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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA Number	208470
Link to EDR	http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=10020904
Submission Dates	10/16/15, 02/12/16 and 03/30/16
Submission Type	Original/ 505(b)
PDUFA Date	11/16/16
Brand Name	INTRAROSA
Generic Name	Prasterone (dehydroepiandrosterone, DHEA)
Dosage Form and Strength	6.5 mg vaginal insert
Route of Administration	Intravaginal
Proposed Indication	Treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy due to menopause
Applicant	EndoCeutics Inc.
Associated IND	IND 078027
Clinical Pharmacology Reviewer	Jihong Shon, M.D., Ph.D.
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OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Bone, Reproductive and Urologic Products

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1 EXECUTIVE SUMMARY

Prasterone (dehydroepiandrosterone, DHEA) is an endogenous hormone precursor and is converted to sex steroid hormones in peripheral tissues. Intravaginal insertion of prasterone is being proposed for treatment for the relief of symptoms due to vulvovaginal atrophy (VVA) in postmenopausal women.
The efficacy and safety data for prasterone vaginal insert were produced from one phase 1/2 study, one dose-finding study, two pivotal phase 3 studies and a long-term safety study. These clinical studies demonstrated that treatment with 6.5 mg prasterone vaginal insert in postmenopausal women causes significant changes in vaginal epithelial cells and has beneficial effects on moderate to severe dyspareunia as their most bothersome symptom of VVA.

This clinical pharmacology review focuses on systemic exposure to sex steroid hormones following daily administration of prasterone vaginal insert and its clinical implication.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 has reviewed the clinical pharmacology information submitted for NDA208470 of 6.5 mg prasterone vaginal insert. We find the application to be acceptable from a Clinical Pharmacology perspective, provided that an agreement on the language in the package insert is reached between the Applicant and the Division.

The key review issues with specific comments/recommendations are summarized below:

Review issues	Comments and recommendations
Supportive evidence of effectiveness	The changes in vaginal cell maturation index and vaginal pH sufficiently support the effectiveness of prasterone vaginal insert on moderate to severe dyspareunia. Two pivotal phase 3 studies using 6.5 mg prasterone vaginal insert demonstrated its clinical benefits in patients with moderate to severe dyspareunia as a symptom of VVA.
Supportive evidence of safety	While daily administration of 6.5 mg prasterone vaginal insert leads to additional systemic exposure to DHEA and its metabolites including testosterone and estrogens, the concentrations of sex hormones observed in most subjects appeared to be within the normal ranges reported in postmenopausal women. However, it is not known whether the additional systemic exposures to androgen and estrogen metabolites would result in any safety risk in postmenopausal women. It may warrant that a long-term safety monitoring in a larger population be evaluated, particularly for patients with the risk factor of hormone dependent diseases.
Dosing regimen for the general patient population	Once daily administration of 6.5 mg prasterone vaginal insert appears to be the lowest efficacious regimen for treatment of postmenopausal women who suffer from moderate to severe dyspareunia as a symptom of VVA.
Dosing regimen for subpopulations	Prasterone vaginal insert should be restricted in women with known, suspected, or history of breast cancer or estrogen-dependent neoplasia.

1.2 Post-Marketing Requirement and Commitment

None.

2 SUMMARY OF CLINICAL PHARMACOLPGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

DHEA (prasterone) is an endogenous steroid precursor that is secreted in the adrenal gland and is converted into active androgens and/or estrogens in peripheral tissues. The mechanism of action of prasterone vaginal insert in postmenopausal women with VVA has not been fully established.

The clinical pharmacokinetics of prasterone is summarized as follows:
Absorption: The absolute bioavailability of DHEA following administration of prasterone vaginal insert was not measured. Daily administration of 6.5 mg prasterone vaginal insert for 12 weeks increased the trough concentration (C_{trough}) of DHEA from 1.81 ng/mL at baseline to 2.67 ng/mL.
Distribution and elimination: Human steroidogenic enzymes such as hydroxysteroid dehydrogenases, 5a-reducatases and aromatases, transform DHEA into androgens and estrogens and their inactive metabolites. Androgen and estrogen metabolites transformed from DHEA are excreted as glucuronide or sulfone metabolite forms from systemic circulation. The treatment with 6.5 mg prasterone vaginal insert once daily for 12 weeks increased the C_{trough} of testosterone from 148.1 pg/mL to 178.9 pg/mL and increased estradiol (E2) from 2.76 pg/mL to 3.28 pg/mL in postmenopausal women with VVA.

2.2 Dosing and Therapeutic Individualization

2.1.1 General dosing

Once daily administration with 6.5 mg prasterone vaginal insert was proposed for treatment of (b) (4) (b) (4) menopausal women who suffer from moderate to severe dyspareunia as a symptom of VVA. The conducted studies demonstrated that the currently proposed prasterone vaginal insert is the lowest effective dose and has no major safety signal.

2.1.2 Therapeutic individualizations

The Applicant proposed no alternative dosing regimen and contraindication for the use of prasterone vaginal insert for subpopulations based on intrinsic or extrinsic factors. However, the use of prasterone vaginal insert should be restricted for patients with estrogen-dependent neoplasms such as breast and endometrial cancers because there is no available supporting safety data in these patient populations, especially as to how the additional systemic exposure to estrogens can affect long-term safety.

2.3 Outstanding Issues

Daily application of 6.5 mg prastereone vaginal insert leads to additional systemic exposure to testosterone and estrogens with DHEA. The mean serum C_{trough} of DHEA, testosterone, estrone (E1) and E2 increased by 47%, 21%, 24% and 19% from baseline after treatment for 12 weeks in two phase 3 studies. The concentrations of those hormones in most subjects appeared to be within the normal ranges reported in postmenopausal women. However, it is not known whether the additional systemic exposures to androgen and estrogen metabolites following use of prasterone vaginal insert in postmenopausal women would lead to any safety risks, including cardiovascular disorders and endometrial and breast cancer. It may warrant that a long-term safety monitoring in a larger population be evaluated, particularly for patients with the risk factor of hormone dependent diseases.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling recommendations:

- The use of prasterone vaginal insert should be restricted in women with known, suspected, or history of breast cancer or estrogen-dependent neoplasia. It should be stated that there is no available safety data in these patient populations.
- Caution should be exercised for the use of prasterone vaginal insert in patients with hepatic impairment.
- Information of drug interaction (7 DRUG INTERACTION) should include a description of the clinical implication regarding clinically significant interactions with sufficient supporting evidence. The current information of a theoretical interaction with drugs that inhibit estrogen and androgen formation should be deleted.
- The mechanism of action should include the established mechanism(s) of the drug's pharmacological action in humans. If it is not addressed, “12.1 Mechanism of Action” should contain a statement about lack of information.
- Information of pharmacokinetics (12.3 Pharmacokinetics) should include a description of the pharmacokinetic profile or the systemic exposure of DHEA and its metabolites including testosterone and estrogen(s). The pharmacokinetic profile (24-hour profile after insertion and serial trough concentration for 12 weeks) of DHEA and major metabolites such testosterone and E2 should be addressed in this section.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1. Currently available treatment options for VVA

VVA is a condition that results from decreased estrogen in the genitourinary tissue and occurs commonly in postmenopausal women. The related symptoms include vaginal dryness, irritation, itching, soreness, burning, dyspareunia, discharge, urinary frequency, and urgency. Treatments for the relief of symptoms due to VVA are non-hormonal vaginal lubricants and moisturizers and systemic and vaginal estrogen

therapies. Estrogen treatments restore vaginal epithelial condition and relive the related symptoms effectively (*Palacios et al. 2015*).

While systemic estrogen treatment can relieve vaginal symptoms due to menopause, systemic hormone therapy is recommended to treat other menopausal symptoms such as vasomotor symptoms. Ten to 15% of women on systemic hormone therapy may not have adequate relief of the symptoms due to VVA and may need additional vaginal estrogen treatment (*The North American Menopause Society 2013*). In addition, systemic estrogen treatment may increase risk of cardiovascular disorders and hormone dependent malignancies such endometrial and breast cancers.

Vaginal estrogen products (cream, tablet and ring) which contain a relatively lower dose of estradiol are recommended preferentially in women whose genitourinary symptoms are the only complaint and do not respond to initial management approaches using non-hormonal treatments (*Stuenkel et al. 2015*). However, the clinical impact of the transient elevation in serum estrogen levels following administration of vaginal estrogen products has not been elucidated clearly especially regarding long-term endometrial safety (*The North American Menopause Society 201*3).

3.1.2. Development background of prasterone vaginal insert

Prasterone is an endogenous hormone precursor and is converted to sex steroid hormones in peripheral tissues. The Applicant has suggested that estrogens and androgens made from DHEA in a cell- and tissue-specific manner could provide beneficial effects to relieve symptoms due to VVA in postmenopausal women (*Labrie 2015; Warner and Gustafsson 2015*).

It has been proposed that intravaginal insertion of prasterone provides DHEA directly inside the vaginal cells and produces the estrogenic and androgenic activities required for the normal morphology and function of the vagina via transformation of DHEA into androgens and estrogens. Vaginal administration of low dose DHEA may avoid clinically significant changes in systemic sex hormones and diminish sex hormones-dependent safety concerns in postmenopausal women.

3.1.3. Regulatory background of prasterone vaginal insert

The Applicant submitted a NDA for prasterone vaginal insert on October 16, 2015. This product is formulated as 6.5 mg prasterone in 1.3 mL vaginal insert for treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause.

In support of this NDA, the Applicant conducted 6 clinical studies in the target patient population. The efficacy and safety data to support an approval of 6.5 mg prasterone vaginal insert for the proposed indication were generated from one phase 1/2 study, one dose-finding study, two pivotal phase 3 studies and a long-term safety study.

The pharmacokinetic profile of DHEA and its metabolite on Day 1 and Day 7 following daily administration of prasterone vaginal insert was characterized in the target population (Study ERC-213). In addition, the trough serum concentrations of DHEA and its metabolites were measured at baseline and post-baseline time-point(s), up to 12 months, in all clinical studies. The Applicant also submitted several non-clinical studies and publications to support this NDA.

