

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208564Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 208564/SN 0034

Drug Name: Imvexxy™ (Estradiol Vaginal Insert, 4mcg and 10 mcg)

Indications: Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

Applicant: TherapeuticsMD, Inc.

Date(s): Submission Date: 11/29/2017
PDUFA Due Date: 5/29/2018

Review Priority: Class 2 Resubmission

Biometrics Division: Division of Biometrics III

Statistical Reviewer: Kate Li Dwyer, Ph.D.

Concurring Reviewers: Mahboob Sobhan, Ph.D.

Medical Division: Division of Bone, Reproductive and Urologic Drug Products

Clinical Team: Theresa H. Van Der Vlugt, M.D., Clinical Reviewer
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Project Manager: Kimberly Shiley

Keywords: NDA review, clinical studies

The Applicant, TherapeuticsMD, Inc., submitted original NDA on July 7, 2016. This is a Class 2 resubmission to address the deficiencies cited in the Complete Response Letter dated 05 May 2017. In this resubmission, the Applicant revised the label to include efficacy data for (b) (4) doses of Invexxy™ (Estradiol Vaginal (b) (4), 4 mcg and 10 mcg) for the treatment of moderate to severe dyspareunia, a symptom of postmenopausal vulvar and vaginal atrophy (VVA) in women with VVA diagnosed at baseline.

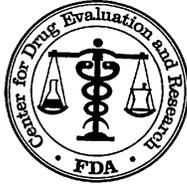
This reviewer has verified the clinical information included in the revised label and no further statistical review is necessary.

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/s/

KATE L DWYER
03/01/2018

MAHBOOB SOBHAN
03/01/2018



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 208564/(b) (4)

Drug Name: TX-004HR (Estradiol Vaginal (b) (4) Capsules, 4, 10 (b) (4) µg)

Indication(s): Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

Applicant: TherapeuticsMD, Inc.

Date(s): Submitted: 7/7/2016
PDUFA: 5/7/2017

Review Priority: Standard

Biometrics Division: Division of Biometrics III

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Concurring Reviewer: Mahboob Sobhan, Ph.D.

Medical Division: Division of Bone, Reproductive and Urologic Products (DBRUP)

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Keywords: NDA review, analysis of covariance, mixed model for repeated measures (MMRM), clinical study

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1 EXECUTIVE SUMMARY

The Applicant, TherapeuticsMD, Inc., is seeking approval of estradiol vaginal (b) (4) capsules (4 µg, 10 µg, (b) (4) code TX-004HR, for the treatment of moderate to severe dyspareunia, a symptom of postmenopausal vulvar and vaginal atrophy (VVA) in women with VVA diagnosed at baseline.

To support the above indication, safety and efficacy data from one phase 3 study (TXV14-01, hereafter referred as Study 14-01) was submitted. This review evaluates from a statistical perspective the adequacy of the submitted efficacy data supporting this claim.

Study 14-01 was a randomized, double-blind, placebo-controlled, multi-center study assessing the efficacy and safety of TX-004HR in treating postmenopausal women with objective findings of VVA who noted dyspareunia as their most bothersome symptom related to their VVA. Postmenopausal subjects who met the study entry criteria were randomized in a 1:1:1:1 ratio to receive TX-004HR 4 µg, TX-004HR 10 µg, TX-004HR 25 µg, or matching placebo. Each subject was to participate for up to 12 weeks followed by a 2-week post-treatment follow-up by phone.

There were no statistical issues noted in this submission. This reviewer confirmed that (b) (4) doses of TX-004HR statistically significantly improved dyspareunia compared to placebo with respect to all four co-primary endpoints using pre-specified statistical analysis methods. Subgroup analyses by race and ethnicity also showed that TX-004HR appear to be more efficacious in Whites/Non-Hispanics compared to Non-whites/Hispanics.

From a statistical perspective, data from study 14-01 provided statistical evidence in support of TX-004HR Vaginal (b) (4) Capsules, in the treatment of treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of VVA due to menopause.

2 INTRODUCTION

2.1 Overview

The Applicant, TherapeuticsMD, Inc., is seeking approval of estradiol vaginal (b) (4) capsule (TX-004HR) for the treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause. The proposed doses are 4 µg, 10 µg, (b) (4) µg administered intravaginally once daily at approximately the same hour.

According to the Applicant, TherapeuticsMD has developed a new muco-adhesive (b) (4) vaginal formulation containing (b) (4) estradiol, code name of TX-004HR, for the treatment of postmenopausal VVA. The new formulation was designed for easy insertion, with no need for an applicator, and formulated to dissolve completely, (b) (4) following administration. The goal of TX-004HR is to provide an (b) (4), low systemic estrogen levels, and improved convenience from existing regimens.

To demonstrate the safety and efficacy of TX-004HR for the treatment of moderate to severe dyspareunia, the Applicant has submitted one phase 3 clinical study: TXV14-01. Table 1 presents a brief summary of the study addressed in this review.

Table 1 – List of all studies included in analysis

Study	Phase and Design*	Treatments	Sample Size [#]	Study Population
TXV14-01	Phase 3, MC, R, DB, PG (12 weeks with 2 weeks follow-up)	TX-004HR 4 µg	191 (186)	Postmenopausal women between 40 and 75 years of age, having ≤5% of superficial cells on vaginal smear, a vaginal pH above 5 and who self-identified moderate to dyspareunia as their MBS.
		TX-004HR 10 µg	191 (188)	
		TX-004HR 25 µg	190 (186)	
		Placebo	192 (187)	

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled

[#] ITT (mITT)

Source: Reviewer’s summary based on study reports.

