the AUC of P (**Table 31**).

Table 30. Baseline-adjusted AUC (Study TXC 17-02)

Compounds	Study Sequence	Baseline-Corrected AUC _{0-t} (pg*hr/mL)			
		Period 1		Period 2	
		Mean ± SD	N	Mean ± SD	N
E2	Fasting/Fed	916.97 ± 345.27	12	997.30 ± 412.20	12
	Fed/Fasting*	1134.18 ± 480.39	11	1094.73 ± 422.87	11
E1	Fasting/Fed	2967.38 ± 1263.15	12	3416.27 ± 1428.17	12
	Fed/Fasting	3802.71 ± 1636.05	12	3519.88 ± 1474.83	12
P	Fasting/Fed	2632.33 ± 1444.32	12	5776.32 ± 2461.24	12
	Fed/Fasting	13515.08 ± 14327.92	12	14513.15 ± 16037.52	12

*Subject ^{(b) (6)} is excluded.

Table 31. Baseline-adjusted Individual AUC of Progesterone Measured under Fasting conditions (Study TXC 17-02)

Fasting, Period 1 (ng*hr/mL)		Fasting, Period 2 (ng*hr/mL)	
TXC17-02-01- ^{(b) (6)}	2.380333	TXC17-02-01- ^{(b) (6)}	26.64445
TXC17-02-01- ^{(b) (6)}	1.79425	TXC17-02-01- ^{(b) (6)}	0.996417
TXC17-02-01- ^{(b) (6)}	0.729	TXC17-02-01- ^{(b) (6)}	12.65162
TXC17-02-01- ^{(b) (6)}	1.6195	TXC17-02-01- ^{(b) (6)}	1.974042
TXC17-02-01- ^{(b) (6)}	4.211833	TXC17-02-01- ^{(b) (6)}	41.63294
TXC17-02-01- ^{(b) (6)}	2.022417	TXC17-02-01- ^{(b) (6)}	4.850333
TXC17-02-01- ^{(b) (6)}	1.702667	TXC17-02-01- ^{(b) (6)}	42.301
TXC17-02-01- ^{(b) (6)}	2.053417	TXC17-02-01- ^{(b) (6)}	29.23463
TXC17-02-01- ^{(b) (6)}	2.776808	TXC17-02-01- ^{(b) (6)}	1.925583
TXC17-02-01- ^{(b) (6)}	4.439417	TXC17-02-01- ^{(b) (6)}	3.088917
TXC17-02-01- ^{(b) (6)}	2.083083	TXC17-02-01- ^{(b) (6)}	0.649
TXC17-02-01- ^{(b) (6)}	5.775267	TXC17-02-01- ^{(b) (6)}	8.208875

- This reviewer recommends that the geometric ratio of AUC_{0-t} represent food effect because a significant fraction of subjects did not have AUC_{0-inf} values of P. After baseline adjustment, some subjects' plasma P concentration at late time points (e.g. 48 and 72 hours) were negative. The values were set as zero. Therefore, some subjects did not have an AUC_{0-inf} value. For example, under fed and fasted conditions, only 13 and 8 subjects had AUC_{0-inf} values, respectively. In contrast, under both fed and fasted conditions, all the 23 subjects had AUC_{0-t} values.

4.3 Single- and Multiple-Dose PK Study

4.3.1 Study TXC16-01

Title: A Phase 1, open-label, parallel-group, randomized, single-center study to assess the pharmacokinetics of two dose levels of TX-001HR (E2 and micronized P capsules) in healthy postmenopausal female subjects after one and seven daily doses under fed conditions

Study design: Forty healthy postmenopausal women received seven-daily doses of TX-001HR of either 1 mg E2/100 P or 0.5 mg E2/100 P in a 1:1 ratio per the randomization schedule. Enrolled subjects were housed in the clinical facility for at least 43 hours before dosing until after the 24-hour postdose blood draw following the first dose. Subjects returned to the research facility on Day 6 at the time of dosing for an out-patient visit and then again on Day 7 approximately 4 hours before dosing and remained in the clinic until the collection of the 48-hour time point. While in the clinic, on Days 1, 2, 6, and 7, dosing took place in the evening, 30 minutes following a standardized, moderate-fat meal. On Days 3 to 5, subjects were instructed to take the dose 30 minutes following a moderate-fat meal.