The Office of Process and Facilities has determined that prasterone is not a new molecular entity (NME) because it has been previously marketed as a drug (refer to the product quality memo in DARRTS dated December 21, 2015).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	DHEA is an inactive endogenous steroid precursor and is converted into active androgens and/or estrogens in peripheral tissues by intracellular metabolism. It has been proposed that this vaginal insert provides DHEA directly inside the vaginal cells and produces the estrogenic and androgenic activities required for the normal morphology and function of the vagina via transformation of DHEA into testosterone, E1 and E2. However, the mechanism of action of DHEA vaginal insert in postmenopausal women with VVA has not been fully established.
QT Prolongation	The effect of exogenous DHEA administration on QT prolongation has not been assessed via preclinical hERG study or thorough QT trial. It has been reported that exogenous estrogen only treatment lengthens the QT interval in women (*Sedlak et al. 2012*). However, when considering the relatively small increase in systemic exposure to estrogens as well as DHEA after administration of DHEA vaginal insert in postmenopausal women, adverse effect on the QT interval is unlikely to happen.
General Information	
Bioanalysis	The serum concentrations of DHEA and its metabolites in clinical studies were analyzed using validated Gas Chromatography - Mass Spectrometry (GC-MS) or Liquid Chromatography - Mass Spectrometry / Mass Spectrometry (LC-MS/MS) (refer to appendix 4.1).
The pharmacokinetic profile of DHEA and its metabolites following daily dosing of 6.5 mg prasterone vaginal insert	The serum concentrations of DHEA appeared to be higher on Day 1 (after the first dose) than Day 7 following daily administration of 6.5mg prasterone vaginal insert. Otherwise, the systemic exposure (based on AUC_{24}) to the metabolites including E1 and E2 tended to be higher on Day 7 compared to Day 1 (Table 1, Study ERC-213). The C_{trough} of DHEA and its metabolites increased up to 2-week or 4-week following daily application of 6.5 mg prasterone vaginal insert and then remain constant without any significant change up to 1 year (Study ERC-210 and ERC-230). When compared to the baseline, the mean C_{trough} of DHEA and its metabolites at 12 weeks increased 19 – 47% (Table 2, Study ERC-231 + ERC-238).

The pharmacokinetic profile of DHEA and its metabolites following daily dosing of 6.5 mg prasterone vaginal insert

Table 1. The baseline uncorrected maximum concentration (C_{max}) and AUC_{24} of DHEA, testosterone, E1 and E2 on Day 1 and Day 7 following daily administration of 6.5 mg prasterone vaginal insert in 10 postmenopausal women with VVA (mean ± S.D).

	Parameter	Day 1 (after the first dose)	Day 7 (after the 7th dose)
DHEA	C_{max} (ng/mL)	5.97 (±1.40)	4.42 (±1.49)
	AUC_{24} (ng·h/mL)	65.49 (±24.67)	56.17 (±28.27)
Testosterone	C_{max} (ng/mL)	0.15 (±0.05)	0.15 (±0.05)
	AUC_{24} (ng·h/mL)	2.79 (±0.92)	2.79 (±0.95)
E1	C_{max} (pg/mL)	17.10 (±6.36)	19.45 (±9.51)
	AUC_{24} (pg·h/mL)	336.52 (±120.04)	369.69 (±154.51)
E2	C_{max} (pg/mL)	4.62 (±2.28)	5.04 (±2.68)
	AUC_{24} (pg·h/mL)	87.79 (±35.86)	96.93 (±51.67)

Table 2. Mean serum C_{trough} of DHEA, testosterone, E1 and E2 on Day 1 (baseline) and 12 weeks following daily administration of 6.5 mg prasterone vaginal insert in postmenopausal women in two phase 3 studies (mean ± S.D).

	Population (N)	Baseline	12 weeks	% change from baseline
DHEA (ng/mL)	336	1.81 ± 1.56	2.67 ± 1.86**	47% ↑
Testosterone (ng/mL)	360	148.1 ± 95.1	178.9 ± 104.3**	21% ↑
E1 (pg/mL)	361	14.81±11.18	18.37±24.43**	24% ↑
E2 (pg/mL)	359	2.76 ± 1.71	3.28 ± 1.99**	19% ↑

This data came from the cITT-S population including all subjects having steroid measurements at both Day 1 and Week 12 and excludes subjects with a serum estrogen signature (suspicious of concomitant estrogen treatment); ** $p < 0.0001$ for comparisons with baseline

Range of effective dose

In two studies, three tested doses, 3.25 mg, 6.5mg and 13 mg prasterone, showed significant changes in vaginal cell maturation and pH in dose-dependent manner (Study ERC-210 and ERC-231). While the treatment with 6.5mg prasterone for 12 weeks showed statistically significant difference in the pain at sexual activity compared to the placebo group, the group with 3.25 mg prasterone did not (Study ERC-231). The changes in the vaginal tissue and the severity score of the most bothersome symptom showed no significant difference between 6.5 mg and 13 mg prasterone vaginal inserts (Study ERC-210). Thus, 6.5 mg prasterone vaginal insert was chosen for the phase 3 studies and became the finally proposed dose.

Absorption

Bioavailability

Absolute bioavailability was not measured.

Elimination

Metabolism

DHEA is an inactive precursor steroid secreted in adrenal gland. Human steroidogenic enzymes such as hydroxysteroid dehydrogenases, 5α-reducatases and aromatases which are expressed in a tissue-specific manner are involved in the transformation of DHEA into active sex hormones including androgens and estrogens and their inactivation. Steroid-inactivating enzymes including uridine

	glucuronosyl transferases (UGT) and sulfontrasferases (SULT) expressed in the liver and extra-hepatic tissues convert active sex hormones into inactive sulfone or glucuronide metabolites.
Excretion	Androgen and estrogen metabolites transformed from DHEA are excreted from the systemic circulation as glucuronide or sulfone metabolites.
In vitro interaction liability (Drug as perpetrator)	
Inhibition of metabolism	Co-incubation of DHEA at various concentrations up to 10 μM did not affect the activities of CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 (Study PH-38062). Pre-incubation study showed no time-dependent inhibition of DHEA on the activities of CYP3A4 (Study PH-38062).

3.3 Clinical Pharmacology Questions

3.3.1 Does the available clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The changes in vaginal cell maturation index (percentage of parabasal and superficial cells) and vaginal pH assessed as efficacy parameters sufficiently support the effectiveness of prasterone vaginal insert on moderate to severe dyspareunia. Two pivotal phase 3 studies administering 6.5 mg prasterone vaginal insert once daily demonstrated its clinical benefits in patients with moderate to severe dyspareunia as a symptom of VVA. Additional details are provided below.

- Dose-efficacy response in patient population:

In the dose-response study (ERC-210) using three dose strengths (3.25 mg, 6.5 mg and 13 mg prasterone), all active treatment groups showed significant changes in vaginal cell maturation and pH at 12 weeks in dose-dependent manner. The treatments with 6.5 mg and 13 mg prasterone appear to reach the maximum changes in the vaginal cells maturation and vaginal pH at 4 or 8 weeks and then these changes tended to remain steady (Figure 1).

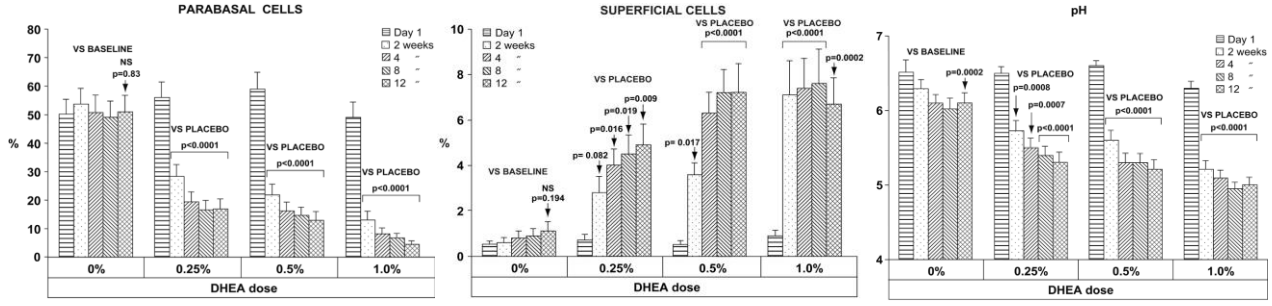


Figure 1. Effect of daily application of placebo (N=41), 3.25 mg (N=43), 6.5 mg (N=50) and 13 mg (N=43) prasterone vaginal insert for 2, 4, 8 and 12 weeks on the percentage of vaginal parabasal and superficial cells and vaginal pH (means ± SEM); p values = comparison with baseline. [Source: page 441 to 444 in the clinical study report of ERC-210]

- Efficacy results from the pivotal phase 3 studies:

Daily application of 6.5 mg prasterone vaginal insert for 12 weeks resulted in significant changes in the percentage of vaginal parabasal and superficial cells and vaginal pH. The results from the pivotal Phase 3 Study (ERC-238) are summarized in the Table 3.

Table 3. The effect of daily application of 6.5 mg prasterone vaginal insert for 12 weeks on the percentage of vaginal parabasal and superficial cells and vaginal pH (ITT population: Study ERC-238)

		Baseline	6 weeks	12 weeks
		Mean ± S.D.		
6.5 mg prasterone vaginal insert (N=325)	% of parabasal cells	54.25 ± 37.59	14.72 ± 19.65*	12.74 ± 18.39*
	% of superficial cells	1.02 ± 1.44	11.71 ± 11.00*	11.22 ± 10.10*
	Vaginal pH	6.34 ± 0.72	5.47 ± 0.90*	5.39 ± 0.90*
Placebo (N=157)	% of parabasal cells	51.66 ± 37.59	42.35 ± 34.21	39.68 ± 33.58
	% of superficial cells	1.04 ± 1.38	2.60 ± 3.38	2.78 ± 3.38
	Vaginal pH	6.32 ± 0.63	6.06 ± 0.88	6.05 ± 0.88

* p-value < 0.0001: comparison with the placebo group.

Daily application of 6.5 mg prasterone vaginal insert for 12 weeks significantly decreased pain at sexual activity (dyspareunia) as the most bothersome symptom of VVA (Figure 2).