2.2 Data Sources

The study data, reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items are located in the Electronic Document Room at <\\CDSESUB1\evsprod\NDA208564> under the submissions dated 7/7/2016 and 8/31/2016.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were several data and analysis quality issues noted by the reviewer in the original submission dated 07/07/2016. Two Information Requests were sent before the filling meeting to ask the Applicant to provide additional raw datasets to duplicate Adam datasets, re-conduct the categorical data analysis without deleting subjects with missing data and additional sensitivity analysis for co-primary endpoints. The Applicant addressed both IRs in a timely fashion and submitted the related information on August 31, 2016.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Study 14-01 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study comparing three doses of TX-004HR with placebo for the treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause. Postmenopausal subjects who met study entry criteria were randomized in a 1:1:1:1 ratio to receive TX-004HR 4 µg, TX-004HR 10 µg, TX-004HR 25 µg, or placebo.

The study population consisted of postmenopausal women, 40 to 75 years of age, with a diagnosis of VVA at baseline, assessed by the percentage of superficial cells in the vaginal smear, vaginal pH, and self-reported MBS of moderate to severe dyspareunia. Approximately 700 subjects were planned for randomization into the study across an estimated 100 investigative sites in the United States and Canada. A total of 764 subjects were randomized.

The primary objective of this study was to assess the safety and efficacy of 3 doses of TX-004HR (4 µg, 10 µg and 25 µg) compared with placebo at week 12.

3.2.2 Statistical Methodologies

3.2.2.1 Analysis Populations

All subjects who were randomly assigned and had at least one dose of investigational product formed the intent-to-treat (ITT) population.

The modified intent to treat (MITT) population was defined as all ITT subjects who received the treatment to which they were randomized, had baseline values for all co-primary variables, and had at least one post-baseline value for any of following four co-primary variables at any visit:

- Parabasal cells
- Superficial cells
- Vaginal pH
- MBS of dyspareunia

Vaginal smears, vaginal pH or Symptoms questionnaire taken within 7 days after the last dose of test article was considered on-therapy. Data collected more than 7 days after the last dose was considered post-therapy and was excluded from the analysis.

The efficacy evaluable (EE) population was defined as: 1) met MITT population criteria; 2) completed the study (defined as having completed the study through 12 weeks per the end of study [EOS] eCRF); 3) $\geq 80\%$ overall study drug compliant based on diary; 4) baseline superficial cells $\leq 5\%$; 5) baseline vaginal pH > 5.0 ; 6) moderate to severe dyspareunia identified as MBS at baseline; 7) no concomitant prohibited medications that could impact the assessment

of the primary endpoints taken during the treatment period (list provided by Sponsor prior to unblinding); 8) must have taken the correct study drug as randomized; 9) have no other major protocol deviations (list provided by Sponsor prior to unblinding).

The primary efficacy analyses were conducted on the MITT subjects with supportive efficacy analyses conducted on the EE population.

A subject must have had completed all visits, up to and including Visit 6 (Week 12), to be considered as having completed the study.

3.2.2.2 Efficacy Endpoints

Four co-primary efficacy endpoints were defined as:

- Change from Baseline at Week 12 in the percentage of vaginal superficial cells (by vaginal cytologic smear) compared to placebo
- Change from Baseline at Week 12 in the percentage of vaginal parabasal cells (by vaginal cytologic smear) compared to placebo
- Change from Baseline to Week 12 on the severity of the MBS of dyspareunia (vaginal pain associated with sexual activity) associated with VVA as compared to placebo
- Change in the vaginal pH from Baseline to Week 12 as compared to placebo

The secondary endpoints were:

- Change from Baseline to Weeks 2, 6 and 8 in the percentage of vaginal superficial cells (by vaginal cytologic smear) compared to placebo
- Change from Baseline to Weeks 2, 6 and 8 in the percentage of vaginal parabasal cells (by vaginal cytologic smear) compared to placebo
- Change from Baseline to Weeks 2, 6 and 8 in vaginal pH as compared to placebo
- Change from Baseline to Weeks 2, 6 and 8 on the severity of the MBS of dyspareunia (vaginal pain associated with sexual activity) associated with VVA as compared to placebo
- Change from Baseline to Weeks 2, 6, 8 and 12 on the severity of vaginal dryness and vaginal and/or vulvar itching or irritation associated with VVA as compared to placebo
- Assessment of standard PK parameters as defined in the SAP for serum estradiol, estrone and estrone conjugates at Screening Visit 1A, Days 1, 14 and 84 of treatment in a subset of subjects (PK substudy) utilizing baseline corrected and uncorrected values [as outlined in the PK Statistical Analysis Plan (PK Section of the SAP)]
- Change in visual evaluation score of the vaginal mucosa from Baseline to Weeks 2, 6, 8 and 12 compared to placebo
- Change from Baseline in the FSFI at Week 12 compared to placebo

The VVA Symptom Self-Assessment Questionnaire is an instrument for subjects to self-assess their symptoms of vulvar and/or vaginal atrophy, including dyspareunia (vaginal pain associated with sexual activity), vaginal dryness, vaginal and/or vulvar itching or irritation. At Screening Visit 1A subjects were asked to complete the Questionnaire and identify their MBS which determined initial eligibility for the study. To be eligible to enter the study, the subjects must have moderate or severe dyspareunia as MBS. The severity of vaginal atrophy symptoms

recorded at sexual activity as follows: none (0), mild (1), moderate (2) or severe (3). This specific symptom of dyspareunia as MBS must be graded as moderate or severe at Screening Visit 1A and Visit 1B for each study subject.

