

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



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 #:** 208470/000

**Drug Name:** INTRAROSA™ (Prasterone Vaginal Insert)

**Indication(s):** Treatment of Moderate to Severe Dyspareunia (or Pain at Sexual Activity), a Symptom of Vulvovaginal Atrophy, Due to Menopause

**Applicant:** EndoCeutics Inc.

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# 1 EXECUTIVE SUMMARY

The Applicant, EndoCeutics Inc., is seeking approval of prasterone [dehydroepiandrosterone (DHEA); hereafter referred to as DHEA], a non-estrogenic vaginal therapy, for the treatment of moderate to severe dyspareunia [REDACTED] (b) (4) a symptom of vulvovaginal atrophy due to menopause.

To support the above indication, safety and efficacy data from two phase 3 studies (ERC-231 and ERC-238) was submitted. This review evaluates from a statistical perspective the adequacy of the submitted efficacy data supporting this claim.

Both studies were randomized, double-blind, multicenter, and placebo-controlled studies conducted in the US and Canada in post-menopausal women. Study ERC-231 was a three-arm (Placebo, 0.25% (3.25 mg) and 0.50% (6.5 mg) DHEA)), while study ERC-238 was a two-arm (placebo and 0.50% DHEA) study. The objectives of the studies were to demonstrate efficacy with respect to the co-primary endpoints: change from baseline to week 12 in the severity of most bothersome symptoms of dyspareunia, percent superficial and parabasal cells, and vaginal pH.

There were no statistical issues noted in this submission. This reviewer confirmed that only 0.50% DHEA vaginal insert statistically significantly improved dyspareunia compared to placebo with respect to all four co-primary endpoints. 0.25% DHEA vaginal insert 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.

From a statistical perspective, data from the two submitted studies provided statistical evidence in support of Prasterone Vaginal Insert, administered intravaginally at the 6.5 mg dose once daily, in the treatment of treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.

## 2 INTRODUCTION

### 2.1 Overview

The Applicant, EndoCeutics Inc., is seeking approval of Intravaginal Prasterone (DHEA) for the treatment of moderate to severe dyspareunia [REDACTED] (b) (4) a symptom of vulvovaginal atrophy due to menopause. The proposed dose is 6.5 mg once daily administered intravaginally at bedtime.

Vulvar and vaginal atrophy (VVA) is a condition associated with declining postmenopausal estrogen levels. Women at menopause are not only subject to a decrease in estrogen activity due to an arrest of ovarian estrogen secretion, but have already been subject to decreasing exposure to androgen caused by declining dehydroepiandrosterone (DHEA) secretion by the adrenals. According to the Applicant, DHEA, the precursor of sex steroids, a compound inactive by itself, is transformed intracellularly into both estrogens and androgens. Thus, the use of DHEA provides an opportunity for women to reach

appropriate levels of androgens and estrogens synthesized in specific tissues by intracrine mechanisms, while avoiding systemic effects of the sex steroids.

To demonstrate the safety and efficacy of Intravaginal DHEA for the treatment of moderate to severe dyspareunia (or pain at sexual activity), the Applicant has submitted two pivotal phase 3 clinical studies (ERC-231 and ERC-238). Table 1 presents a brief summary of the two studies addressed in this review.

**Table 1 – List of all studies included in analysis**

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
ERC-231	Phase 3, double-blind, Randomized, multicenter, placebo-controlled	12-week	7 days	Randomized: 0.25% DHEA: 87 0.50% DHEA: 87 Placebo: 81	Postmenopausal women between 40 and 75 years of age, having $\leq 5\%$ of superficial cells on vaginal smear, a vaginal pH above 5 and who self-identified moderate to severe dyspareunia as their MBS
ERC-238	Phase 3, double-blind, Randomized, multicenter, placebo-controlled	12-week	7 days	Randomized: 0.50% DHEA: 376 Placebo: 180	Postmenopausal women between 40 and 80 years of age, having $\leq 5\%$ of superficial cells on vaginal smear, a vaginal pH above 5 and who self-identified moderate to dyspareunia as their MBS.

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\NDA208470> under the submissions dated 10/16/2015 and 2/12/2016.

## 3 STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

The efficacy evaluation of Intravaginal Prasterone (DHEA) is based on studies ERC-231 and ERC-238.

#### 3.1.1 Study Design

Study ERC-231 was a randomized, placebo-controlled, double-blind, parallel-group Phase III study to confirm the efficacy of daily intravaginal administration of a 0.25% (3.25 mg) DHEA and 0.50% (6.5 mg) DHEA suppositories for 12 weeks compared to placebo in postmenopausal women. Women were randomized between 3 treatment arms in a 1:1:1 ratio as follows:

- A. Daily placebo ovule for 12 weeks.
- B. Daily 0.25% DHEA ovule for 12 weeks.
- C. Daily 0.50% DHEA ovule for 12 weeks.

Subject population in Study ERC-231 was postmenopausal women (non-hysterectomized or hysterectomized), between 40 and 75 years of age, having  $\leq 5\%$  of superficial cells on vaginal smear, a vaginal pH above 5 and having self-identified moderate to severe vaginal pain associated with sexual activity (dyspareunia) as their most bothersome symptom (MBS) of VVA. Two hundred ten (210) evaluable participants (70 subjects to be treated with each dose of DHEA or placebo) were planned to be enrolled. A total of 255 subjects have been enrolled in the study.