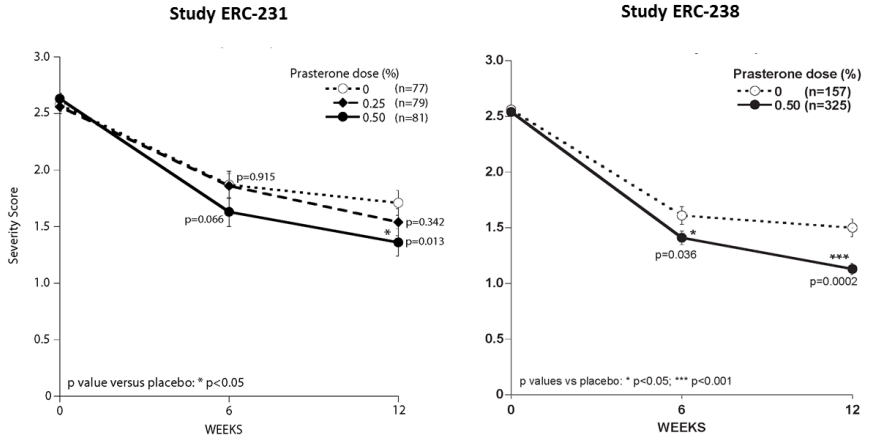


Figure 2. Effect of daily application of placebo, 0.25 % and 0.50% DHEA vaginal inserts for 6 and 12 weeks on the severity score of pain at sexual activity (dyspareunia) as being the most bothersome symptom (means ± SEM); p-values = comparisons with placebo. [Source: page 93 and page 100 in the clinical study reports of ERC-231 and ERC-238, respectively]

- Effects of once daily dosing regimen of 3.25 mg prasterone and twice weekly dosing regimen of 6.5 mg parstereone:

Daily administration with the tested lowest dose, 3.25 mg prasterone, also showed significant changes in vaginal cell maturation and pH in the patient population (Study ERC-231). However, this dose regimen failed to show statistically significant difference in the pain at sexual activity as a primary parameter compared to the placebo group. The clinical trial of twice weekly regimen with 6.5 mg prasterone following daily treatment for 2 weeks demonstrated that the effect on the parabasal and superficial cells and vaginal pH appeared to be diminished after reaching the maximum at 2 weeks (Study ERC-234). Therefore, these dosing regimens were not further evaluated by the Applicant.

3.3.2 Does the available clinical pharmacology information provide supportive evidence of safety?

Yes. While daily administration of 6.5 mg prasterone vaginal insert leads to additional systemic exposure to testosterone and estrogens with DHEA in postmenopausal women with VVA (the mean serum C_{trough} of DHEA, testosterone, E1 and E2 increased by 47%, 21%, 24% and 19 %, respectively after treatment for 12 weeks), the concentrations of sex hormones observed in most subjects appeared to be within the normal ranges reported in postmenopausal women. In addition, there was no serious adverse event related with administration of prasterone vaginal insert except for one case of breast cancer. The concentrations of estrogens following administration of prasterone vaginal insert observed in the patient with breast cancer do not support a relationship between exposure to prasterone vaginal insert and occurrence of breast cancer (see below for additional details). In 752 subjects who exposed to prasterone vaginal insert and underwent an endometrial biopsy at screening as well as after treatment (up to 52 weeks), there were no clinically significant histologic findings. However, it is not known whether the additional systemic exposures to androgen and estrogen metabolites following prasterone vaginal insert have any association with safety risks including cardiovascular disorders and endometrial and breast cancer in postmenopausal women. It may warrant that a long-term safety monitoring in a larger population should be evaluated, particularly for the group with the risk factor of hormone dependent diseases.

- Adverse events reported following application of DHEA vaginal insert:

There was no serious adverse event related with administration of prasterone vaginal insert except for one case of breast cancer. Application site discharge was the most common drug-related adverse event in all treatment groups including placebo (7.1% for all active treatment groups vs 3.4% for placebo group). The incidence of other commonly reported adverse events showed no statistical difference between active treatment and placebo groups in the safety population.

One subject (230-02-061, 57-year-old) was diagnosed as infiltrating ductal breast carcinoma in March 2012 after the completion of treatment with 6.5 mg prasterone vaginal insert for 52 weeks (March 2011 to February 2012). She declared that she did not take any hormone therapy and had no previous history of breast disease at screening, but it was found later that she underwent a stereotaxic biopsy of the right breast for microcalcifications in September 2005. No malignant change was found at that time. The pre-study mammogram performed in December 2010 was considered normal based on the absence of changes compared to the previous exam. The Investigator estimated that this event was possibly drug-related to prasterone. However, the Applicant concluded that this breast tumor cannot be attributed to treatment with prasterone vaginal insert because (1) breast tumors evolve over a much longer time period before reaching such a stage, (2) prasterone inhibits breast tumor growth in numerous breast cancer models, and (3) this woman's serum steroid concentrations did not vary significantly and remained well within the normal postmenopausal range during the study. The serum concentrations of estrogens following treatment with prasterone vaginal insert were not significantly different from her baseline value and those in other subjects (Table 4). This finding suggests that the concentrations estrogens observed in this patient is unlikely to support a relationship between exposure to estrogen and occurrence of breast cancer.

Table 4. The serum concentration of DHEA and estrogen concentrations in subject 230-02-061.

	Day 1 (baseline)	Week 12	Week 26	Week 52
DHEA (ng/mL)	1.39	3.09	2.29	3.83
E1 (pg/mL)	18.3	20.7	23.3	17.9
E2 (pg/mL)	4.4	4.5	5.7	5.0
Estrone sulfate (pg/mL)	254	279	242	200

3.3.3 Is the proposed dosing regimen appropriate for the general patient population?

Yes. When considering the efficacy profile of various concentrations of DHEA vaginal inserts and no major safety signal from the conducted studies, the currently proposed daily dose with 6.5 mg prasterone appears to be the lowest efficacious regimen for treatment of postmenopausal women who suffer from moderate to severe dyspareunia as a symptom of VVA.

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

Yes. The Applicant proposed no contraindication for the use of prasterone vaginal insert and no alternative dosing regimen for specific populations. This reviewer recommends that the use of prasterone vaginal insert be restricted in patients with breast and endometrial cancer because there is insufficient information to support the use of prasterone vaginal insert in these patient populations. Additional details are discussed below.

- Use of prasterone vaginal insert in patients with breast and endometrial cancer:

All estrogen treatments for postmenopausal women, including products administered vaginally, are contraindicated in patients with history of breast cancer or estrogen-dependent neoplasia. Anti-estrogen treatments such as aromatase inhibitors can have a significant negative effect on urogenital atrophy and thus require the treatment of the related symptoms (Mazzarello et al. 2015). There is no available treatment other than the use of topical non-hormonal products. While estradiol vaginal ring and tablet have been shown to improve quality of life and vaginal mucosal maturation index in small number of women with significant symptoms of urogenital atrophy, the clinical impact of the transient elevation in serum estradiol levels were not assessed fully and needs further investigation (Simmons et al. 2012).

While the Applicant proposed no contraindication of prasterone vaginal insert women with estrogen-dependent neoplasia such as breast and endometrial cancers, women with these conditions were excluded from all performed clinical trials. In addition, there is no available data as to how the additional systemic exposure to estrogens due to application of prasterone vaginal insert can affect the long-term safety in these patient populations. Additional safety data from a long-term follow-up study should be provided to support the use of prasterone vaginal insert in patients with estrogen-dependent neoplasia. From the clinical pharmacology perspective, this reviewer recommends that prasterone vaginal insert be restricted for patients with estrogen-dependent neoplasia until there is adequate data demonstrating acceptable safety profile in these populations.

- Use of prasterone vaginal insert in patients with hepatic impairment:

Estrogen products for treatment of postmenopausal symptoms are contraindicated in patients with liver disease. Estrogens are transformed and undergo enterohepatic recirculation mainly in the liver. Thus, they may be poorly metabolized in women with impaired hepatic function. Given that systemic exposure to DHEA and its metabolites increases in postmenopausal women following administration of prasterone vaginal insert, it is anticipated that there may be a certain level of additional increase in systemic exposure to them in patients with hepatic impairment. Systemic safety concern related to systemic exposure to androgens and estrogens cannot be ruled out without data evaluating changes in sex hormones concentration or safety after treatment of prasterone vaginal insert in patients with hepatic disease.

Patients with hepatic impairment were not restricted from participating in the two phase 3 studies (Study ERC-231 and ERC-238). There were subjects whose liver function tests (aspartate aminotransferase [ALT], alanine aminotransferase [AST] and total bilirubin) at screening and Day 1 that were above the upper limit of normal range (ULN), but most of them showed mild increases of ALT and AST (the proportions of subjects showing ALT and AST higher than 2-fold of their ULN at screening were approximately 1.2% and 0.4% out of study population, respectively) and there were few (approximately 0.7% of study population) patient(s) who had abnormality of total bilirubin at screening. Therefore, this reviewer concludes that the data submitted in the NDA do not provide adequate safety information for the population with hepatic disease.

Given that there is a lack of evidence to support the safety of this product in patients with liver disorders, this reviewer recommends that more clinical data is needed to support the use of prasterone vaginal insert in patients with hepatic disorders.

- Use of prasterone vaginal insert for patients with renal impairment:

Estrogen products for treatment of postmenopausal symptoms currently do not have any restriction or dose adjustment recommendation for patients with renal impairment. The Applicant proposed no dose adjustment of prasterone vaginal insert in women with renal impairment. Patients with renal impairment were not restricted from participating in the two phase 3 studies (Study ERC-231 and ERC-238). However, there was a limited number of patients with moderate or severe renal impairment (only two subjects had serum creatinine higher than 1.5-fold of its ULN) in the two phase 3 studies.

A pharmacokinetic study of oral E2 in postmenopausal women with end stage renal disease (ESRD) demonstrated that the mean free E2 concentration in women with ESRD was higher by 20% than that in healthy control group, even though women with renal impairment received half a dose of E2 (Stehman-Breen et al. 2003). The mean total E2 concentrations in women with ESRD tended to be slightly lower than that in healthy control group, but this difference was not statistically significant. These results may suggest that a dose reduction of estrogen products is necessary for women with ESRD. However, this study using oral E2 product was conducted only in patients with ESRD and may have a limitation to generalize its result to all types of estrogen products as well as DHEA. In addition, when considering the limited contribution of kidney to metabolism and excretion of sex hormones and the local route of administration of this vaginal insert, it is not anticipated that there would be clinically significant changes in systemic exposure to DHEA and its metabolites in patients with renal impairment.

From the clinical pharmacology perspective, there is no convincing evidence to support recommending a dose adjustment or restriction in patients with renal impairment even though prasterone vaginal insert has not been evaluated in the populations with moderate or severe chronic kidney disease.

3.3.5 Are there clinically relevant drug-drug interactions?

No. A clinically significant pharmacokinetic interaction of prasterone vaginal insert with concomitant drugs is unlikely to happen. The Applicant evaluated the in vitro interaction potential of DHEA (up to 10 μM of DHEA; the C_{max} of DHEA after the 1st dose of 6.5 mg prasterone vaginal insert was approximately 0.02 μM) on CYP isoforms using human liver microsomes. The results showed that drug-drug interactions through inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 by DHEA was unlikely.