Randomized subjects were asked to complete the VVA Symptom Self-Assessment Questionnaire at Visits 3, 4, 5, and 6. Screening Visit 1B evaluation results were considered as Baseline data for the statistical analyses.

3.2.2.3 Analysis of Co-Primary Endpoints

Three doses of TX-004HR were compared to placebo. Within each dose level/placebo comparison, four co-primary endpoints were tested using a closed fixed sequence serial testing procedure, in which each primary endpoint was tested at level alpha (0.025, one-tailed) until no hypothesis could be rejected and then all subsequent hypotheses were also accepted. This closed testing procedure guarantees the overall type I error rate for all four hypotheses.

To account for the multiple comparisons of testing placebo to each of the three doses of TX-004HR (4 µg, 10 µg and 25 µg) and the multiple testing of the four co-primary endpoints, the procedural testing started by examining the highest dose (25 µg) for each of the co-primary endpoints in the following order: 1) vaginal superficial cells, 2) vaginal parabasal cells, 3) vaginal pH, and 4) severity of the MBS of dyspareunia (vaginal pain associated with sexual activity). If all of the p-values for each of the four co-primaries were significant ($p \leq 0.05$) then the hypothesis testing would continue on to the next lowest dose (10 µg) for each of the co-primaries, as described above. If all of the 4 co-primaries were significant ($p \leq 0.05$ for TX-004HR 10 µg, then the hypothesis testing would continue for the next lowest dose (4 µg). If at any point the hypothesis testing yielded a non-significant result, the testing would be stopped.

Primary and secondary efficacy endpoints were measured at Baseline and at 2, 6, 8 and 12 weeks. The analysis of change from baseline was based on analyses of covariance (ANCOVA) using Mixed Model Repeated Measures approach with subject as the random effect, treatment and Visit (2, 6, 8 and 12 weeks) as fixed effects. Baseline measures and age were used as covariates.

The following three pair-wise comparisons in the changes from baseline in co-primaries were performed at Week 12 (primary) and Weeks 2, 6 and 8 (secondary):

- Active treatment, high dose (25 µg) group vs placebo
- Active treatment, middle dose (10 µg) group vs placebo
- Active treatment, low dose group (4 µg) vs placebo

Results were reported as Least Square (LS) mean changes between treatment and placebo with the corresponding 95% CI for the difference.

For MBS dyspareunia, an additional sensitivity analysis based on five possible values for the change in dyspareunia (from -3 (severe to none) to +1 (moderate to severe)) was performed

using Mantel-Haenzel test. Therefore, for dyspareunia sensitivity analysis, the following three pair-wise comparisons were also performed at Week 12 (primary) and at Weeks 2, 6 and 8 (secondary):

- Active treatment, high dose group vs. placebo
- Active treatment, middle dose group vs. placebo
- Active treatment, low dose group vs. placebo

A responder analysis was also conducted based on the proportion of subjects classified as responders at Week 12. Responders were defined as women who had at least two of the following: proportion of vaginal superficial cells greater than 5%; vaginal pH less than 5.0; improvement from Baseline in MBS of at least one category (e.g., moderate to mild).

Subjects missing Week 12 data were not included in this analysis. No LOCF was used. If a subject was missing part of the scheduled Week 12 data, the subject was classified as a responder. The proportions of responders were compared between active treatment groups and placebo using Fisher's exact test.

Missing data: For the primary analysis, missing/invalid data were not imputed, instead MMRM was fit using all the available information for estimating the treatment effect.

Sample Size: The sample size calculation for the co-primary of Dyspareunia was based on percent change rather than the absolute change. Based on the effect sizes and power, the Applicant claimed that 175 subjects per treatment arm appeared to be adequate even for testing absolute change as endpoint.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In study 14-01, a total of 764 subjects were randomized into the study with 191 subjects randomized to TX-004HR 4 µg, 191 subjects to TX-004HR 10 µg, 190 subjects to TX-004HR 25 µg, and 192 subjects to placebo. Of the randomized subjects, 747 subjects met the criteria to be included in the MITT population; 186 in TX-004HR 4 µg, 188 in TX-004HR 10 µg, 186 in TX-004HR 25 µg, and 187 in the placebo group. In the MITT population, there were 703 completers and 44 discontinuations.

A similar percentage of subjects in three TX-004HR treatment groups and placebo group completed the study (94.1% TX-004HR 4 µg, 92.6% TX-004HR 10 µg, 95.2% TX-004HR 25 µg and 94.7% Placebo). The main reasons for discontinuation were "Withdraw Consent" (2.7% TX-004HR 4 µg, 2.1% TX-004HR 10 µg, 2.7% TX-004HR 25 µg and 2.1% Placebo). Details of subject disposition in study 14-01 are summarized in Table 2.

Table 2: Subjects Disposition, Study 14-01 (MITT Population)

Category	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
Randomly Assigned	191	191	190	192
MITT Population	186 100%	188 100%	186 100%	187 100%
EE Population	172 92.5%	171 91.0%	176 94.6%	176 94.1%
Completed the Study	175 94.1%	174 92.6%	177 95.2%	177 94.7%
Discontinued Study Drug	11 5.9%	14 7.4%	9 4.8%	10 5.3%
Reason for Discontinued				
Adverse Event	1 0.5%	3 1.6%	2 1.1%	3 1.6%
Investigator/Physician	0 0.0%	1 0.5%	1 0.5%	0 0.0%
Lack of Efficacy	2 1.1%	2 1.1%	0 0.0%	0 0.0%
Lost to Follow-up	2 1.1%	3 1.6%	1 0.5%	3 1.6%
Protocol Violation	1 0.5%	1 0.5%	0 0.0%	0 0.0%
Withdrew Consent	5 2.7%	4 2.1%	5 2.7%	4 2.1%

Source: Table 11 in study report and Reviewer's Analysis.