Study ERC-238 was a randomized, placebo-controlled, double-blind Phase III study to confirm the efficacy on pain at sexual activity of daily intravaginal administration of 0.50% (6.5 mg) DHEA ovules (suppositories) for 12 weeks compared to placebo in postmenopausal women. Women were randomized in a 2:1 ratio between the 0.50% DHEA and placebo DHEA groups as follows:

- A. Daily placebo ovule for 12 weeks.
- B. Daily 0.50% DHEA ovule for 12 weeks.

Subject population in Study ERC-238 was similar to that of Study ERC-231 except subjects were up to 80 years old. Four hundred eighty-three (483) subjects in a 2:1 ratio between the DHEA (n=322) and placebo (n=161) groups were planned to be enrolled. A total of 558 subjects women have been enrolled in the study.

Both studies were divided into two phases, a screening period up to 6 weeks and a treatment period of 12 weeks. Study participants were instructed to apply one intravaginal insert daily before bedtime (usually in the evening) during the 12-week trial.

### 3.1.2 Statistical Methodologies

#### 3.1.2.1 Analysis Populations

In both studies, the following analysis populations were pre-specified in the protocol:

**Safety Population:** All subjects who received any amount of study medication based on the diary card and/or study drug accountability, and who have any post-baseline safety information available.

**Intent-to-Treat Population (ITT):** All subjects who have received at least one dose of study drug (based on the diary card) with a baseline (Day 1) evaluation meeting the study entry criteria.

**Per-Protocol (PP):** Subset of subjects from the ITT population who have completed the study with no major protocol violations.

The following dataset was pre-specified for Study ERC-238 only:

**Modified ITT Population (mITT):** Subset of ITT population who had post-baseline sexual activity at least once before evaluation of dyspareunia at Weeks 6 and 12 and/or discontinuation during the 12-week treatment period.

Following blinded review of steroid data (DHEA and its metabolites); the Applicant found that some subjects have taken concomitant medication estrogens. Prior to study unblinding, based on steroid metabolism and levels found in normal postmenopausal women, the Applicant have established certain criteria to identify suspicious subjects and created the following post-hoc analysis data set.

**Corrected ITT:** Subset of ITT population excluding subjects suspected of using concomitant estrogens.

***Statistical Reviewer's Comments:***

*The clinical/statistical reviewer's did not agree with the cITT population in determining the effectiveness of 0.50% DHEA vaginal insert to relieve moderate to severe dyspareunia due to menopause. The primary analysis is based on pre-specified ITT population.*

**3.1.2.2 Efficacy Endpoints**

In both studies, four co-primary efficacy endpoints were defined as:

- Percentage change from baseline to Week 12 in superficial and parabasal cells;
- Change from baseline to Week 12 in vaginal pH;
- Mean Change from baseline to Week 12 in moderate to severe dyspareunia self-identified by subjects as the most bothersome VVA symptom to her at screening and at baseline (Day 1).

Self-assessment of the other symptoms of vulvar and VVA associated with menopause were evaluated by a questionnaire as secondary endpoints:

- Vaginal dryness (none, mild, moderate, or severe) and
- Vaginal and/or vulvar irritation/itching (none, mild, moderate, or severe);

The symptom score parameters of vaginal dryness and vaginal irritation/itching being moderate/severe at screening and Day 1 was tested statistically as second-order and third order, therefore, the primary symptom score parameter of dyspareunia must be statistically significant prior to the test for vaginal dryness, which in turn must be significant prior to the test for significance of vaginal irritation/itching.

In addition, the domains of the FSFI questionnaires on sexual dysfunction were also evaluated as secondary endpoints with the following rank order: arousal/lubrication, subjective arousal (arousal/psychological), desire, satisfaction and orgasm.

Vaginal cell MI was done at screening, baseline (Day 1), Week 6 and Week 12 (or at discontinuation visit, if applicable). Vaginal smears were obtained by gently scraping the middle or second third of the side wall of the vagina using a wooden or plastic spatula that was gently applied to a glass slide and immediately fixed with Cytospray or equivalent. These samples were sent to the central laboratory for determination of the MI.

Vaginal pH was done at screening, baseline (Day 1), Week 6 and Week 12 (or at discontinuation visit, if applicable). A pH strip fixed on an Ayre spatula (or equivalent) was applied directly to the opposite lateral wall of the vagina.

Self-assessment of the severity score of the symptoms of VVA associated with menopause, namely dyspareunia (pain at sexual activity), vaginal dryness and vulvovaginal irritation/itching was evaluated by the Vaginal Atrophy Symptoms Questionnaire (VASQ) at screening, baseline (Day 1), Week 6 and Week 12 (or at discontinuation visit, if applicable). The severity of vaginal atrophy symptoms recorded as at sexual activity takes the following values: none, mild, moderate or severe to be analyzed using values of 0, 1, 2 or 3, respectively. This specific symptom must be graded as 2 (moderate) or 3 (severe) at screening and Day 1 for each study subject.

At screening and baseline (Day 1) visits, in addition to rating the severity of symptoms, women had to self-identify which of the 3 vaginal atrophy symptoms listed above was the most bothersome to her. To be enrolled in the study, women had to self-identify moderate to severe dyspareunia (pain at sexual activity) as their MBS, at both screening and Day 1.