The Applicant described an interaction potential of antiestrogen treatment on the efficacy of DHEA vaginal insert in the submitted label (Section 7) based on a theoretical mechanism. However, there was no information supporting any clinical significance due to this interaction. In addition, prasterone vaginal insert is not recommended to use for women with breast cancer or estrogen-dependent neoplasia. This reviewer concluded that this theoretical interaction should be deleted at this point.

3.3.6 Is there adequate safety data for male partners?

No. However, given that the dose of DHEA applied on this vaginal insert is small and penile skin tissue has relatively inefficient absorptive capacity, acute or temporary exposure of the male partner to DHEA vaginal insert through sexual activity is unlikely to cause any significant systemic adverse effects. Additional details are provided below.

- Evaluation of the subject's male partners:

In a subset population of the subject's male partners (66 male partners) who had intercourse for the last 2 months in Study ERC-238, the effect of prasterone vaginal insert was evaluated using questionnaires at screening and 12 weeks. There was no adverse event reported voluntarily from the male partners in this study. However, all questions given to the participants were related to satisfaction before and after the women's use of prasterone vaginal insert. In addition, there was no evaluation of systemic exposure to sex hormones in the male partners. This reviewer concludes that this evaluation is not sufficient to address safety related issue in the exposed partners.

- Absorption of topical agents through the dermis of the penis:

Systemic absorption can occur following topical application to the penis. In general, however, transferring through dermal matrix of penis is inefficient and requires a large amount of applied drug for systemic exposure because penis has a unique set of anatomy and physiology such as multi-layers between skin and corpora cavernosa (Male Sexual Function: A Guide to Clinical Management. John Mulcathy 2006). This suggests that there would be limited transfer to the male partner.

- Safety of treatments with DHEA supplements in men:

Oral treatments with DHEA as exogenous substance have been studied in men for diverse indications. These studies showed satisfactory safety profile and reported no serious adverse event following oral

administration of daily doses from 25 mg up to 1600 mg DHEA (Labrie 2010). However, data on the safety profile of long-term DHEA supplementation are still lacking (Samaras et al. 2013).

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The serum concentrations of DHEA and its metabolites, androst-5-ene-3, β17β-diol (5-diol), Dihydrotestoterone (DHT), Testosterone, Androstenedione (4-dione), E1, E2, Dehydroepiandrosterone Sulfate (DHEA-S), Estrone sulfate (E1-S), Androsterone Glucuronide (ADT-G), Androstane-3α, 17β – diol 3-glucuronide (3α-diol-3G), Androstane-3α,17β-diol 17-Glucuronide (3α-diol-17G), in clinical studies were analyzed using validated GC-MS or LC-MS/MS (Table 5). The bioanalytical methods for each analyte were adequately validated. The results of bioanalytical methods for DHEA, testosterone, E1 and E2 are summarized in table 6.

Table 5. Bioanalytical methods for the measurement of DHEA and its metabolites in clinical study samples

Clinical study number	Analytes	Methods
ERC-210 and ERC-213	DHEA, 5-diol, DHT, testosterone, 4-dione, E1, and E2	GC-MS
	ADT-G, 3α-diol-3G, 3α-diol-17G, DHEA-S and E1-S	LC-MS/MS
ERC-230, ERC-231, ERC-234 and ERC-238	DHEA, 5-diol, DHT, testosterone, 4-dione, E1, E2, DHEA-S, E1-S, ADT-G, 3α-diol-3G, and 3α-diol-17G	LC-MS/MS

Table 6. Summary of bioanalysis performance characteristics for measurement of DHEA and three sex hormones

Analyte	Methods	Assay range	Performance characteristics of QC samples				Long term stability
			Intra-run accuracy	Intra-run precision	Inter-run accuracy	Inter-run precision	
DHEA	GC-MS	0.5-50 ng/mL	-10.3 - +11.1 %	1.6 - 8.6 %	+0.4 - +4.6%	4.6 - 9.2 %	111 days at -20 ºC
	LC-MS/MS	0.5-25 ng/mL	-7.4 - -2.7 %	2.7 - 3.9 %	-6.7 - -4.8 %	3.8 - 5.5 %	
Testosterone	GC-MS	0.4-10 ng/mL	-4.5 - +5.9 %	1.0 - 2.8 %	-3.2 - +2.7 %	1.7 - 3.2 %	113 days at -20 ºC
	LC-MS/MS	0.05-2.5 ng/mL	-5.9 - -1.8 %	2.3 - 2.7 %	-4.4 - -1.8 %	3.5 - 4.0 %	
E1	GC-MS	20-400 pg/mL	-4.6 - +7.5 %	1.8 - 8.0 %	-1.1 - +2.0 %	4.1 - 7.0 %	111 days at -20 ºC
	LC-MS/MS	4-200 pg/mL	-6.8 - +0.2 %	0.8 - 6.0 %	-4.2 - -1.1 %	4.5 - 5.4 %	
E2	GC-MS	5-400 pg/mL	-6.2 - +5.7 %	1.7 - 3.4 %	-5.2 - +2.8%	2.5 - 3.1 %	113 days at -20 ºC
	LC-MS/MS	1-50 pg/mL	-3.2 - +2.2 %	2.5 - 4.4 %	-6.0 - -0.1%	4.5 - 6.2 %	

The bioanalytical methods met the Agency's recommended acceptance criteria. The laboratories for bioanalysis were (b) (4)

4.2 Clinical Pharmacokinetic Assessment

4.2.1 Systemic exposure of DHEA

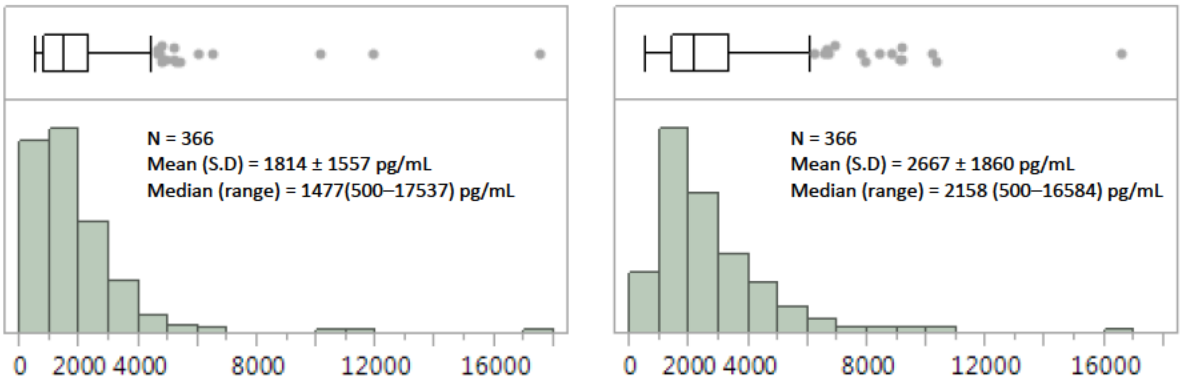
Daily application of 6.5 mg prasterone vaginal insert for 12 weeks increased C_{trough} of DHEA by up to about 50% when compared to the baseline value (Table 6).

Table 6. Mean serum trough concentrations of DHEA (ng/mL) on Day 1 (baseline) and 12 weeks following daily administration of 6.5 mg prasterone vaginal insert in postmenopausal women in two phase 3 studies.

	Study ERC-231				Study ERC-238			
	N	Baseline	12 weeks	% change	N	Baseline	12 weeks	% change
ITT-S	72	1.89±1.19	2.49±1.37**	32% ↑	300	1.80±1.63	2.69±1.95**	49% ↑
cITT-S	71	1.86±1.18	2.48±1.38**	33% ↑	295	1.80±1.64	2.71±1.96**	51% ↑

ITT-S = Intent-to-treat population having measurements at both baseline and 12 weeks; cITT-S = excluding subjects with a serum estrogen signature; * $p < 0.05$ and ** $p < 0.0001$ for comparisons with baseline

The comparison of before and after daily administration of 6.5 mg prasterone vaginal insert for 12 weeks in the cITT-S populations of two pivotal phase 3 studies (ERC-231 and ERC-238) demonstrated that the overall distribution of individual trough serum concentrations of DHEA appeared to be shifted to the right and more widely scattered after treatment (Figure 3). The arithmetic mean and median values increased by 47% and 46%, respectively.



(a) DHEA at baseline (pg/mL) (b) DHEA at 12 weeks (pg/mL)

Figure 3. Distribution of trough serum concentrations of DHEA with box and whiskers plots before (a) and after (b) daily application of 6.5 mg prasterone vaginal inserts for 12 weeks in the cITT-S populations pooled from two phase 3 studies (ERC-231 and ERC-238). [Analysis using the dataset of ERC-231 and ERC-238 studies]

The percentage of subjects showing C_{trough} of DHEA above the upper normal range (3990 pg/mL) in postmenopausal women (the 95th percentile of the normal population proposed by the Applicant) increased from 5.19% (19/366) at baseline to 17.76% (65/366) after 12 weeks of treatment with 6.5 mg prasterone vaginal insert.

4.2.2 Systemic exposure of sex steroid hormones

All performed clinical studies measured the trough serum concentrations of sex steroid hormones including testosterone, E1 and E2, which can be transformed from DHEA, to address the safety issues related with additional exposure to those hormones in postmenopausal women. The mean serum C_{trough} of testosterone and E1 appeared to be higher at 12 weeks than the values at baseline (Table 7). It should be noted that this comparison based on C_{trough} may underestimate the magnitude of increase in drug

exposure since it does not take into account the C_{max} or the overall concentration-time profile following administration of prasterone vaginal insert.