The demographics and baseline characteristics of the treatment groups for the MITT population are summarized by treatment group in the Tables 3 & 4. The overall mean age of subjects was 59.1 years and ranged from 40 to 75 years. The majority of subjects were White (86.7%) and the overall mean BMI was 26.7 kg/m². Demographic data were similar across treatment groups.

Table 3: Subject Demographics, Study 14-01 (MITT Population)

Demographic Parameters	TX-004HR 4 µg N=186 n (%)	TX-004HR 10 µg N=188 n (%)	TX-004HR 25 µg N=186 n (%)	Placebo N=187 n (%)
Age (years)				
Mean years (SD)	59.8 (6.0)	58.6 (6.3)	58.8 (6.2)	59.4 (6.0)
Median	59	58	58	59
Range (Min - Max)	41 - 75	42 - 75	40 - 74	40 - 73
Age Group				
≤ 56 years	57 (31)	72 (38)	73 (39)	62 (33)
>56 to <62 years	60 (32)	59 (31)	52 (28)	59 (32)
>=62 years	69 (37)	57 (30)	61 (33)	66 (35)
Race				
White	162 (87.1)	165 (87.8)	161 (86.6)	160 (85.6)
Black or African American	20 (10.8)	21 (11.2)	24 (12.9)	21 (11.2)
Asian	3 (1.6)	2 (1.1)	1 (0.5)	1 (0.5)
Other	1 (0.5)	0 (0)	0 (0)	5 (2.7)
Ethnicity				
Hispanic or Latino	18 (9.7)	24 (12.8)	24 (12.9)	24 (12.8)
Not Hispanic or Latino	168 (90.3)	164 (87.2)	162 (87.1)	163 (87.2)

Source: Table 17 in study report and Reviewer's Analysis.

Table 4: Baseline Characteristics, Study 14-01 (MITT Population)

Baseline characteristics	TX-004HR 4 µg N=186	TX-004HR 10 µg N=188	TX-004HR 25 µg N=186	Placebo N=187
Anthropometric measurements (mean)				
Height (cm)	162.9	162.9	162.4	162.1
Weight (kg)	69.8	68.6	69.8	68.0
Body Mass Index (kg/m ²)	26.6	26.8	26.8	26.6
Reproductive history				
Years since last menses (mean)	14.2	14.3	13.8	13.9
Type of Menopause				
Natural (%)	111 (59.7)	114 (60.6)	118 (63.4)	124 (66.3)
Surgical (%)	75 (40.3)	74 (39.4)	68 (36.6)	63 (33.7)
Prior Hormone Replacement Therapy				
No	152 (81.7)	155 (82.4)	162 (87.1)	151 (80.7)
Yes	34 (18.3)	33 (17.6)	24 (12.9)	36 (19.3)

Source: Table 17 & 18 in study report and Reviewer's Analysis.

3.2.4 Results and Conclusions

3.2.4.1 Results for Co-Primary Efficacy Endpoints

The efficacy results for 4 co-primary endpoints are presented in this section. To support VVA indication, efficacy must be demonstrated with respect to all four co-primary efficacy endpoints. The primary efficacy analysis for Study 14-01 was conducted on the modified intent to treat (MITT) population utilizing the mixed model for repeated measures (MMRM) method.

Severity of MBS of Dyspareunia:

The Most Bothersome Symptom (MBS) dyspareunia based on the pre-specified MMRM are shown in Table 5. A statistically significant reduction in the change from Baseline to Week 12 in the severity of dyspareunia was noted for all three doses of TX-004HR compared to placebo.

Because subjects with either no reported sexual activity at Week 12 (N=68, 9.1% of women) or missing data on dyspareunia at Week 12 (N=52, 7.0% of women) were excluded from MMRM analysis of the MBS of dyspareunia, information request was sent to the Applicant to provide additional sensitivity analysis using LOCF to handle missing data. As showed in Table 6 similar statistically significant reduction in the severity of dyspareunia was noted for all three doses of TX-004HR compared to placebo.

Table 5: MBS of Dyspareunia: Observed and Mean Change in Severity from Baseline to Week 12 (MITT Population)

	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
Baseline (n)	186	188	186	187
Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.44)	2.7 (0.46)
Median	3	3	3	3
Min, Max	2, 3	2, 3	2, 3	2, 3
Week 12 (n)	151	154	159	163
Mean (SD)	1.1 (0.98)	0.9 (0.92)	1.0 (0.99)	1.4 (1.02)
Median	1	1	1	1
Min, Max	0, 3	0, 3	0, 3	0, 3
Change from Baseline (n)	151	154	159	163
Mean (SD)	-1.54 (1.04)	-1.68 (0.96)	-1.72 (0.94)	-1.28 (1.04)
Median	-2	-2	-2	-1
Min, Max	-3, 1	-3, 0	-3, 0	-3, 1
LS Mean (s.e.) ¹	-1.52 (0.07)	-1.69 (0.07)	-1.69 (0.07)	-1.28 (0.07)
Diff. from Placebo (95% CI) ¹	-0.24 (-0.44, -0.05)	-0.41 (-0.61, -0.21)	-0.41 (-0.61, -0.22)	
P-value vs placebo ¹	0.0149	<0.0001	<0.0001	

Abbreviations: MITT – modified intent-to-treat; SD – standard deviation; Min – minimum; Max- maximum; LS – least square; s.e. – standard error; ¹MMRM - Mixed Model Repeated Measures

Source: Table 27 in Clinical Report and Reviewer’s analysis.