***Statistical Reviewer's Comments:***

*EndoCeutics was advised that no secondary endpoints would be considered in evaluating the effectiveness of the DHEA vaginal insert to relieve moderate to severe dyspareunia due to menopause, and would not appear in product labeling.*

### **3.1.2.3 Analysis of Co-Primary Endpoints**

The primary objective of the studies was to evaluate the intravaginal DHEA compared to placebo on moderate to severe pain at sexual activity (dyspareunia) as most bothersome symptom (MBS) of vulvovaginal atrophy (VVA) due to menopause. The co-primary efficacy endpoints to address this objective are decrease in percentage of parabasal cells, decrease in vaginal pH, increase in percentage of superficial cells and improvement of vaginal pain at sexual activity (dyspareunia) as self-reported by the subject as being the most bothersome symptom of VVA at both screening and baseline (Day 1). This specific symptom must be graded as 2 (moderate) or 3 (severe) at screening and Day 1 for each study subject.

All 4 co-primary endpoints must demonstrate statistically significant effect relative to placebo at Week 12, and therefore, no statistical adjustment is required for multiple endpoints. The primary time point for analysis and data presentation is the 12-week assessment, with additional secondary time point of the data at 6 weeks.

**Analysis Methods:** Statistical analysis methods included analysis of covariance (ANCOVA) with the treatment group as the main factor and the baseline value as the covariate to compare the changes from baseline in vaginal pH, and vaginal maturation (parabasal, intermediate and superficial cells) between DHEA dose groups and placebo. The p-value for the baseline adjusted least square mean (LSM) difference between treatment groups were presented (specifically, p-values for the placebo versus DHEA). Additionally, change from baseline for each treatment group were presented and assessed via a 1-sample t-test. A similar model was used for the secondary endpoints.

**Multiplicity:** For Study ERC-231 only, the adjustment in p-value for the 2 dose comparisons of DHEA to placebo was based on the Hochberg modification of the Bonferroni procedure. The largest of all p-values was determined for both dose group comparisons and tested at the 0.05 level and, if significant, the other dose is considered significant as well. If the largest p-value is  $>0.05$ , then the p-values for the 4 endpoints for the other dose group is tested at the 0.025 level; if  $<0.025$  for all 4 endpoints, the comparison was considered significant. This procedure preserves the overall Type I error of 0.05 for testing the 2 doses versus placebo.

**Missing data:** For the ITT analysis of efficacy parameters, if there were missing time points due to the discontinuation of a subject, the LOCF approach was used to impute the missing data. It may be the case that a woman's most bothersome symptom at screening is pain associated with sexual activity, but the woman may not have engaged in sexual activity between screening and Day 1. If this is the case, the screening value was used as baseline. Further, if the woman does not have sexual activity after baseline, the baseline value was carried forward in the analysis of dyspareunia.

Primary analysis was based on ITT population using LOCF and the Per-Protocol population as supportive efficacy analyses. As a sensitivity analysis (For Study ERC-238 only) to evaluate the impact of the LOCF approach, co-primary efficacy endpoints were analyzed using a mixed model repeated measures (MMRM) analysis as implemented in SAS Proc Mixed. This sensitivity analysis included all available baseline and post-baseline data as-recorded (without imputing missing values).

### 3.1.3 Patient Disposition, Demographic and Baseline Characteristics

In study ERC-231, a total of 255 subjects were randomized into the study (87 subjects per DHEA group and 81 subjects to the placebo group). A total of 16 treated subjects (3, 7 & 6 for Placebo, 0.25% HDEA, and 0.50% DHEA, respectively) excluded from ITT population because they failed the baseline (Day 1) study entry criteria. A similar percentage of subjects in both DHEA treatment groups and placebo group completed the study (94.5% Placebo, 92.4% 0.25% HDEA, and 93.8% 0.50% DHEA). The main reasons for discontinuation were adverse event for DHEA treatment group (5.1% in 0.25% DHEA and 2.5% in 0.50% DHEA) and “Patent Withdrew Consent” for placebo group (5.2% of treated subjects). Details of subject disposition in study ERC-231 are summarized in Table 2.

**Table 2: Subjects Disposition, Study ERC-231**

Category	Placebo	0.25% DHEA	0.50% DHEA	Total
Number Randomized	81	87	87	255
Safety Population	80	86	87	253
Intent-to-Treated (ITT)	77 100%	79 100%	81 100%	237 100%
Corrected ITT	75 97.4%	77 97.5%	80 98.8%	232 97.9%
Per-Protocol (PP)	65 84.4%	69 87.3%	70 86.4%	204 86.1%
Completed the Study	72 93.5%	73 92.4%	76 93.8%	221 93.2%
Discontinued Study Drug	5 6.5%	6 7.6%	5 6.2%	16 6.8%
Reason for Discontinued				
Adverse Event	1 1.3%	4 5.1%	2 2.5%	7 3.0%
Non-Compliance	1 1.3%	0 0.0%	0 0.0%	1 0.4%
Patient Withdrew Consent	4 5.2%	0 0.0%	2 2.5%	6 2.5%
Investigator's Decision	0 0.0%	1 1.3%	0 0.0%	1 0.4%
Lack of Efficacy	0 0.0%	1 1.3%	1 1.2%	2 0.8%

Source: Table 14.1.1a and Table 14.1.1b in ERC-231 study report and Reviewer’s Analysis.