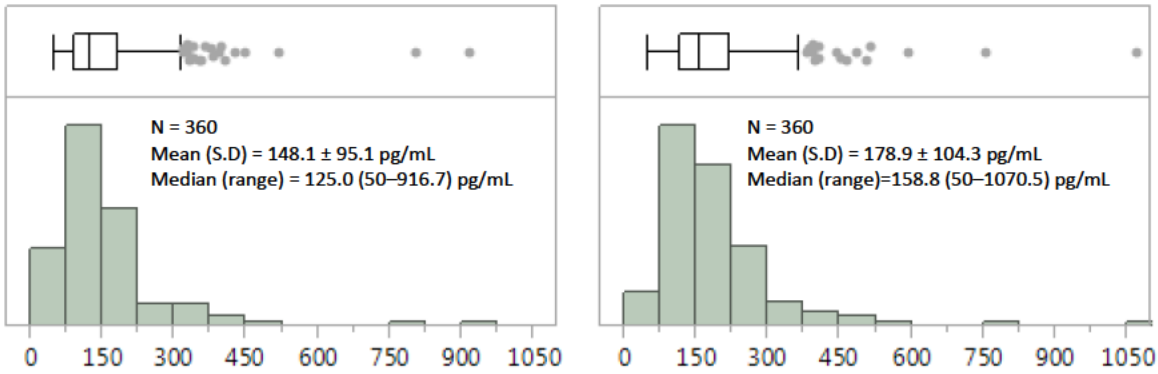
Table 7. Mean trough serum concentrations of testosterone, E1 and E2 on Day 1 (baseline) and 12 weeks following daily application of 6.5 mg prasterone vaginal insert in postmenopausal women in two phase 3 studies (Reanalysis by the reviewer using the Applicant's dataset)

		ERC-231				ERC-238			
		N	Baseline	12 weeks	% change	N	Baseline	12 weeks	% change
Testosterone (pg/mL)	ITT-S	72	139.3±75.9	160.6±83.0**	15% ↑	293	150.6±98.7	183.5±107.9**	22% ↑
	cITT-S	71	139.8±76.3	160.6±83.6**	15% ↑	289	150.1±99.2	183.4±108.4**	22% ↑
E1 (pg/mL)	ITT-S	72	15.79±15.46	17.97±11.02	14% ↑	295	15.32±12.49	19.11±27.38*	25% ↑
	cITT-S	71	15.8±15.57	17.28±9.36	9% ↑	290	14.57±9.83	18.64±26.87*	28% ↑
E2 (pg/mL)	ITT-S	72	2.93±1.65	4.76±11.82	62% ↑	293	3.39±8.71	3.41±2.53	< 1% ↑
	cITT-S	71	2.92±1.66	3.39±1.89*	16% ↑	288	2.72±1.72	3.26±2.02**	20% ↑

ITT-S = Intent-to-treat population having measurements at both baseline and 12 weeks; cITT-S = excluding subjects with a serum estrogen signature; * $p < 0.05$ and ** $p < 0.0001$ for comparisons with baseline

While mean trough serum concentrations of E2 at 12 weeks were statistically different from the baseline in the two cITT-S populations, both sets of data for the ITT-S populations were not. These results may suggest that the cITT populations excluding the E2 signature subjects (suspicious of concomitant estrogen treatment) better reflect the actual increase in the systemic exposure to sex hormones following administration of prasterone vaginal insert.

The distribution of individual C_{trough} of testosterone and E2 in the cITT-S populations of the two pivotal phase 3 studies (ERC-231 and ERC-238) showed a similar pattern of change compared to DHEA before and after treatment with 6.5 mg prasterone vaginal insert (i.e., shifted to the right and more widely scattered) (Figure 4 and 5).



(a) Testosterone at baseline (pg/mL)

(b) Testosterone at 12 weeks (pg/mL)

Figure 4. Distribution of trough serum concentrations (pg/mL) of testosterone with box and whiskers plots before (a) and after (b) daily application of 0.50% DHEA vaginal inserts for 12 weeks in the cITT-S populations pooled from two phase 3 studies (ERC-231 and ERC-238). [Analysis using the dataset of ERC-231 and ERC-238 studies]

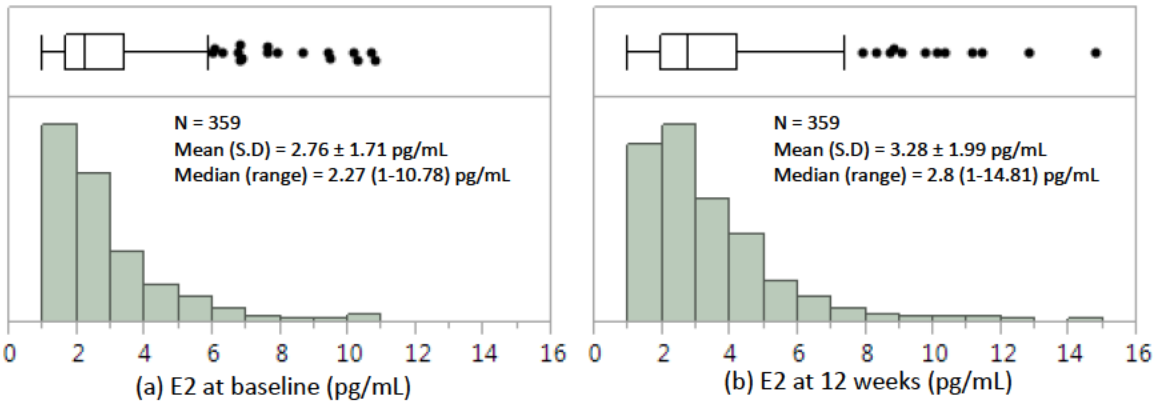
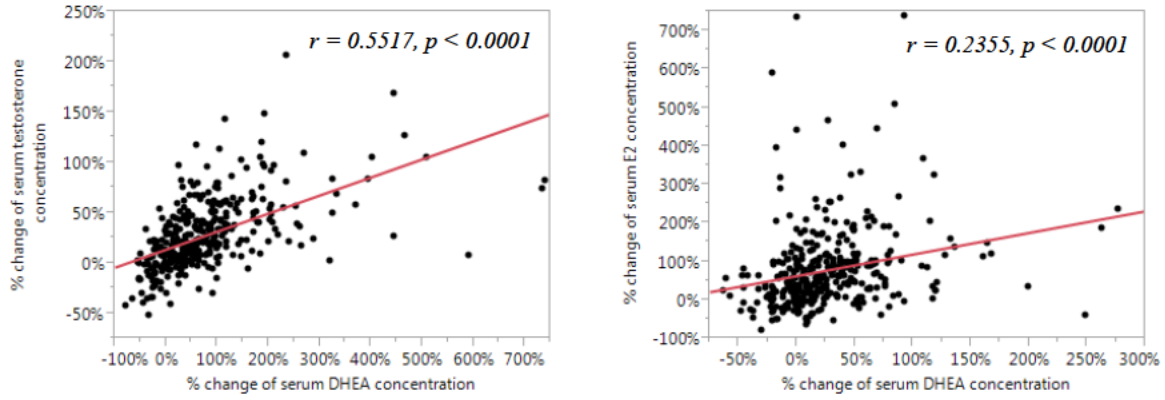


Figure 5. Distribution of trough serum concentrations (pg/mL) of E2 with box and whiskers plots before (a) and after (b) daily application of 0.50% DHEA vaginal inserts for 12 weeks in the cITT-S populations pooled from two phase 3 studies (ERC-231 and ERC-238). [Reanalysis using the dataset of ERC-231 and ERC-238 studies]

The percentage changes of trough serum testosterone and E2 concentrations before and after treatment with 6.5 mg prasterone vaginal insert for 12 weeks appeared to be significantly correlated with those of DHEA concentrations (Figure 6).



(a) Testosterone (b) E2

Figure 6. Correlation between % changes of trough testosterone (a) and E2 (b) and DHEA concentrations after daily application of 0.50% DHEA vaginal inserts for 12 weeks in the cITT-S populations pooled from two phase 3 studies (ERC-231 and ERC-238) [r (correlation coefficient) and p value from Spearman's rank correlation].

These results indicate that administration of DHEA vaginal insert leads to additional systemic exposure to testosterone and estrogens in postmenopausal women with VVA.

The percentage of subjects showing serum C_{trough} of testosterone above the upper normal range (260 pg/mL; the 95th percentile of normal postmenopausal women proposed by the Applicant) increased from 8.61% (31/360, baseline) to 15% (54/360) after 12 weeks of treatment with 6.5 mg prasterone vaginal insert. The percentage of subjects showing serum C_{trough} of E2 above the upper normal range (9.3 pg/mL; the 95th percentile of normal postmenopausal women proposed by the Applicant) was not significantly different between before and after 12 weeks of treatment with 6.5 mg prasterone vaginal insert (from 1.67% [6/359] to 1.95% [7/359]). While the serum E2 concentrations measured after treatment with 6.5 mg prasterone vaginal insert tended to be increased, the values in most subjects appeared to be within the

normal ranges reported in postmenopausal women when excluding the subjects who are suspected of concomitant use of estrogen.

4.2.3 Pharmacokinetic profile of DHEA and its metabolites after administration of prasterone vaginal insert

The time-concentration profile of DHEA and its metabolites was characterized on Day 1 and 7 following daily treatments of three strengths, 6.5, 13 and 23.4 mg prasterone vaginal inserts for 7 days in 10 postmenopausal women with VVA (Study ERC-213). The systemic exposure to DHEA and its metabolites increased in a dose-dependent manner (Figure 7).

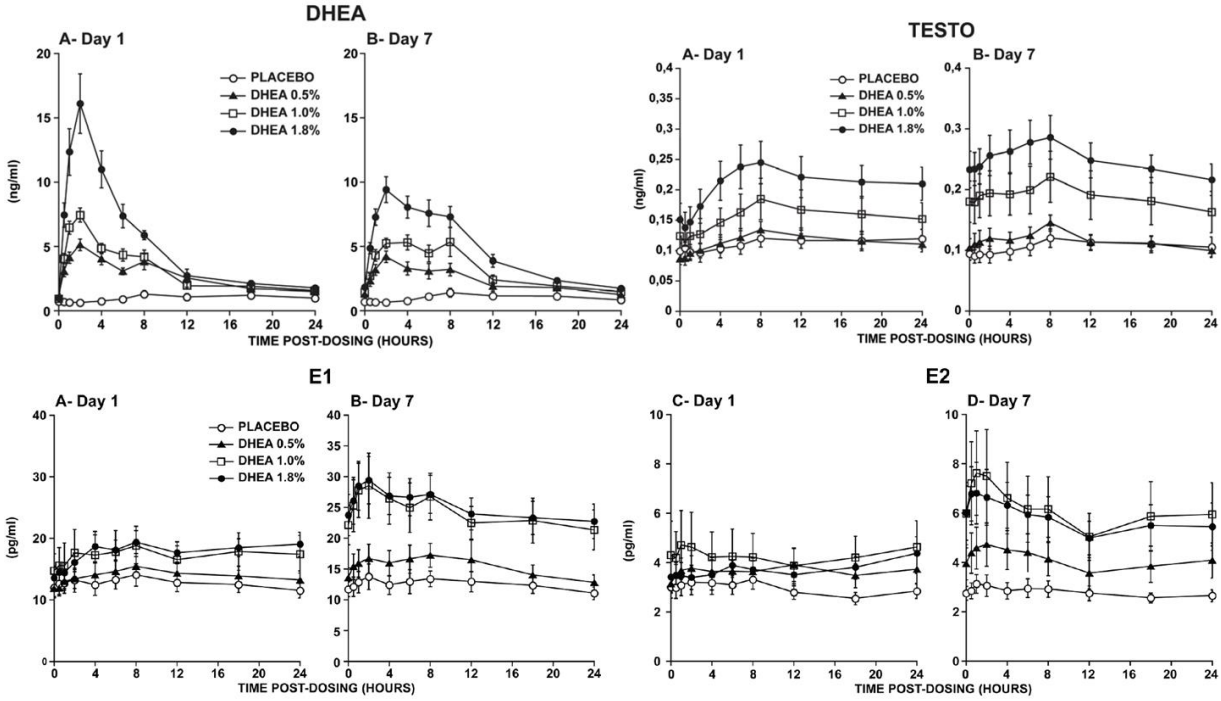


Figure 7. Mean serum concentrations of DHEA, testosterone (TESTO), E1 and E2 on Day 1 and 7 following daily administration of placebo, 6.5 mg (0.5%), 13 mg (1%) and 23.4 mg (1.8%) DHEA vaginal insert (n= 10 per group).