Table 6: MBS of Dyspareunia: Change in Severity from Baseline to Week 12 (MITT Population, LOCF)

	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
Baseline (n)	186	188	186	187
Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.44)	2.7 (0.46)
Median	3	3	3	3
Min, Max	2, 3	2, 3	2, 3	2, 3
Week 12 (n)	178	176	174	183
Mean (SD)	1.18 (0.97)	1.03 (0.95)	1.03 (0.97)	1.45 (1.03)
Median	1	1	1	1
Min, Max	0, 3	0, 3	0, 3	0, 3
Change from Baseline				
LS Mean (s.e.)	-1.50 (0.07)	-1.64 (0.07)	-1.67 (0.07)	-1.25 (0.07)
Diff. from Placebo (95% CI) ¹	-0.25 (-0.44, -0.05)	-0.38 (-0.58, -0.19)	-0.42 (-0.62, -0.22)	
P-value vs placebo ²	0.0156	0.0002	<0.0001	

¹ Difference from placebo = TX-004HR (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

² ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.1.4X in Clinical Information Amendment and Reviewer’s analysis.

Additional sensitivity analysis to evaluate severity of dyspareunia, categorical analysis was conducted using Mantel-Haenszel test (row mean scores test). The sponsor's categorical analysis results are shown in Table 7. However, only the subjects with Week 12 data are included in the analysis (without imputing for missing data).

Table 7: MBS of Dyspareunia: Change in Severity from Baseline to Week 12

Change in Severity	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
MITT Population	186	188	186	187
3 less pain	32 (17.2)	34 (18.1)	32 (17.2)	24 (12.8)
2 less pain	45 (24.2)	55 (29.3)	71 (38.2)	43 (23.0)
1 less pain	49 (26.3)	46 (24.5)	35 (18.8)	53 (28.3)
0 no change	22 (11.8)	19 (10.1)	21 (11.3)	41 (21.9)
1 more pain	3 (1.6)	0 (0)	0 (0)	2 (1.1)
No Sex with Vaginal penetration	20 (10.8)	19 (10.1)	17 (9.1)	12 (6.4)
Missing	15 (8.1)	15 (8.0)	10 (5.4)	12 (6.4)
With Week 12 Data	151	154	159	163
P- Value ¹	0.0317	0.0006	0.0001	NA

¹ Only subjects with Week 12 data were used in the analysis.

Source: Table 28 in Clinical Report and Reviewer's analysis.

Information request was sent to the Applicant to re-conduct the categorical data analysis without deleting subjects with missing data for MITT population. As showed in Table 8, sensitivity analysis using all available data for subjects with at least one post baseline measurement via LOCF, a statistically significant reduction in the severity of dyspareunia, was noted only in two higher doses of TX-004HR compared to placebo, but not significant in the TX-004HR 4 µg group with a p-value of 0.0501.

Table 8: MBS of Dyspareunia: Change in Severity from Baseline to Week 12 (MITT Population)

Change in Severity	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
MITT Population	178	176	174	183
3 less pain	34 (18.3)	35 (18.6)	34 (18.3)	26 (13.9)
2 less pain	54 (29.0)	61 (32.4)	76 (40.9)	49 (26.2)
1 less pain	58 (31.2)	56 (29.8)	41 (22.0)	58 (31.0)
0 no change	28 (15.1)	24 (12.8)	23 (12.4)	48 (25.7)
1 more pain	4 (2.2)	0 (0)	0 (0)	2 (1.1)
P-Value ¹	0.0501	0.0014	0.0001	NA

¹ Subjects with any post treatment data are included via LOCF.

Source: Table 14.2.1.4X in Clinical Information Amendment and Reviewer's analysis.

Vaginal Maturation: As shown in Table 9 & 10, treatment with all three dosages of TX-004HR resulted in an increase in the percentage of superficial cells and a decrease in the percentage of parabasal cells compared to placebo in MITT analysis population for Study 14-01.

Table 9: Percent Parabasal Cells: Observed and Mean Change from Baseline to Week 12, Study 14-01 (MITT Population, MMRM)

	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
Baseline (n)	186	188	186	187
Mean (SD)	52.3 (39.2)	51.3 (38.0)	53.5 (38.3)	52.0 (39.2)
Median	62	54	64	53
Min, Max	0, 100	0, 100	0, 100	1, 100
Week 12 (n)	170	171	174	172
Mean (SD)	12.0 (22.3)	7.8 (18.5)	6.6 (16.6)	45.2 (40.3)
Median	2	0	0	39
Min, Max	0, 98	0, 98	0, 97	0, 100
Change from Baseline				
Mean (SD)	-41.1 (41.6)	-43.8 (37.8)	-46.2 (40.0)	-6.3 (29.8)
Median	-36	-42	-56	-4
Min, Max	-99, 80	-100, 63	-99, 67	-96, 91
LS Mean (s.e.)	-40.6 (1.75)	-44.1 (1.75)	-45.5 (1.74)	-6.7 (1.75)
Diff. from Placebo (95% CI) ¹	-33.90 (-38.76, -29.04)	-37.34 (-42.19, -32.48)	-38.82 (-43.67, -33.97)	
P-value vs placebo ¹	<0.0001	<0.0001	<0.0001	

Abbreviations: MITT – modified intent-to-treat; SD – standard deviation; Min – minimum; Max- maximum; LS – least square; s.e. – standard error; ¹MMRM - Mixed Model Repeated Measures
Source: Table 24 in Clinical Report and Reviewer’s analysis.