In study ERC-238, a total of 558 subjects were randomized into the study (376 subjects to the paroxetine group and 182 subjects to the placebo group). A total of 23 subjects in the randomized placebo group and 49 women in the DHEA group who met all the study entry criteria (including VVA criteria) at screening but failed one or more required study entry criteria at baseline (Day 1) were excluded these from the ITT population. The percentage of subjects who completed the study was 94% in the placebo group and 95% in the 0.50% DHEA group. Details of subject disposition in study ERC-238 are summarized in Table 3. For both studies, the most common reasons for study discontinuation were AE and patient withdrawal of consent.

**Table 3: Subjects Disposition, Study ERC-238**

Category	Placebo	0.50 DHEA	Total
Number Randomized	182	376	558
Safety Population	180	374	554
Intent-to-Treated (ITT)	157 100%	325 100%	482 100%
Corrected ITT	154 98.1%	318 97.8%	472 97.9%
Modified ITT (mITT)	143 91.1%	305 93.8%	448 92.9%
Per-Protocol (PP)	119 75.8%	254 78.2%	373 77.4%
Completed the Study	152 96.8%	311 95.7%	463 96.1%
Discontinued Study Drug	5 3.2%	14 4.3%	19 3.9%
Reason for Discontinued			
Adverse Event	3 1.9%	5 1.5%	8 1.7%
Lost to Follow-up	0 0.0%	2 0.6%	2 0.4%
Patient Withdrew Consent	2 1.3%	7 2.2%	9 1.9%
Others	0 0.0%	0 0.0%	0 0.0%

Source: Table 14.1.1a and Table 14.1.1b in ERC-238 study report and Reviewer's Analysis.

The demographics and baseline characteristics of the treatment groups in ITT population are summarized in the Tables 4-7 for study ERC-231 and ERC-238, respectively. In both studies, more than 90% of subjects were white (93% in ERC-231; 91% in ERC-238). The mean age of subjects was 58.8 years in study ERC-231 and was 59.6 years in ERC-238. At baseline, the mean BMI was 26.0 kg/m<sup>2</sup> in study ERC-231 and 26.1 kg/m<sup>2</sup> in ERC-238. There were more percentage of subjects with natural menopause in study ERC-238 than that of study ERC-231 (65% in ERC-238; 48% in study ERC-231).

**Table 4: Subject Demographics, Study ERC-231 (ITT Population)**

Demographic Parameters	Placebo	0.25% DHEA	0.50% DHEA	Total
	N=77 n (%)	N=79 n (%)	N=81 n (%)	N=237 n (%)
<b>Age (years)</b>				
Mean years (SD)	59.1 (5.8)	59.7 (6.1)	57.7 (5.5)	58.8 (5.9)
Median	59	60	57	59
Range (Min - Max)	45 - 73	40 - 75	41 - 69	40 - 75
<b>Age Group</b>				
< 60 years	39 (51)	36 (46)	52 (64)	127 (54)
>=60 years	38 (49)	43 (54)	29 (36)	110 (46)
<b>Race</b>				
White	67 (87)	75 (95)	79 (98)	221 (93)
Black or African American	8 (10)	3 (4)	1 (1.2)	12 (5)
Asian	1 (1.3)	0 (0)	1 (1.2)	2 (0.8)
Other	1 (0.6)	1 (1.3)	0 (0)	2 (0.8)
<b>Ethnicity</b>				
Hispanic or Latino	1 (1)	5 (6)	8 (10)	14 (6)
Not Hispanic or Latino	76 (99)	74 (94)	73 (90)	223 (94)

Source: Reviewer's Analysis.

**Table 5: Baseline Characteristics, Study ERC-231 (ITT Population)**

<b>Baseline characteristics</b>	<b>Placebo N=77</b>	<b>0.25% DHEA N=79</b>	<b>0.50% DHEA N=81</b>	<b>Total N=482</b>
<b>Anthropometric measurements (mean)</b>				
Height (cm)	161.1	160.6	160.5	160.7
Weight (kg)	66.9	67.8	66.8	67.2
Body Mass Index (kg/m <sup>2</sup> )	25.7	26.2	25.9	26.0
<b>Reproductive history</b>				
Years since last menses (mean)	14.3	15.8	14.2	14.8
<b>Cause of last menses</b>				
Natural (%)	36 (47)	39 (49)	39 (48)	114 (48)
Surgical (%)	41 (53)	40 (51)	42 (52)	123 (52)
<b>Age (years) at last menses (mean)</b>				
All women	44.8	43.9	43.5	44.1
Natural menopause	47.4	49.2	48.5	48.4
Surgical menopause	42.6	38.8	38.9	40.1

Source: Reviewer's Analysis.

**Table 6: Subject Demographics, Study ERC-238 (ITT Population)**

<b>Demographic Parameters</b>	<b>Placebo N=157 n (%)</b>	<b>0.50% DHEA N=325 n (%)</b>	<b>Total N=482 n (%)</b>
<b>Age (years)</b>			
Mean years (SD)	59.6 (5.6)	59.6 (6.7)	59.6 (6.4)
Median	59	59	59
Range (Min - Max)	47 - 75	40 - 80	40 - 80
<b>Age Group</b>			
< 60 years	79 (50)	169 (52)	248 (51)
>=60 years	78 (50)	156 (48)	234 (49)
<b>Race</b>			
White	144 (92)	296 (91)	440 (91)
Black or African American	10 (6)	21 (6)	31 (6)
Asian	2 (1.3)	4 (1.2)	6 (1.2)
Other	1 (0.6)	4 (1.2)	5 (1.0)
<b>Ethnicity</b>			
Hispanic or Latino	11 (7)	38 (12)	49 (10)
Not Hispanic or Latino	146 (93)	287 (88)	433 (90)

Source: Reviewer's Analysis.