The serum concentrations of DHEA appeared to be higher on Day 1 than Day 7. This result indicates a relatively higher absorption after the first dose than the following doses, which may be attributed to a higher vaginal permeability due to thinner mucosal epithelium before treatment in women with VVA. Otherwise, the systemic exposure (based on AUC_{24}) to the metabolites including E1, E2 and testosterone tended to be higher on Day 7 compared to Day 1 (Table 8).

The systemic exposure to E1, E2 and testosterone in all active treatment groups appeared to be higher than that in the placebo group. It indicates that administration of DHEA vaginal inserts in patients with VVA leads to additional systemic exposure to estrogens and androgens above the endogenous levels. There was a greater peak trough fluctuation in DHEA concentration following treatment with prasterone vaginal insert compared to placebo (i.e., endogenous profile). This suggests that the comparison using C_{trough} in the Phase 3 trials may underestimate the magnitude of increase in DHEA exposure. For example, the Phase 3 Ctrough data showed an increase from baseline of 32% for DHEA while a

comparison between prasterone vaginal insert and placebo on Day 7 showed a difference of 126% in AUC_{0-24} for DHEA.

Table 8. The C_{max} and AUC_{24} of DHEA, testosterone, E1 and E2 on Day 1 and Day 7 following daily administration of placebo or 6.5 mg prasterone vaginal insert (mean ± S.D).

		Placebo (N=9)		**6.5 mg prasterone** (N=10)	
		Day 1	**Day 7**	**Day 1**	**Day 7**
DHEA	C_{max} (ng/mL)	1.52 (±0.93)	1.60 (±0.95)	5.97 (±1.40)	4.42 (±1.49)
	AUC_{24} (ng·h/mL)	24.47 (±14.40)	24.82 (±14.31)	65.49 (±24.67)	56.17 (±28.27)
Testosterone	C_{max} (ng/mL)	0.17 (±0.15)	0.17 (±0.15)	0.15 (±0.05)	0.15 (±0.05)
	AUC_{24} (ng·h/mL)	2.71 (±1.02)	2.58 (±0.99)	2.79 (±0.92)	2.79 (±0.95)
E1	C_{max} (pg/mL)	15.19 (±5.00)	15.88 (±6.05)	17.10 (±6.36)	19.45 (±9.51)
	AUC_{24} (pg·h/mL)	305.58 (±103.68)	301.92 (±101.31)	336.52 (±120.04)	369.69 (±154.51)
E2	C_{max} (pg/mL)	3.59 (±1.46)	3.33 (±1.31)	4.62 (±2.28)	5.04 (±2.68)
	AUC_{24} (pg·h/mL)	69.51 (±22.89)	66.49 (±20.70)	87.79 (±35.86)	96.93 (±51.67)

4.3 Individual Study Reports

Tables and figures under this section are numbered independently.

❖ Study ERC-213

Title: DHEA bioavailability following administration of vaginal suppositories in postmenopausal women with vaginal atrophy - Phase I randomized, placebo-controlled, double-blind study.

Objectives:

· The primary objective: evaluation of the systemic bioavailability (BA) of DHEA and its metabolites and the PK of vaginal suppositories (inserts) at three different DHEA concentrations and a placebo.
· The secondary objective: safety and tolerance of the suppositories and efficacy using vaginal maturation index and pH

Study Design:

· A randomized, placebo-controlled, double-blind phase 1 trial with 4 arms
· Clinical trial site: Hormonal Treatment Clinic of the Laval University Hospital Research Center, Canada
· The number of subjects: 10 per arm
· Subjects: postmenopausal women with self-assessed vaginal atrophy and dryness
· Treatments: daily administration of vaginal inserts in the evening between 22:00 and 23:00 for 1 week
  - Placebo, 6.5, 13, and 23.4 mg prasterone (0.5%, 1.0%, and 1.8% prasterone)
· PK evaluation
  - Blood collection: at 0 and 0.5, 1 , 2, 4, 6, 8, 12,18 and 24 hours after dosing on Day 1 and 7
  - Measurement of serum DHEA and related steroids (DHEA-S, 5-diol, DHT, testosterone, 4-dione, E1, E2, estrone sulfate, ADT-G, 3α-diol-3G and 3α-diol-17G) using validated LC-MS/MS for conjugated steroids and GC-MS/MS for unconjugated steroids
  - Major PK parameters: AUC_{24}, C_{max} and C_{ave} (the average 24h serum concentration = AUC_{24}/24 hours)
· Efficacy evaluation
  - Vaginal pH and maturation index were assessed at baseline and after one week.
· Safety evaluation
  - Reported adverse events, clinical laboratory and gynecological examination

Results:

· Study Population: 24 naturally postmenopausal and 16 surgically postmenopausal women were included and completed the study.
· Serum data for one subject (S-213-037 in the placebo group) who had increased estrogen levels between Screening and Day 1- were excluded for all steroid statistical analyses, and serum data for another subject (S-213-040 in the placebo group) who had abnormal testosterone levels were excluded for testosterone statistical calculations.
· PK results: Figure 1
· Efficacy results: At Day 7, vaginal maturation values were significantly increased and vaginal pH was significantly decreased in the three active treatment groups.
· Safety:
  - Well tolerated and no drug-related adverse event
  - No clinically significant changes in laboratory parameters

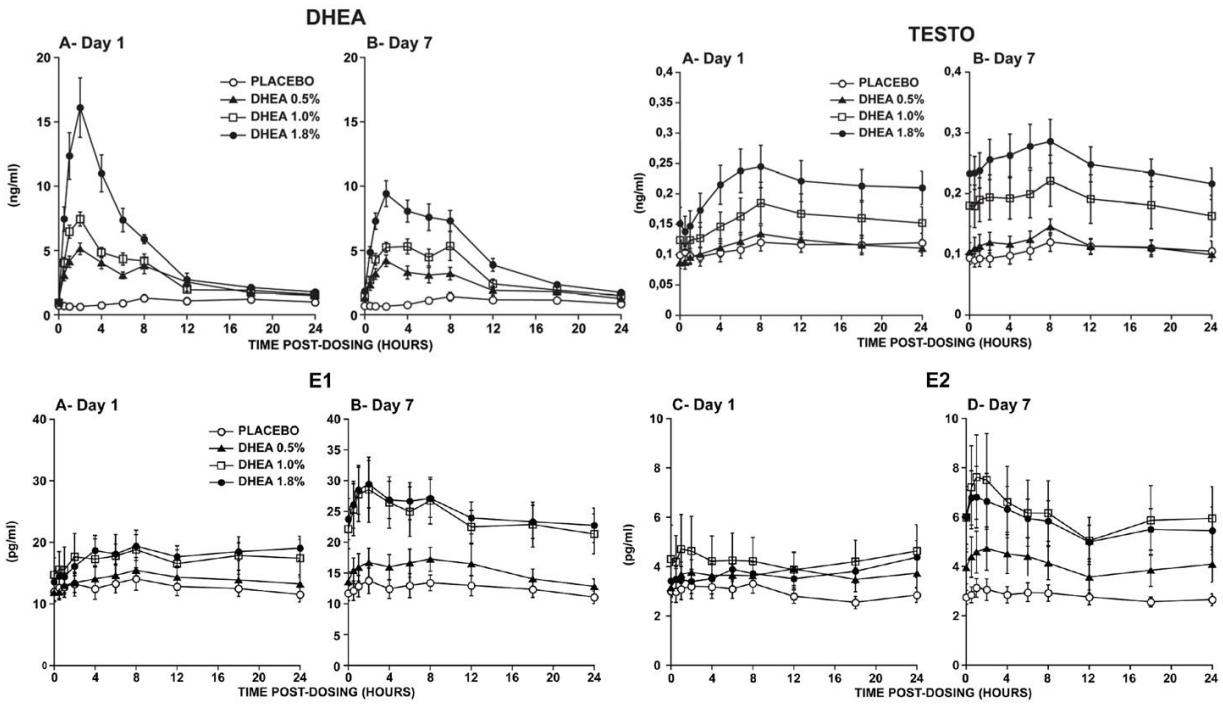


Figure 1. Mean serum concentrations of DHEA, testosterone (TESTO), E1 and E2 on Day 1 and 7 following daily administration of placebo, 0.5%, 1% and 1.8% DHEA vaginal insert (n= 10 per group).
[Source: page 63 – 68 in the study report of ERC-213]

Table 1. The C_{max} and AUC_{24} of DHEA, testosterone, E1 and E2 on Day 1 and Day 7 following daily administration of placebo or 6.5 mg prasterone vaginal insert (mean ± S.D).