Table 10: Percent Superficial Cells: Observed and Mean Change from Baseline to Week 12, Study 14-01 (MITT Population, MMRM)

	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
Baseline (n)	186	188	186	187
Mean (SD)	1.3 (1.24)	1.2 (1.23)	1.3 (1.16)	1.3 (1.31)
Median	1	1	1	1
Min, Max	0, 4	0, 5	0, 4	0, 4
Week 12 (n)	170	171	174	172
Mean (SD)	18.7 (19.54)	18.5 (19.95)	24.9 (24.23)	7.0 (14.70)
Median	12	12	12	12
Min, Max	0, 85	0, 85	0, 88	0, 89
Change from Baseline				
Mean (SD)	-1.54 (1.04)	-1.68 (0.96)	-1.72 (0.94)	-1.28 (1.04)
Median	11	10	15	0
Min, Max	-3, 81	-2, 80	-3, 87	-3, 87
LS Mean (s.e.)	17.50 (1.54)	16.72 (1.54)	23.20 (1.53)	5.63 (1.54)
Diff. from Placebo (95% CI) ¹	11.87 (7.60, 16.14)	11.09 (6.82, 15.36)	17.57 (13.32, 21.82)	
MMRM P-value vs placebo ¹	<0.0001	<0.0001	<0.0001	

Abbreviations: MITT – modified intent-to-treat; SD – standard deviation; Min – minimum; Max- maximum; LS – least square; s.e. – standard error; ¹MMRM - Mixed Model Repeated Measures
Source: Table 25 in Clinical Report and Reviewer’s analysis.

Vaginal pH: The mean change from baseline in vaginal pH to Week 12 based on the Reviewer and Applicant’s analyses are shown in Table 11. A statistically significant reduction in Vaginal pH, change from Baseline to Week 12, was found for all three doses of TX-004HR compared to placebo.

Table 11: Vaginal pH: Observed and Mean Change from Baseline to Week 12, Study 14-01 (MITT Population, MMRM)

	TX-004HR 4 µg	TX-004HR 10 µg	TX-004HR 25 µg	Placebo
Baseline (n)	186	188	186	187
Mean (SD)	6.3 (0.87)	6.3 (0.83)	6.3 (0.91)	6.3 (1.04)
Median	6	6	6	6
Min, Max	5, 10	5, 10	5, 10	5, 12
Week 12 (n)	170	171	174	174
Mean (SD)	1.1 (0.98)	0.9 (0.92)	1.0 (0.99)	1.4 (1.02)
Median	4.7	4.7	4.7	6.0
Min, Max	3, 10	4, 8	4, 10	4, 11
Change from Baseline (n)				
Mean (SD)	-1.33 (1.111)	-1.41 (1.027)	-1.37 (1.143)	-0.26 (1.048)
Median	-1.3	-1.3	-1.3	-0.2
Min, Max	-4.6, 1.7	-6.0, 1.7	-6.0, 2.3	-2.3, 5.7
LS Mean (s.e.)	-1.32 (0.07)	-1.42 (0.07)	-1.34 (0.07)	-0.28 (0.07)
Diff. from Placebo (95% CI) ¹	-1.03 (-1.22, -0.85)	-1.14 (-1.32, -0.95)	-1.06 (-1.24, -0.88)	
MMRM P-value vs placebo ¹	<0.0001	<0.0001	<0.0001	

Abbreviations: MITT – modified intent-to-treat; SD – standard deviation; Min – minimum; Max- maximum; LS – least square; s.e. – standard error; ¹MMRM - Mixed Model Repeated Measures

Source: Table 26 in Clinical Report and Reviewer’s analysis.

The efficacy analyses for 4 co-primary endpoints using MMRM methods were also conducted in EE population; results are similar to that of MITT population.

Responder Analysis (EE Population)

A responder was defined as any subject who had at least two of the following at Week 12: 1) Vaginal superficial cells > 5%; 2) vaginal pH < 5.0; 3) improvement from Baseline in MBS of at least one category. As showed in Table he number of responders were statistically significant compared to placebo for all TX-004HR treatment groups (p<0.0001).

Table 12: Summary of Responder Analysis at Week 12 (EE Population): Treatment vs Placebo

	TX-004HR 4 µg (N=172)	TX-004HR 10 µg (N=171)	TX-004HR 25 µg (N=176)	Placebo (N=176)
Responder	113 (65.7)	126 (73.7)	132 (75)	55 (31.3)
Non-Responder	43 (25.0)	31 (18.1)	36 (20.5)	114 (64.8)
Cannot be determined	16 (9.3)	14 (8.2)	8 (4.5)	7 (4.0)
Fisher Exact Test	<0.0001	<0.0001	<0.0001	----

Source: Table 40 in Clinical Report.

Results for Secondary Efficacy Endpoints

Per consultation with medical reviewer, secondary endpoints pertaining to moderate to severe symptoms of vaginal dryness and vulvovaginal irritation/itching, and secondary endpoints pertaining to menopause specific quality of life, arousal, desire, satisfaction and orgasm, and local signs of VVA are not likely to be included in the label and, therefore, not evaluated in this review.