**Table 7: Baseline Characteristics, Study ERC-238 (ITT Population)**

<b>Baseline characteristics</b>	<b>Placebo N=157</b>	<b>0.50% DHEA N=325</b>	<b>Total N=482</b>
<b>Anthropometric measurements (mean)</b>			
Height (cm)	161.7	161.2	161.4
Weight (kg)	66.8	68.6	68.0
Body Mass Index (kg/m <sup>2</sup> )	25.6	26.3	26.1
<b>Reproductive history</b>			
Years since last menses (mean)	13.4	14.0	13.8
<b>Cause of last menses</b>			
Natural (%)	105 (67)	208 (64)	313 (65)
Surgical (%)	52 (33)	117 (36)	169 (35)
<b>Age (years) at last menses (mean)</b>			
All women	46.2	45.6	45.8
Natural menopause	48.8	48.6	48.7
Surgical menopause	41.1	40.2	40.5

Source: Reviewer's Analysis.

### 3.1.4 Results and Conclusions

#### 3.1.4.1 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.

#### **Moderate to severe dyspareunia as most bothersome symptom of vulvovaginal atrophy:**

The Most Bothersome Symptom (MBS) dyspareunia based on the pre-specified ANCOVA model with the treatment group as the main factor and the baseline value as the covariate are shown in Table 8 and 9 for Study ERC-231 and ERC-238, respectively. The subjects treated with 0.50% DHEA showed significantly greater improvement in their MBS than placebo-treated subjects in both studies in ITT population with LOCF. For Study ERC-231, the change from baseline in 0.25% DHEA treatment group was not significantly different from that of placebo in ITT population ( $p = 0.3423$ ). In order to support VVA indication, efficacy must be demonstrated with respect to all four co-primary efficacy endpoints, therefore only efficacy results for treatment group 0.50% DHEA will be discussed from this point on.

**Table 8: Change from Baseline to end-of-treatment for the most bothersome symptom dyspareunia (pain at sexual activity), Study ERC-231 (ITT Population, LOCF)**

<b>Pain at Sexual Activity</b>	<b>0.25% DHEA</b>	<b>0.50% DHEA</b>	<b>Placebo</b>
N	79	81	77
Baseline	2.56	2.63	2.58
Week 12	1.54	1.36	1.71
Mean Change (SD)	-1.01 (1.02)	-1.27 (0.99)	-0.87 (0.95)
Difference from Placebo <sup>1</sup>	-0.14	-0.40	
p-value <sup>2</sup>	0.3423	0.0132	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.6.3a in Clinical Report and Reviewer's analysis.

For study ERC-238, about 13% of patients excluded from ITT population after randomization due to failure of one or more required study entry criteria at baseline (Day 1). Our sensitivity analysis using safety population including these patients resulted in similar efficacy (Table 9).

**Table 9: Change from Baseline to end-of-treatment for the most bothersome symptom dyspareunia (pain at sexual activity), Study ERC-238 (LOCF)**

<b>Pain at Sexual Activity</b>	<b>0.50% DHEA</b>	<b>Placebo</b>
<b>Safety</b>		
N	374	180
Baseline	2.54	2.57
Week 12	1.13	1.48
Mean Change (SD)	-1.42 (1.00)	-1.09 (1.03)
Difference from Placebo <sup>1</sup>	-0.34	
p-value <sup>2</sup>	0.0001	
<b>ITT</b>		
N	325	157
Baseline	2.54	2.56
Week 12	1.13	1.50
Mean Change (SD)	-1.42 (1.00)	-1.06 (1.02)
Difference from Placebo <sup>1</sup>	-0.35	
p-value <sup>2</sup>	0.0002	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.6.3a in Clinical Report and Reviewer’s analysis.

As a sensitivity analysis to evaluate the impact of the LOCF approach, co-primary efficacy endpoints were analyzed using a mixed model repeated measures (MMRM) analysis as implemented in SAS Proc Mixed for Study ERC-238. This analysis has used all available data across time to estimate treatment effects, without the use of imputed values. The results for MBS (Table 10) showed essentially the same results and statistical significance as the ITT analysis using LOCF.

**Table 10: Change from Baseline to end-of-treatment for the most bothersome symptom dyspareunia (pain at sexual activity) without LOCF, Study ERC-238 (ITT)**

<b>Pain at Sexual Activity</b>	<b>0.50% DHEA</b>	<b>Placebo</b>
N	325	157
Baseline	2.54	2.56
Week 12	0.98	1.33
LS Mean Change (SEM)	-1.54 (0.05)	-1.20 (0.08)
Difference from Placebo <sup>1</sup>	-0.35	
p-value <sup>2</sup>	0.0004	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.1.1a.5s in Clinical Report and Reviewer’s analysis.

The results from additional supportive analysis conducted on corrected ITT and PP population for Study ERC-231 and ERC-238 in Tables 15-16 (Appendices) are also similar as the primary analysis.

**Vaginal Maturation:** As shown in Table 11 & 12, treatment with 0.50% DHEA resulted in an increase in the percentage of superficial cells and a decrease in the percentage of parabasal cells compared to placebo in ITT analysis population for Study ERC-231 and ERC-238.