At total of 15 venous blood samples were collected on Day 1 at the following times: -60, -30, and 0 minutes (the average of which represents baseline) and then 20, 40, 60, and 90 minutes and 2, 3, 4, 6, 8, 12, 18, and 24 hours after dosing. A single blood sample was collected immediately predose on Day 6. A total of 14 venous blood samples were collected on Day 7 at the following times: 0, 20, 40, 60, and 90 minutes and 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours after dosing. Blood samples were processed to serum and analyzed for their content of E2 and E1 simultaneously using a validated GC-MS/MS method and P using separate validated LC-MS/MS method. Analysis was performed at (b) (4).

For each analyte, the baseline-adjusted and baseline-unadjusted PK parameters including C_{max}, t_{max}, and AUC_τ, after the first dose and C_{avg}, C_{max}, t_{max}, λ_z, t_{1/2}, AUC_τ and C_{min} after the seventh dose were calculated and summarized descriptively.

Results:

Table 32. Summary of Single and Multi-dose PK Parameters – Estradiol (Study TXC16-01)

Day	Pharmacokinetic Parameter	Baseline-adjusted				Unadjusted			
		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
1	AUC _τ (pg·h/mL)	20	400.5 (157.9)	20	167.8 (100.0)	20	542.9 (250.0)	20	558.6 (695.3)
	C _{max} (pg/mL)	20	31.54 (29.70)	20	13.52 (9.320)	20	37.55 (35.47)	20	33.94 (48.57)
	t _{max} (h)	20	10.00 (6.786)	20	11.08 (7.197)	20	10.00 (6.786)	20	11.08 (7.197)
7	AUC _τ (pg·h/mL)	20	772.4 (384.1)	17	386.8 (356.6)	20	910.8 (338.8)	17	698.5 (566.9)
	C _{avg} (pg/mL)	19	33.99 (14.53)	17	16.64 (14.50)	20	38.07 (14.17)	17	29.20 (23.70)

	C_{max} (pg/mL)	20	42.27 (18.60)	17	23.95 (16.86)	20	48.23 (15.84)	17	37.19 (28.74)
	t_{max} (h)	19	4.93 (4.966)	17	5.90 (4.442)	20	5.59 (5.648)	17	5.90 (4.442)
	t_½ (h)^a	19	26.47 (14.61)	11	28.01 (9.987) ^b	19	21.73 (10.26)	13	27.95 (36.31)

^a Effective t_½ (h) = 24•ln(2)/ ln(accumulation ratio/(accumulation ratio-1)) which was derived for subjects with accumulation ratio >1.

^b Results exclude Subjects (b) (6)

Table 33. Summary of Single and Multi-dose PK Parameters – Progesterone (Study TXC16-01)

Day	Pharmacokinetic Parameter	Baseline-adjusted				Unadjusted			
		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
1	AUC_τ (ng·h/mL)	20	14.12 (9.928)	20	10.06 (9.409)	20	14.25 (9.900)	20	10.63 (9.466)
	C_{max} (ng/mL)	20	6.48 (6.206)	20	3.73 (3.211)	20	6.49 (6.205)	20	3.77 (3.216)
	t_{max} (h)	20	2.23 (1.468)	20	2.52 (1.944)	20	2.23 (1.468)	20	2.52 (1.944)
7	AUC_τ (ng·h/mL)	20	18.05 (15.58)	17	12.19 (11.01)	20	18.19 (15.50)	17	12.49 (10.89)
	C_{avg} (ng/mL)	20	0.76 (0.645)	17	0.55 (0.446)	20	0.77 (0.642)	17	0.53 (0.448)
	C_{max} (ng/mL)	20	11.31 (23.10)	17	4.40 (5.720)	20	11.32 (23.10)	17	4.41 (5.720)
	t_{max} (h)	20	2.64 (1.505)	17	2.89 (2.285)	20	2.64 (1.505)	17	2.89 (2.285)
	t_½ (h)	18	9.98 (2.565)	13	8.77 (2.776)	18	10.23 (2.509)	14	9.32 (1.826)

Table 34. Summary of Single and Multi-dose PK Parameters – Estrone (Study TXC16-01)