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Efficacy of TX-004HR Vaginal (b) (4) Capsules was explored by subgroups defined by race and age group. In both studies, analyses of each co-primary efficacy endpoint by subgroups were performed using the same MMRM model described previously in section 3.2.2.3.

4.1 Gender, Race, Age, and Geographic Region

Study 14-01 was conducted in the U.S. and Canada and enrolled female subjects only, and therefore, analysis by gender and geographical region was not performed.

The efficacy results for all four primary endpoints by age and race groups are presented in Tables 13-16 (Appendices). As shown in these Tables, although there appeared to be increase in efficacy in Whites/Non-Hispanics women compared to Non-whites/Hispanics, the study was not powered to make any reasonable conclusions from these subgroup analyses. The results did not show any consistent pattern of treatment effect of TX-004HR Vaginal (b) (4) Capsules relative to placebo across age groups.

5 SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

There were no statistical issues regarding the design and statistical analysis methods in this submission. The four co-primary efficacy endpoints were evaluated based on the MITT population, which included subjects having vaginal pH >5, vaginal superficial cell ≤5%, and a most bothersome moderate to severe vaginal symptom of dyspareunia at baseline.

Using pre-specified approaches, this reviewer confirmed that (b) (4) doses of TX-004HR Vaginal (b) (4) Capsules statistically significantly improved vaginal pH, superficial and basal/parabasal epithelial cell counts, and relieved dyspareunia, the most bothersome symptom of VVA identified by women. The lower dose TX-004HR 4 µg, however, did not show statistically significant improvement compared to placebo in primary endpoint change from baseline to week 12 in the severity of most bothersome symptoms of dyspareunia using categorical sensitivity analysis.

From a statistical perspective, data from study 14-01 provided statistical evidence in support of TX-004HR, in the treatment of treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.

APPENDICES

Table 13: Subgroup Analysis of Primary Endpoint Dyspareunia, Study 14-01 (MITT Population, MMRM)

	TX-004HR 4 µg vs Placebo Diff. (N, N) (LL, UL)		TX-004HR 10 µg vs Placebo Diff. (N, N) (LL, UL)		TX-004HR 25 µg vs Placebo Diff. (N, N) (LL, UL)	
All Women	-0.24 (151, 163)	(-0.44, -0.05)	-0.41 (154, 163)	(-0.61, -0.21)	-0.39 (159, 163)	(-0.61, -0.22)
Age Group						
≤ 56 years	-0.33 (50, 52)	(-0.66, 0.01)	-0.52 (61, 52)	(-0.84, -0.20)	-0.61 (65, 52)	(-0.92, -0.29)
57-61 years	-0.03 (50, 53)	(-0.37, 0.30)	-0.24 (49, 53)	(-0.58, 0.09)	-0.41 (47, 53)	(-0.74, -0.07)
≥ 62 years	-0.33 (51, 58)	(-0.68, 0.01)	-0.48 (44, 58)	(-0.84, -0.12)	-0.19 (47, 58)	(-0.55, 0.16)
Race						
White	-0.30 (132, 141)	(-0.50, -0.09)	-0.47 (135, 141)	(-0.68, -0.27)	-0.48 (137, 141)	(-0.69, -0.27)
Black	-0.09 (16, 18)	(-0.68, 0.50)	-0.12 (17, 18)	(-0.70, 0.47)	-0.15 (21, 18)	(-0.72, 0.42)
Other	0.54 (3, 4)	(-1.36, 2.43)	0.73 (2, 4)	(-1.30, 2.76)	1.84 (1, 4)	(-0.95, 4.63)
Ethnicity						
Hispanic or Latino	0.49 (14, 21)	(-0.09, 1.06)	-0.40 (19, 21)	(-0.94, 0.15)	-0.06 (20, 21)	(-0.58, 0.47)
Not Hispanic or Latino	-0.33 (137, 142)	(-0.54, -0.13)	-0.43 (135, 142)	(-0.64, -0.23)	-0.48 (139, 142)	(-0.68, -0.27)

¹ Difference from placebo = TX-004HR (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

² ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 6.1.7d in Multiple Module Information Amendment and Reviewer's analysis.

Table 14: Subgroup Analysis of Primary Endpoint Parabasal Cells, Study 14-01 (MITT Population, MMRM)

	TX-004HR 4 µg vs Placebo		TX-004HR 10 µg vs Placebo		TX-004HR 25 µg vs Placebo	
	Diff. (N, N)	(LL, UL)	Diff. (N, N)	(LL, UL)	Diff. (N, N)	(LL, UL)
All Women	-33.90 (170, 172)	(-38.76, -29.04)	-37.34 (171, 172)	(-42.19, -32.48)	-38.82 (174, 172)	(-43.67, -33.97)
Age Group						
≤ 56 years	-25.91 (51, 56)	(-33.83, -17.98)	-27.31 (67, 56)	(-34.78, -19.83)	-29.58 (70, 56)	(-37.00, -22.16)
57-61 years	-34.46 (57, 56)	(-42.87, -26.04)	-35.34 (54, 56)	(-43.81, -26.88)	-32.96 (47, 56)	(-41.70, -24.22)
≥ 62 years	-40.25 (62, 60)	(-48.80, -31.69)	-49.31 (50, 60)	(-58.32, -40.30)	-53.64 (57, 60)	(-62.42, -44.86)
Race						
White	-36.62 (150, 149)	(-41.88, -31.37)	-39.04 (150, 149)	(-44.29, -33.79)	-41.08 (149, 149)	(-46.35, -35.81)
Black	-16.59 (16, 19)	(-29.89, -3.29)	-30.43 (19, 19)	(-43.47, -17.39)	-28.61 (24, 19)	(-41.00, -16.23)
Other	-5.10 (4, 4)	(-33.89, 23.69)	-18.48 (2, 4)	(-58.46, 21.50)	-8.49 (1, 4)	(-50.94, 33.97)
Ethnicity						
Hispanic or Latino	-19.23 (17, 22)	(-35.29, -3.17)	-31.72 (19, 22)	(-46.91, -16.52)	-30.45 (19, 22)	(-45.64, -15.25)
Not Hispanic or Latino	-35.67 (153, 150)	(-40.71, -30.64)	-38.14 (152, 150)	(-43.21, -33.08)	-39.99 (155, 150)	(-45.04, -34.94)