**Table 11: Change from Baseline to end-of-treatment for Percentage of Superficial and Parabasal Cells, Study ERC-231 (ITT Population, LOCF)**

	0.25% DHEA	0.50% DHEA	Placebo
<b>Superficial Cells</b>			
N	79	81	77
Baseline	0.68	0.70	0.73
Week 12	5.43	6.30	1.64
Mean Change (SD)	4.75 (5.15)	5.62 (5.49)	0.91 (2.69)
Difference from Placebo <sup>1</sup>	3.84	4.71	
p-value <sup>2</sup>	<0.0001	<0.0001	
<b>Parabasal Cells</b>			
N	79	81	77
Baseline	65.72	65.05	68.48
Week 12	28.43	17.65	66.86
Mean Change (SD)	-37.29 (37.00)	-47.40 (42.50)	-1.62 (28.22)
Difference from Placebo <sup>1</sup>	-35.67	-45.8	
p-value <sup>2</sup>	<0.0001	<0.0001	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.06.2a in Clinical Report and Reviewer's analysis.

**Table 12: Change from Baseline to end-of-treatment for Percentage of Superficial and Parabasal Cells, Study ERC-238 (ITT Population, LOCF)**

	0.50% DHEA	Placebo
<b>Superficial Cells</b>		
N	325	157
Baseline	1.0	1.04
Week 12	11.22	2.78
Mean Change (SD)	10.20 (10.35)	1.75 (3.33)
Difference from Placebo <sup>1</sup>	8.46	
p-value <sup>2</sup>	<0.0001	
<b>Parabasal Cells</b>		
N	325	157
Baseline	54.25	51.66
Week 12	12.74	39.68
Mean Change (SD)	-41.51 (36.26)	-11.98 (29.58)
Difference from Placebo <sup>1</sup>	-29.53	
p-value <sup>2</sup>	<0.0001	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.06.2a 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 13-14. Treatment with 0.50% DHEA Vaginal Insert resulted in a statistically significant decrease in vaginal pH in both studies.

**Table 13: Change from Baseline to end-of-treatment for Percentage of vaginal pH, Study ERC-231 (ITT Population, LOCF)**

	0.25% DHEA	0.50% DHEA	Placebo
<b>Vaginal pH</b>			
N	79	81	77
Baseline	6.48	6.47	6.51
Week 12	5.70	5.43	6.31
Mean Change (SD)	-0.77 (0.90)	-1.04 (1.00)	-0.21 (0.69)
Difference from Placebo <sup>1</sup>	-0.57	-0.83	
p-value <sup>2</sup>	<0.0001	<0.0001	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.6.1a in Clinical Report and Reviewer's analysis.

**Table 14: Change from Baseline to end-of-treatment for Percentage of vaginal pH, Study ERC-238 (ITT Population, LOCF)**

	0.50% DHEA	Placebo
<b>Vaginal pH</b>		
N	325	157
Baseline	6.34	6.32
Week 12	5.39	6.05
Mean Change (SD)	-0.94 (0.94)	-0.27 (0.74)
Difference from Placebo <sup>1</sup>	-0.67	
p-value <sup>2</sup>	<0.0001	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.6.1a in Clinical Report and Reviewer’s analysis.

### 3.1.4.2 Results for Secondary Efficacy Endpoints

As discussed 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 evaluated in this review.

## 3.2 Evaluation of Safety

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

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Efficacy of DHEA Vaginal Insert 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 ANCOVA model described previously in section 3.1.2.3.

### 4.1 Gender, Race, Age, and Geographic Region

Both phase 3 studies were 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 shown in Tables 17-20 (Appendices). As shown in Table 19 (parabasal cells) and Table 18 (superficial cells), there is a tendency in the pooled data from ERC-231 and ERC-238 for some increased efficacy in the women aged  $\geq 65$  years while the opposite was observed for vaginal pH (Table 20) and dyspareunia (Table 17), although the studies were not powered to make valid conclusions from the subgroup analysis.

Based on these results by race, studies ERC-231 and ERC-238 did not show consistent pattern of treatment effect of DHEA vaginal insert relative to placebo in white and non-white subjects, Hispanic or Non-Hispanic.

## **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 ITT population, which contains subjects having vaginal pH >5, vaginal superficial cell  $\leq$ 5%, and a most bothersome moderate to severe vaginal symptom of dyspareunia at baseline and day 1.

Using pre-specified approaches, this reviewer confirmed that only 0.50% DHEA vaginal insert 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 0.25% DHEA vaginal insert, 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.

From a statistical perspective, data from the two submitted studies provided statistical evidence in support of Prasterone Vaginal Insert, administered intravaginally at the 6.5 mg dose (0.50% DHEA) once daily, in the treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.