Day	Pharmacokinetic Parameter	Baseline-adjusted				Unadjusted			
		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P		1 mg E2/ 100 mg P		0.5 mg E2/ 100 mg P	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
1	AUC_τ (pg·h/mL)	20	2410 (867.7)	20	1069 (457.1)	20	2860 (883.2)	20	1754 (835.7)
	C_{max} (pg/mL)	20	152.5 (65.68)	20	67.15 (28.07)	20	171.4 (67.26)	20	99.19 (54.52)
	t_{max} (h)	20	11.07 (5.802)	20	11.80 (5.831)	20	11.07 (5.802)	20	11.80 (5.831)
7	AUC_τ (pg·h/mL)	20	4594 (2138)	17	1981 (976.0)	20	5046 (2155)	17	2538 (1170)
	C_{avg} (pg/mL)	20	192.1 (89.43)	17	82.81 (40.80)	20	210.9 (90.14)	17	106.1 (48.90)
	C_{max} (pg/mL)	20	238.5 (100.4)	17	108.0 (48.58)	20	257.4 (100.6)	17	131.3 (56.24)
	t_{max} (h)	20	5.45 (3.466)	17	8.48 (4.866)	20	5.45 (3.466)	17	8.48 (4.866)
	t_½ (h)^a	19	22.37 (7.638)	17	20.46 (5.612)	19	19.72 (6.609)	17	15.78 (4.634)

Table 35. Trough Levels of Estradiol, Estrone, and Progesterone at Steady State – Baseline-Adjusted (Study TXC16-01)

	Mean Estradiol (SD) (pg/mL)			Mean Estrone (SD) (pg/mL)			Mean Progesterone (SD) (ng/mL)		
	Day 6 Predose	Day 7 Predose	Day 7 24 h Postdose	Day 6 Predose	Day 7 Predose	Day 7 24 h Postdose	Day 6 Predose	Day 7 Predose	Day 7 24 h Postdose
1 mg E2/ 100 mg P	22.85 (12.84)	28.63 (18.14)	24.44 (14.35)	152.6 (79.09)	154.9 (81.42)	157.2 (84.38)	0.14 (0.134)	0.17 (0.154)	0.14 (0.112)
0.5 mg E2/ 100 mg P	10.60 (7.882)	11.41 (9.562)	10.98 (9.940)	65.05 (31.35)	64.75 (32.93)	65.45 (39.17)	0.15 (0.138)	0.15 (0.140)	0.10 (0.079)

Table 36. PK Parameters of Estradiol (Mean ± SD) Following Single and Multiple Doses of TX-001HR - Baseline-Adjusted (Study TXC16-01).

	Dose	Mean Estradiol (SD)		
		AUC _τ (pg·h/mL)	C _{max} (pg/mL)	C _{avg} (pg/mL)
Day 1	1 mg E2/100 mg P	400.5 (157.9)	31.54 (29.70)	16.75 (6.603)
	0.5 mg E2/100 mg P	167.8 (100.0)	13.52 (9.320)	7.49 (3.776)
Day 7	1 mg E2/100 mg P	772.4 (384.1)	42.27 (18.60)	33.99 (14.53)
	0.5 mg E2/100 mg P	386.8 (356.6)	23.95 (16.86)	16.64 (14.50)

Reviewer's comments:

- Comparable C_{trough} levels of E2, E1 and P were observed on Day 6, Day 7 and Day 8 (24 hours post Day 7 dosing) for both doses (**Table 35**), indicating a steady-state PK was achieved within 7 days.
- As shown in **Table 36**, baseline adjusted E2 showed a dose-dependent increase in PK (baseline adjusted AUC_{0-t} and C_{max}) on Day 1 and Day 7. On both Day 1 and Day 7, baseline adjusted E1 showed a more than proportionality increase in AUC_{0-t} and C_{max} when the dose of E2 was increased from 0.5 mg to 1 mg (**Table 34**).
- On both Day 1 and Day 7, the AUC of baseline adjusted P increased by 40-50% and baseline adjusted C_{max} doubled when the dose of E2 was increased from 0.5 mg to 1 mg. The differences in the PK of P between two dose regimens may be explained by the large inter-subject variability in PK.