		Placebo (N=9)		**6.5 mg prasterone** (N=10)	
		Day 1	**Day 7**	**Day 1**	**Day 7**
DHEA	C_{max} (ng/mL)	1.52 (±0.93)	1.60 (±0.95)	5.97 (±1.40)	4.42 (±1.49)
	AUC_{24} (ng·h/mL)	24.47 (±14.40)	24.82 (±14.31)	65.49 (±24.67)	56.17 (±28.27)
Testosterone	C_{max} (ng/mL)	0.17 (±0.15)	0.17 (±0.15)	0.15 (±0.05)	0.15 (±0.05)
	AUC_{24} (ng·h/mL)	2.71 (±1.02)	2.58 (±0.99)	2.79 (±0.92)	2.79 (±0.95)
E1	C_{max} (pg/mL)	15.19 (±5.00)	15.88 (±6.05)	17.10 (±6.36)	19.45 (±9.51)
	AUC_{24} (pg·h/mL)	305.58 (±103.68)	301.92 (±101.31)	336.52 (±120.04)	369.69 (±154.51)
E2	C_{max} (pg/mL)	3.59 (±1.46)	3.33 (±1.31)	4.62 (±2.28)	5.04 (±2.68)
	AUC_{24} (pg·h/mL)	69.51 (±22.89)	66.49 (±20.70)	87.79 (±35.86)	96.93 (±51.67)

Sponsor's conclusion:

- The present clinical data suggest that DHEA vaginal suppositories are well-tolerated.
- Exposure to DHEA was dose-related, based on AUC_{24} and C_{avg} of serum DHEA and metabolites concentrations. At the three tested DHEA doses, vaginal maturation value was significantly increased and vaginal pH was significantly decreased from Day 1 to Day 7, at the three tested doses.

· These results obtained in a short term period support the potential benefit of using DHEA suppositories for the indication of vaginal atrophy and dryness.

Reviewer's comments:

· The systemic exposure to DHEA and its metabolites showed dose-dependent increase pattern. The serum concentrations of DHEA appeared to be higher on Day 1 than Day 7. A relatively higher absorption after the first dose than the following doses may be attributed to a higher vaginal permeability of prasterone due to thinning mucosal epithelium in women with VVA before treatment. Otherwise, the systemic exposure (based on AUC_{24}) to the metabolites including E1, E2 and testosterone tended to be higher on Day 7 compared to Day 1.

· The systemic exposure to E1, E2 and testosterone in all active treatment groups appeared to be higher than that in the placebo group. It indicates that administration of DHEA vaginal inserts in the patients with VVA leads to additional systemic exposure to estrogens and androgens above endogenous hormone levels.

· The treatments of all three concentrations of DHEA vaginal inserts for 7 days led to significant changes of vaginal maturation and pH compared to baseline.

❖ Study ERC-210

Title: Topical DHEA against vaginal atrophy (3-month placebo-controlled double-blind randomized phase 3 study)

Objectives:

· The primary objective: 1) To determine the dose-response of vaginal mucosa parameters to the local action of DHEA in postmenopausal women suffering from vaginal atrophy and 2) The local activity of DHEA (changes in epithelial cell maturation and vaginal pH) and the most bothersome symptom of vaginal atrophy.

· The secondary objective: 1) Changes in sexual function and quality of life, 2) Self-assessment was made of the three symptoms of vaginal atrophy and visual evaluation of four parameters of vaginal health and 3) Tolerance to local DHEA application was to be evaluated.

Study Design:

· A randomized, placebo-controlled, double-blind phase 3 trial with 4 arms
· Clinical trial site: 8 sites in USA and Canada
· Planned subject number: 200 postmenopausal women (50 per arm)
· Subjects: postmenopausal women suffering from vaginal atrophy
· Treatments: daily administration of vaginal insert for 12 weeks
  - Placebo, 3.25 mg (0.25%), 6.5mg (0.5%) and 13mg(1.0%) prasterone
· Efficacy evaluation
  - Vaginal cell maturation (a 100-cell count) and vaginal pH at day 1 and weeks 2, 4, 8, and 12
  - Self-reported most bothersome symptom: vaginal dryness, vaginal and/or vulvar itching/ irritation, and vaginal pain associated with sexual activity
  - Sexual function as well as quality of life
  - Vaginal secretions and color / epithelial integrity and surface thickness
· Safety evaluation
  - Reported adverse events, vital signs, physical examinations, hematology and coagulation, blood chemistry, urinalysis and gynecological examinations including endometrial histology
· Measurements of DHEA and its metabolites

- Blood collection: at day 1 before dosing and weeks 2, 4, 8, and 12
- Measurement of serum DHEA and related steroids

Results:

· Study Population: 218 patients were randomized and 216 were analyzed in the ITT population.

· Efficacy results: Figure 1

· Safety:
  - Intravaginal administration of DHEA was well tolerated.
  - The overall incidence of adverse events was comparable across dose groups, including placebo, and no drug-related serious adverse event or discontinuation occurred.

· Serum concentrations of DHEA and its metabolites:

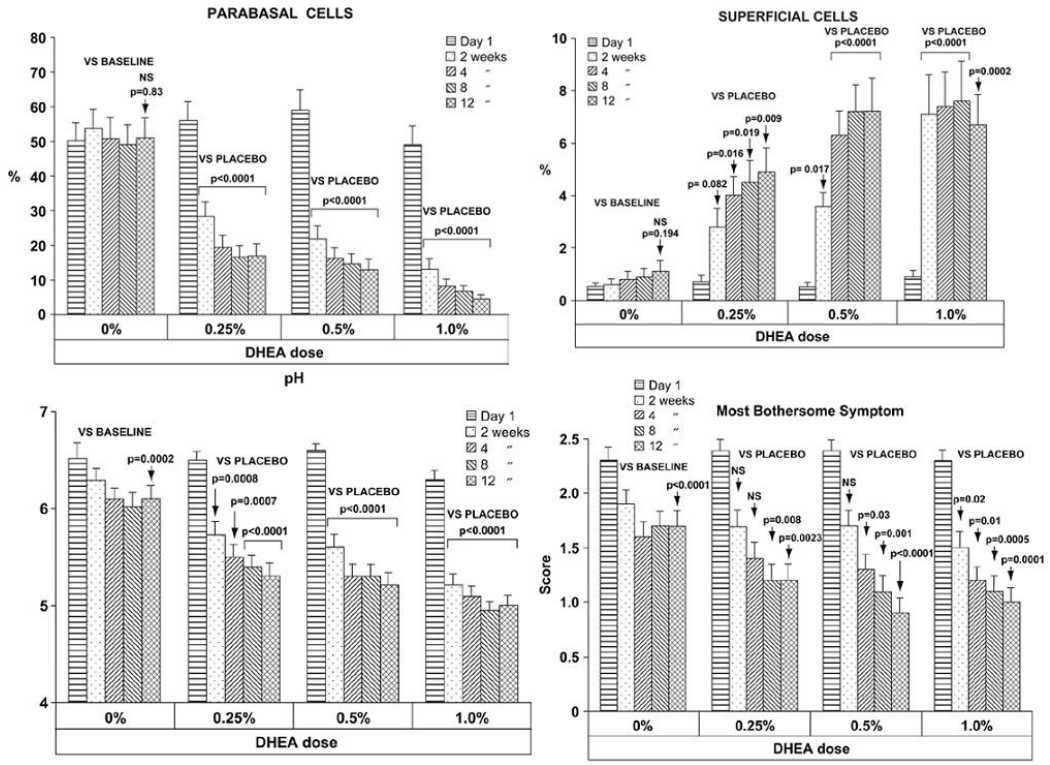


Figure 1. Effect of daily application of placebo (N=41), 3.25 mg (N=43), 6.5mg (N=50) and 13mg (N=43) prasterone vaginal insert for 12 weeks on the percentage of vaginal parabasal and superficial cells, vaginal pH and the severity score of the symptom of vaginal atrophy at baseline as being the most bothersome. Values are expressed as means ± SEM; the p values from the comparison with baseline or placebo. [Source: page 441 to 444 in the clinical study report of ERC-210]

· <u>The concentrations of DHEA and its metabolites</u>:

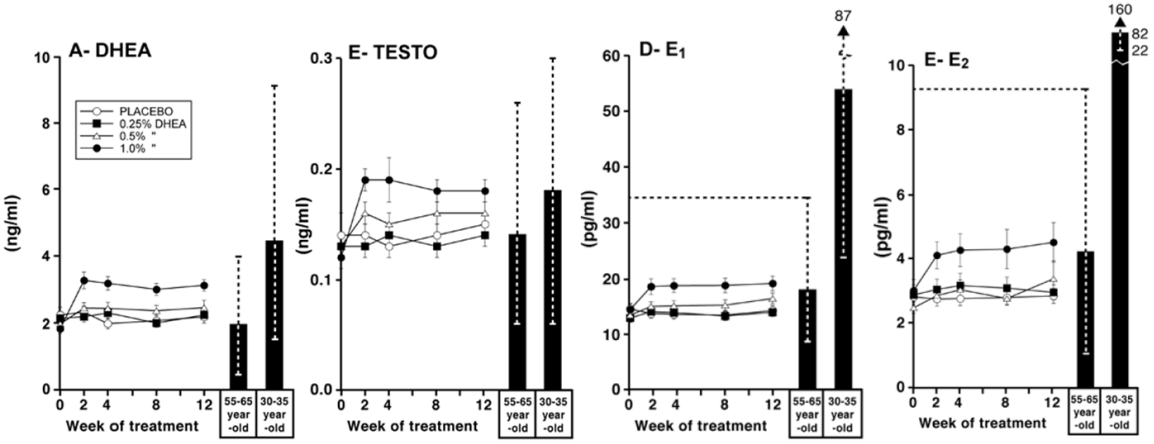


Figure 2. Trough serum concentrations of DHEA, testosterone (Testo), E1 and E2 measured on day 1 and at weeks 2, 4, 8 and 12 during once daily administration of placebo, 3.25 mg, 6.5mg and 13mg prasterone vaginal insert vaginal insert. Data are expressed as means ± S.E.M. (n=53-56): serum steroid concentrations measured in 30-35 year-old premenopausal (n=47) as well as in 55-65 year old postmenopausal (n=377) women as reference data which are expressed as means and 5th and 95th centiles (dashed lines). [Source: page 457 to 458 in the clinical study report of ERC-210]

Sponsor's conclusion:

- Treatment with local DHEA causes a rapid and efficient reversal of all the symptoms and signs of vaginal atrophy while circulating estrogens and androgens as well as the total metabolites of androgens reflecting the total androgen pool and estrone sulfate, a parameter of total estrogens, all remained within the range observed in normal postmenopausal women.
- The same treatment exerts major effects on libido and sexual dysfunction by a local action of DHEA which is likely to be exerted through the local conversion of DHEA into androgens and their stimulatory action on the collagen component of the lamina propria and on the muscularis as well as some effects on the epithelial component
- This approach avoids the fear of systemic effects and adds an important physiological androgenic component to therapy.