## APPENDICES

**Table 15: Change from Baseline to end-of-treatment for the most bothersome symptom dyspareunia (pain at sexual activity), Supportive Analysis for Study ERC-231**

<b>Pain at Sexual Activity</b>	<b>0.25% DHEA</b>	<b>0.50% DHEA</b>	<b>Placebo</b>
<b>corrected ITT</b>			
N	77	80	75
Baseline	2.56	2.63	2.59
Week 12	1.52	1.36	1.76
Mean Change (SD)	-1.04 (1.02)	-1.26 (0.99)	-0.83 (0.92)
Difference from Placebo <sup>1</sup>	-0.21	-0.44	
p-value <sup>2</sup>	0.1661	0.0069	
<b>PP</b>			
N	69	70	65
Baseline	2.55	2.63	2.63
Week 12	1.49	1.33	1.71
Mean Change (SD)	-1.06 (1.03)	-1.30 (1.01)	-0.92 (0.91)
Difference from Placebo <sup>1</sup>	-0.13	-0.38	
p-value <sup>2</sup>	0.3648	0.0265	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.1.2.5 & 14.2.6.3b in Clinical Report and Reviewer's analysis.

**Table 16: Change from Baseline to end-of-treatment for the most bothersome symptom dyspareunia (pain at sexual activity) without LOCF, Supportive Analysis for Study ERC-238**

<b>Pain at Sexual Activity</b>	<b>0.50% DHEA</b>	<b>Placebo</b>
<b>mITT</b>		
N	305	143
Baseline	2.53	2.54
Week 12	1.02	1.37
Mean Change (SD)	-1.51 (0.96)	-1.17 (1.01)
Difference from Placebo <sup>1</sup>	-0.34	
p-value <sup>2</sup>	0.0003	
<b>PP</b>		
N	254	119
Baseline	2.52	2.55
Week 12	0.94	1.34
Mean Change (SD)	-1.57 (0.95)	-1.21 (1.03)
Difference from Placebo <sup>1</sup>	-0.39	
p-value <sup>2</sup>	0.0001	

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

Source: Table 14.2.6.3a.2 & 14.2.6.3b in Clinical Report and Reviewer's analysis.

**Table 17: Subgroup Analysis of Primary Endpoint Dyspareunia - Individual and Pooled Pivotal Clinical Trials ERC-231 and ERC-238 (ITT Population, LOCF)**

Subgroup	ERC-231		ERC-238		Pooled Studies	
	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)
<b>All Women</b>	-0.40 (81, 77)	(-0.71, -0.10)	-0.35 (325, 157)	(-0.54, -0.16)	-0.39 (406, 234)	(-0.55, -0.23)
<b>Age Group</b>						
<50 years	-0.67 (3, 6)	(-2.21, 0.88)	-1.08 (25, 5)	(-2.07, -0.09)	-0.92 (28, 11)	(-1.61, -0.23)
50-64 years	-0.34 (68, 60)	(-0.68, 0.01)	-0.41 (222, 122)	(-0.62, -0.19)	-0.41 (290, 182)	(-0.59, -0.22)
> 65 years	-0.68 (10, 11)	(-1.58, 0.21)	-0.11 (78, 30)	(-0.55, 0.33)	-0.21 (88, 41)	(-0.59, 0.18)
<b>Race</b>						
White	-0.44 (79, 67)	(-0.76, -0.12)	-0.34 (296, 144)	(-0.54, -0.13)	-0.38 (375, 211)	(-0.55, -0.21)
Black	-0.88 (1, 8)	(-3.70, 1.95)	-0.42 (21, 10)	(-1.11, 0.26)	-0.43 (22, 18)	(-1.02, 0.15)
Asia	NA (1, 1)	NA	-0.75 (4, 2)	(-2.09, 0.59)	-0.33 (5, 3)	(-1.52, 0.86)
Other	NA (0, 1)	NA	-0.25 (4, 1)	(-2.03, 1.53)	-0.75 (4, 2)	(-2.09, 0.59)
<b>Ethnicity</b>						
Hispanic or Latino	1.75 (8, 1)	(-0.85, 4.35)	-0.84 (38, 11)	(-1.55, -0.13)	-0.59 (46, 12)	(-1.28, 0.10)
Not Hispanic or Latino	-0.43 (73, 76)	(-0.74, -0.12)	-0.30 (287, 146)	(-0.50, -0.10)	-0.36 (360, 222)	(-0.53, -0.20)

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> 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 18: Subgroup Analysis of Primary Endpoint Superficial Cells - Individual and Pooled Pivotal Clinical Trials ERC-231 and ERC-238 (ITT Population, LOCF)**

Subgroup	ERC-231		ERC-238		Pooled Studies	
	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)
<b>All Women</b>	4.71 (81, 77)	(3.36, 6.06)	8.46 (325, 157)	(7.21, 9.70)	7.82 (406, 234)	(6.79, 8.85)
<b>Age Group</b>						
<50 years	0.50 (3, 6)	(-5.55, 6.55)	7.24 (25, 5)	(2.53, 11.95)	6.01 (28, 11)	(1.82, 10.20)
50-64 years	5.32 (68, 60)	(3.87, 6.77)	8.08 (222, 122)	(6.56, 9.59)	7.55 (290, 182)	(6.34, 8.75)
> 65 years	2.64 (10, 11)	(-1.73, 7.00)	10.07 (78, 30)	(7.60, 12.54)	9.14 (88, 41)	(6.81, 11.47)
<b>Race</b>						
White	4.70 (79, 67)	(3.31, 6.09)	8.62 (296, 144)	(7.32, 9.91)	7.88 (375, 211)	(6.82, 8.95)
Black	7.88 (1, 8)	(-0.54, 16.29)	7.14 (21, 10)	(2.43, 11.84)	7.16 (22, 18)	(2.75, 11.57)
Asia	NA (1, 1)	NA	13.75 (4, 2)	(-31.66, 59.16)	11.87 (5, 3)	(-12.55, 36.28)
Other	NA (0, 1)	NA	-1.75 (4, 1)	(-10.65, 7.15)	-0.75 (4, 2)	(-6.23, 4.73)
<b>Ethnicity</b>						
Hispanic or Latino	6.75 (8, 1)	(-11.91, 25.41)	9.48 (38, 11)	(6.09, 12.87)	9.15 (46, 12)	(6.20, 12.10)
Not Hispanic or Latino	4.38 (73, 76)	(3.03, 5.73)	8.40 (287, 146)	(7.07, 9.73)	7.72 (360, 222)	(6.62, 8.82)