¹ Difference from placebo = TX-004HR (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

² ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 6.1.7c in Multiple Module Information Amendment and Reviewer's analysis.

Table 15: Subgroup Analysis of Primary Endpoint Superficial Cells, Study 14-01 (MITT Population, MMRM)

	TX-004HR 4 µg vs Placebo Diff. (N, N) (LL, UL)		TX-004HR 10 µg vs Placebo Diff. (N, N) (LL, UL)		TX-004HR 25 µg vs Placebo Diff. (N, N) (LL, UL)	
All Women	11.87 (170, 172)	(7.60, 16.14)	11.09 (171, 172)	(6.82, 15.36)	17.57 (174, 172)	(13.32, 21.82)
Age Group						
≤ 56 years	9.92 (51, 56)	(2.17, 17.66)	7.62 (67, 56)	(0.34, 14.89)	15.14 (70, 56)	(7.94, 22.34)
57-61 years	13.52 (57, 56)	(5.98, 21.05)	14.40 (54, 56)	(6.79, 22.00)	22.95 (47, 56)	(15.09, 30.81)
≥ 62 years	12.70 (62, 60)	(5.86, 19.54)	12.12 (50, 60)	(4.89, 19.35)	15.91 (57, 60)	(8.91, 22.91)
Race						
White	13.11 (150, 149)	(8.64, 17.59)	11.60 (150, 149)	(7.12, 16.08)	18.90 (149, 149)	(14.41, 23.39)
Black	1.39 (16, 19)	(-12.91, 15.69)	5.69 (19, 19)	(-8.28, 19.66)	10.59 (24, 19)	(-2.67, 23.85)
Other	2.43 (4, 4)	(-18.77, 23.62)	70.73 (2, 4)	(42.79, 98.67)	-26.45 (1, 4)	(-59.24, 6.35)
Ethnicity						
Hispanic or Latino	5.51 (17, 22)	(-5.05, 16.07)	5.95 (19, 22)	(-4.12, 16.03)	9.42 (19, 22)	(-0.66, 19.51)
Not Hispanic or Latino	12.47 (153, 150)	(7.90, 17.03)	11.83 (152, 150)	(7.24, 16.41)	18.69 (155, 150)	(14.12, 23.26)

¹ Difference from placebo = TX-004HR (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

² ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 6.1.7b in Multiple Module Information Amendment and Reviewer’s analysis.

Table 16: Subgroup Analysis of Primary Endpoint Vaginal pH, Study 14-01 (MITT Population, MMRM)

	TX-004HR 4 µg vs Placebo		TX-004HR 10 µg vs Placebo		TX-004HR 25 µg vs Placebo	
	Diff. (N, N)	(LL, UL)	Diff. (N, N)	(LL, UL)	Diff. (N, N)	(LL, UL)
All Women	-1.03 (170, 174)	(-1.22, -0.85)	-1.14 (171, 174)	(-1.32, -0.95)	-1.06 (174, 174)	(-1.24, -0.88)
Age Group						
≤ 56 years	-0.87 (51, 56)	(-1.18, -0.57)	-0.81 (67, 56)	(-1.10, -0.52)	-0.89 (70, 56)	(-1.18, -0.61)
57-61 years	-1.03 (57, 58)	(-1.35, -0.70)	-1.24 (54, 58)	(-1.57, -0.91)	-1.08 (47, 58)	(-1.42, -0.74)
≥ 62 years	-1.18 (62, 60)	(-1.50, -0.87)	-1.35 (50, 60)	(-1.69, -1.02)	-1.19 (57, 60)	(-1.51, -0.86)
Race						
White	-1.11 (150, 150)	(-1.30, -0.91)	-1.16 (150, 150)	(-1.36, -0.97)	-1.13 (149, 150)	(-1.32, -0.93)
Black	-0.40 (16, 20)	(-0.90, 0.10)	-0.79 (19, 20)	(-1.27, -0.31)	-0.43 (24, 20)	(-0.89, 0.03)
Other	-0.01 (4, 4)	(-1.45, 1.44)	-1.01 (2, 4)	(-2.61, 0.58)	0.53 (1, 4)	(-1.58, 2.63)
Ethnicity						
Hispanic or Latino	-0.80 (17, 22)	(-1.47, -0.14)	-0.99 (19, 22)	(-1.63, -0.35)	-0.31 (19, 22)	(-0.96, 0.33)
Not Hispanic or Latino	-1.06 (153, 152)	(-1.24, -0.87)	-1.15 (152, 152)	(-1.33, 0.97)	-1.15 (155, 152)	(-1.33, -0.97)

¹ Difference from placebo = TX-004HR (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

² ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 6.1.7a in Multiple Module Information Amendment and Reviewer’s analysis.

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/s/

KATE L DWYER
04/04/2017

MAHBOOB SOBHAN
04/04/2017