4.4 Cross-Study Pharmacokinetic Comparison

As shown in **Table 16**, by using (b) (4) 2 mg E2/200 mg P as test product and Estrace 2mg/Prometrium 200 mg as reference products, the Applicant conducted one comparative fasting BA studies (Study 351) and two comparative fed BA studies (Study 352 and Study 459). The reviewer conducted a cross-study comparisons of fed and fasting PK of baseline adjusted P (Study 351, 352, 459, and TXC17-02) and the PK data are summarized in **Table 37**. A large variability in the C_{max} and AUC_{0-t} of P administered under fed conditions among Study 459 and Study TXC17-02 was observed. For example, the geometric mean AUC_{0-t} of P (63.37 ng·h/mL) observed in Study 459 was 9.2-fold higher than that observed in Study TXC17-02 (6.88 ng·h/mL). After dose normalization (Study 459, 200 mg and Study TXC17-02

100 mg), there is still a 4.6-fold difference in the AUC of P between the two studies. As a comparison, the geometric mean AUC_{0-t} of Prometrium 200 mg administered under fed conditions showed a 3.3-fold difference (ANDA 200456, 19.90 ng*h/mL vs. ANDA 200900, 66.34 ng*h/mL).

Table 37. Summarized Pharmacokinetics and Food Effect of Progesterone in Current NDA and FDA-Approved ANDAs.

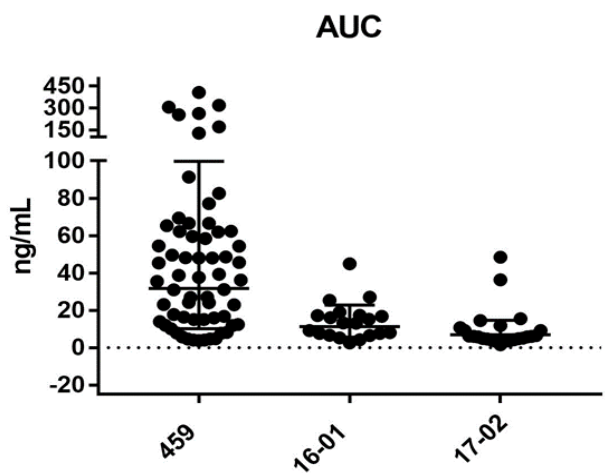
NDA/ ANDA	Bioanalytic al Site	Products (Study No.)	Fasting / Fed	Geometric Mean C _{max} (ng/mL)	Geometric Mean AUC _{0-t} (ng*h/mL)	Fed/Fasting Geometric Ratio (fold)	
						C _{max}	AUC _{0-t}
NDA 210132	(b) (4)	(b) (4) 2 mg E2/200 mg P (351)	Fasting	2.28	8.36	N.A.	N.A.
		Prometrium 200 mg (351)		2.96	10.89	N.A.	N.A.
		(b) (4) 2 mg E2/200 mg P (352)	Fed	47.04	107.57	20.6*#	12.9*#
		Prometrium 200 mg (352)		42.99	97.81	14.5*#	8.98*#
		(b) (4) 2mg E2/200 mg P (459)	Fed	35.11	63.37	15.4*#	7.58*#
		Prometrium 200 mg (459)		23.26	60.01	10.2*#	5.51*#
		Catalent 1mg E2/100 mg P (17-02)	Fasting	1.00	3.86	2.62	1.79
Fed		2.63	6.88				
ANDA 200456		Test 200 mg	Fasting	2.11	7.79	5.92*	2.58*
			Fed	12.50	20.08		
		Prometrium 200 mg	Fasting	2.00	7.83	6.09*	2.54*
			Fed	12.18	19.90		
ANDA 200900		Test 200 mg	Fasting	3.56	12.14	3.64*	3.78*
			Fed	12.97	45.90		
	Prometrium 200 mg	Fasting	3.59	12.98	7.20*	5.11*	
		Fed	25.85	66.34			
ANDA 202121	Test 200 mg	Fasting	3.57	13.96	5.05*	3.05*	
		Fed	18.01	42.56			
	Prometrium 200 mg	Fasting	3.67	13.88	5.05*	3.22*	
		Fed	18.54	44.66			
ANDA 205229	Test 200 mg	Fasting	2.51	9.54	9.30*	4.37*	
		Fed	23.32	41.71			
	Prometrium 200 mg	Fasting	2.12	8.58	9.99*	4.35*	
		Fed	21.14	37.45			
ANDA 207724	Test 200 mg	Fasting	1.81	6.83	10.5*	5.14*	
		Fed	19.07	19.13			
	Prometrium 200 mg	Fasting	1.70	6.86	11.3*	5.10*	
		Fed	35.14	35.01			
ANDA 208801	Test 200 mg	Fasting	3.47	15.31	8.33*	4.22*	
		Fed	28.92	64.68			
	Prometrium 200 mg	Fasting	3.44	15.97	8.58*	4.14*	
		Fed	29.53	66.19			