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> 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 19: Subgroup Analysis of Primary Endpoint Parabasal Cells - Individual and Pooled Pivotal Clinical Trials ERC-231 and ERC-238 (ITT Population, LOCF)**

Subgroup	ERC-231		ERC-238		Pooled Studies	
	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)
<b>All Women</b>	-45.77 (81, 77)	(-57.07, -34.48)	-29.53 (325, 157)	(-35.63, -23.43)	-34.11 (406, 234)	(-39.38, -28.85)
<b>Age Group</b>						
<50 years	-41.33 (3, 6)	(-102.92, 20.25)	-43.60 (25, 5)	(-62.01, -25.19)	-37.86 (28, 11)	(-63.79, -11.94)
50-64 years	-43.85 (68, 60)	(-56.50, -31.20)	-24.61 (222, 122)	(-31.72, -17.50)	-30.24 (290, 182)	(-36.37, -24.10)
> 65 years	-60.23 (10, 11)	(-90.78, -29.67)	-44.24 (78, 30)	(-58.64, -29.83)	-47.56 (88, 41)	(-60.14, -34.98)
<b>Race</b>						
White	-45.01 (79, 67)	(-56.81, -33.22)	-29.91 (296, 144)	(-36.31, -23.52)	-34.25 (375, 211)	(-39.81, -28.70)
Black	-97.88 (1, 8)	(-161.68, -34.07)	-28.93 (21, 10)	(-57.90, 0.05)	-31.81 (22, 18)	(-53.71, -9.92)
Asia	NA (1, 1)	NA	-28.00 (4, 2)	(-124.72, 68.72)	-27.40 (5, 3)	(-87.49, 32.69)
Other	NA (0, 1)	NA	-8.00 (4, 1)	(118.36, 102.36)	-18.50 (4, 2)	(-85.51, 48.51)
<b>Ethnicity</b>						
Hispanic or Latino	-50.63 (8, 1)	(-142.25, 41.00)	-49.26 (38, 11)	(-63.12, -35.40)	-50.63 (46, 12)	(-63.21, -38.05)
Not Hispanic or Latino	-44.62 (73, 76)	(-56.52, -32.73)	-27.86 (287, 146)	(-34.31, -21.42)	-32.89 (360, 222)	(-38.44, -27.35)

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> 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 20: Subgroup Analysis of Primary Endpoint Vaginal pH- Individual and Pooled Pivotal Clinical Trials ERC-231 and ERC-238 (ITT Population, LOCF)**

Subgroup	ERC-231		ERC-238		Pooled Studies	
	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)	0.50% DHEA vs Placebo Diff. (N, N)	95% CI (LL, UL)
<b>All Women</b>	-0.83 (81, 77)	(-1.10, -0.56)	-0.67 (325, 157)	(-0.82, -0.51)	-0.39 (406, 234)	(-0.55, -0.23)
<b>Age Group</b>						
<50 years	-0.93 (3, 6)	(-1.50, -0.37)	-0.92 (25, 5)	(-1.81, -0.02)	-0.92 (28, 11)	(-1.49, -0.36)
50-64 years	-0.86 (68, 60)	(-1.17, -0.55)	-0.72 (222, 122)	(-0.90, -0.54)	-0.75 (290, 182)	(-0.91, -0.60)
> 65 years	-0.42 (10, 11)	(-1.10, 0.26)	-0.52 (78, 30)	(-0.90, -0.13)	-0.54 (88, 41)	(-0.82, -0.25)
<b>Race</b>						
White	-0.84 (79, 67)	(-1.12, -0.56)	-0.66 (296, 144)	(-0.82, -0.50)	-0.71 (375, 211)	(-0.85, -0.57)
Black	-0.68 (1, 8)	(-2.35, 1.00)	-1.13 (21, 10)	(-1.79, -0.46)	-1.04 (22, 18)	(-1.56, -0.53)
Asia	NA (1, 1)	NA	-0.63 (4, 2)	(-2.14, 0.89)	-0.54 (5, 3)	(-1.70, 0.62)
Other	NA (0, 1)	NA	1.55 (4, 1)	(0.08, 3.02)	0.95 (4, 2)	(-0.38, 2.28)
<b>Ethnicity</b>						
Hispanic or Latino	0.10 (8, 1)	(-2.28, 2.48)	-0.96 (38, 11)	(-1.59, -0.33)	-0.87 (46, 12)	(-1.46, -0.27)
Not Hispanic or Latino	-0.84 (73, 76)	(-1.13, -0.56)	-0.64 (287, 146)	(-0.80, -0.48)	-0.69 (360, 222)	(-0.83, -0.56)

<sup>1</sup> Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean)

<sup>2</sup> 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/  
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KATE L DWYER  
06/30/2016

MAHBOOB SOBHAN  
07/01/2016