*Cross-study comparison; # Compare to fasting PK data from Study 351

On July 30, 2018, the Agency sent an Information Request to the Applicant and request an explanation of the large cross-study variability in the Cmax and AUC0-t of P administered under fed conditions among Study 459, Study TXC16-01, and Study TXC17-02. In its written response dated August 6, 2018, the Applicant explained that cross-study comparison is difficult given:

- The fed component of all three studies differed. Study 459 was performed in India where the type of fat utilized in the high-fat meal differed from the high-fat meal in Study 17-02 that was conducted in the US. Women in Study 459 received a high-fat meal that included primarily vegetable oil (medium-chain, unsaturated fatty acids) whereas Study 17-02 provided a high-fat meal that included primarily butter (long-chain, saturated fatty acids). Women in Study 16-01 received a moderate-fat meal.
- Sample sizes and demographics were different. Women in Study 459 were younger, thinner, and had earlier menopause than women in the US studies.
- Dosages studied were different (1 mg E2/100 mg P vs. 2 mg E2/200 mg P).
- Variability was higher in Study 459 compared to Study Txc17-02 and Study TXC16-01 (**Figure 6**).
- The bioanalytical assays utilized in the three studies were different. Although all three studies used LC-MS/MS, the methods used in Study 459 differed from those used in Studies 16-01 and 17-02 in the extraction process and the internal standard used. In addition, the samples collected in Study 16-01 were serum while Studies 459 and 17-02 collected plasma.
- Plasma P Cmax and AUC0-t obtained in Study 459 for both TX-001HR and Prometrium were higher than anticipated.

Figure 6. Normalized Individual AUC0-t Data for Women in Studies 459, 16-01, and 17-02



Reviewer's point-by point comments on the Applicant's responses:

- We acknowledge that the 27 gram vegetable oil in Study 459's meal may increase the solubility and oral absorption of P in gastrointestinal tract. However, the ANDA studies (ANDA 200900, ANDA 202121 and ANDA 205229) conducted in Canada showed that the geometric mean of AUC of Prometrium 200 mg under fed conditions was 66.34 ng*h/mL, 44.66 ng*h/mL and 37.45 ng*h/mL, respectively, which are still 4.8-fold, 3.2-fold and 2.7-fold higher than that observed in Study TXC17-02 ($6.88 \text{ ng*h/mL} \times 2 = 13.76 \text{ ng*h/mL}$) even after dose normalization. Butter rather than vegetable oil was included in the high fat meal in the two ANDA fed studies.*

Therefore, the differences in meal components or demographics do not completely explain the large cross-study variability.

- b) Similar demographic characteristics and sample size were found among Study TXC17-02 and two fed studies in ANDA 202121 and ANDA 205229. The differences in demographics and sample size cannot completely explain the large cross-study variability.*
- c) Considering the low solubility of P in gastrointestinal tract, we acknowledge that a more significant positive food effect is anticipated for 200 mg P dose compared to 100 mg dose. However, the 4.6-fold difference (dose normalized) in the AUC of P between Study 459 and Study TXC17-02 under fed conditions is more than our anticipation.*
- d) We acknowledge in a higher variability in individual AUC and Cmax of Study 459 compared to Study TXC17-02 and Study TXC16-01. It is unknown whether the large variability was caused by the differences in clinical study design or the formulation quality of (b) (4) 2 mg E2/200 mg P and Catalent 1 mg E2/100 mg P.*
- e) The differences in sample extraction process and internal standards are not expected to cause a 4.6-fold difference in the exposure to P.*
- f) We acknowledge the Cmax and AUC0-t of P obtained in Study 459 for both TX-001HR and Prometrium were higher than anticipated.*

Overall, even though each differences would not account for the up to 4.6-fold differences in exposure there were no reason known that would bring into question the reliability of each set of data from individual studies. P in general also appears to have relatively high inter-subject variability that may partially contribute to the observed differences.

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/

PENG ZOU
09/06/2018

DOANH C TRAN
09/07/2018