Reviewer's comments:

- All active treatment groups showed significant changes in vaginal cell maturation and pH and improvement in the bothersome symptom in dose-dependent manner. Placebo group also showed significant changes in vaginal pH and improvement in the bothersome symptom after 12 weeks, but lesser than active treatment groups and no significant change in vaginal cells.
- The treatments with 6.5mg and 13mg prasterone tended to reach at the steady state of changes in the vaginal cells maturation and vaginal pH at 4 or 8 weeks. There was no significant difference between 6.5mg and 13mg prasterone treatment groups in the efficacy parameters.
- The trough serum concentrations of DHEA and its metabolites in the active treatment groups were increased at 2-week and then remain constant without any significant change. In the treatment group with 6.5mg and 13mg prasterone, the trough concentrations of E1, E2 and testosterone tended to be slightly higher compared to those in the placebo group throughout the treatment period.

❖ Study ERC-231

Title: DHEA against vaginal atrophy (placebo-controlled, double-blind and randomized phase 3 study of 3-month intravaginal DHEA)

Objectives:

- The primary objective:
  - To confirm the efficacy of intravaginal DHEA on the symptoms and signs of vaginal atrophy in postmenopausal women suffering from vaginal atrophy.
- The secondary objective:
  - To evaluate the efficacy on arousal/lubrication, subjective arousal, desire, pain at sexual activity, satisfaction and orgasm using the female sexual function index (FSFI) questionnaire.
  - To examine the tolerance to local administration of DHEA.

Study Design:

- Multi-center, randomized, double-blind, placebo-controlled study with 3 arms
- Clinical trial sites: 33 sites in the U.S. and Canada
- The planned subject number: 210 postmenopausal women (70 per arm)
- Subjects: postmenopausal women suffering from vaginal atrophy
- The subjects with hepatic or renal impairment were excluded initially, but the eligibility criteria were modified for those patients to participate in the study.
- Treatments: the vaginal inserts daily for 12 weeks
  - Placebo, 3.25 mg (0.25%) and 6.5mg (0.5%) prasterone vaginal inserts
- Efficacy evaluation
  - Primary endpoints: change in severity score of pain at sexual activity and changes in % of parabasal cells, % of superficial cells, and vaginal pH.
  - Secondary endpoints: arousal/lubrication, subjective arousal, desire, satisfaction and orgasm
- Safety evaluation
  - Reported adverse events, vital signs, physical examinations, hematology and coagulation, blood chemistry, urinalysis and endometrial biopsy of the non-hysterectomized subjects
- Measurements of DHEA and its metabolites
  - Blood collection: at baseline before dosing and weeks 12

Results:

- Study population: 218 patients were randomized and 216 were analyzed in the ITT population.
- E2 signature subjects (suspected of concomitant use with estrogen products):
  - As indicated by marked elevations (based on the proposed criteria) in serum estrogens without parallel changes in serum DHEA as well as androsterone glucuronide, the main androgen metabolite.
  - Excluded for the corrected ITT, per protocol (PP) and corrected safety population analysis set as a major protocol violation.
  - 6 subjects: 2 per each treatment arm
- Efficacy results: Figure 1
- Safety results:
  - Daily administration of DHEA vaginal insert for 12 weeks was well tolerated. There were no drug-related serious adverse events or deaths reported.
  - Daily administration of 3.25 mg or 6.5mg prasterone vaginal inserts for 12 weeks had no effect on the endometrium.
  - Application site discharge occurred in 5.7 to 7.0% of subjects per group, was mild to moderate in intensity, and was generally well tolerated with only one subject discontinuing treatment for that reason.

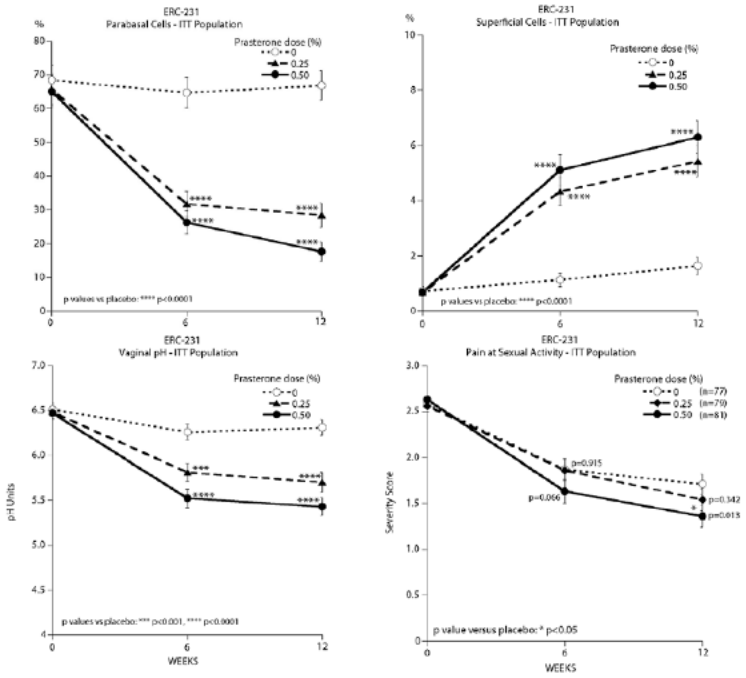


Figure 1. Effect of daily application of placebo, 3.25 mg or 6.5mg prasterone vaginal inserts for 12 weeks on the percentage of vaginal parabasal and superficial cells, vaginal pH and the pain at sexual activity in the ITT population (means ± SEM; p values - comparisons with placebo). [Source: page 72 to 98 in the study report of ERC-231]

- The concentrations of DHEA and its metabolites:

Table 1. Mean trough serum concentrations of DHEA, testosterone, E1 and E2 on Day 1 (baseline) and 12 weeks following daily administration of 6.5mg prasterone vaginal insert in postmenopausal women (Reanalysis by the reviewer using the Sponsor's dataset)

	Population(N)	Baseline (mean± S.D.)	12 weeks (mean± S.D.)	% change from baseline
DHEA (ng/mL)	ITT-S (72)	1.89±1.19	2.49±1.37**	32% ↑
	cITT-S (71)	1.86±1.18	2.48±1.38**	33% ↑
Testosterone (pg/mL)	ITT-S (72)	139.3±75.9	160.6±83.0**	15% ↑
	cITT-S (71)	139.8±76.3	160.6±83.6**	15% ↑
E1 (pg/mL)	ITT-S (72)	15.79±15.46	17.97±11.02	14% ↑
	cITT-S (71)	15.8±15.57	17.28±9.36	9% ↑
E2 (pg/mL)	ITT-S (72)	2.93±1.65	4.76±11.82	62% ↑
	cITT-S (71)	2.92±1.66	3.39±1.89*	16% ↑

ITT-S = Intent-to-treat population having measurements at both baseline and 12 weeks; cITT-S = excluding subjects with a serum estrogen signature; * p < 0.05 and ** p < 0.0001 for comparisons with baseline

Sponsor's conclusion:

- Clinically and statistically significant beneficial effects of treatment with daily intravaginal 0.50% (6.5 mg) DHEA are observed on the four co-primary objectives, namely dyspareunia, the moderate to severe symptom identified by women as most bothersome at both screening and baseline, percentage of parabasal cells, percentage of superficial cells and vaginal pH.

· Parallel and highly significant beneficial effects were also observed at examination of the vaginal mucosa while serum steroid levels did not show, in agreement with the mechanisms and physiology of intracrinology and menopause, any clinically or biologically meaningful change.
· No significant drug-related adverse effect was reported, in line with the strictly local action of the treatment, thus leading to a high benefit-risk ratio of intravaginal prasterone.

Reviewer's comments:
· Two treatment groups, 3.25 mg or 6.5mg prasterone, showed significant changes in vaginal epithelium maturation and pH. While the group with 6.5mg prasterone showed statistically significant difference in the pain at sexual activity compared to the placebo group, the group with 0.25 mg prasterone did not.
· Application site discharge was the most common drug-related adverse event in all groups. There was no clinically significant adverse event including the result from endometrial examination.
· The trough serum concentration of DHEA in the group with 6.5mg prasterone was increased significantly at 12 weeks compared to that that at baseline. The trough concentrations of testosterone and E1 were statically different between baseline and 12 weeks in both analysis populations, ITT-S and cITT-S. The trough concentrations of E2 appeared to be increased after treatment with 6.5mg prasterone vaginal insert for 12 weeks (by 62% and 16% in ITT-S and cITT-S populations, respectively) and this difference was statistically significant in cITT-S population which excludes the subjects who are suspicious of concomitant use of estrogen.
· The results of efficacy analysis were similar between ITT and cITT populations.
· Enrollment of patients with hepatic or renal impairment was allowed in the middle of study, but this amendment was implemented after approximately 75% of the subjects had been randomized. Only one subject showed ALT and AST higher than 2-fold of their upper limit of normal range at screening. There was no subject who had serum creatinine higher than 1.5-fold of its upper limit of normal range. As results, there was no subject who had moderate or severe renal or hepatic function failure based on the results of renal and liver function laboratory tests at screening and Day 1.

❖ Study ERC-234

Title: DHEA against vaginal dryness (placebo-controlled, double-blind and randomized phase 3 study of 3-month intravaginal DHEA)

Objectives:
· The primary objective: to confirm the efficacy of intravaginal DHEA on vaginal dryness, a symptom of vaginal atrophy, in postmenopausal women suffering from vaginal dryness.
- The secondary objective: tolerance/ arousal/lubrication, subjective arousal, desire, satisfaction, pain at sexual activity and orgasm/ pain at sexual activity and irritation/itching.

Study Design:
· Multi-center, randomized, double-blind, placebo-controlled study with 3 arms
· Clinical trial sites: 42 sites in USA and Canada
· The planned subject number: 345 postmenopausal women (115 per each treatment group)
· Subjects: postmenopausal women - ≤5% of superficial cells on vaginal smear, a vaginal pH above 5 and self-identified moderate to severe moderate to severe vaginal dryness as their most bothersome symptom

· Treatments: the vaginal inserts daily for 2 weeks followed by twice weekly for 10 weeks
  - Placebo, 3.25mg (0.25%) and 6.5mg (0.5%) prasterone
· Efficacy evaluation
  - Primary endpoints: change in severity score of vaginal dryness and changes in % of parabasal cells, % of superficial cells, and vaginal pH.
  - Secondary endpoints: arousal/lubrication, subjective arousal, desire, satisfaction, orgasm and tolerance to local administration of DHEA
· Safety evaluation
  - Reported adverse events, vital signs, physical examinations, hematology and coagulation, blood chemistry, urinalysis and endometrial biopsy of the non-hysterectomized subjects
· Measurements of DHEA and its metabolites
  - Blood collection: at baseline before dosing and weeks 12

Results:

· Study Population
  - Enrolled: 450 (152 for placebo, 148 for 0.25% and 150 for 0.5% DHEA)
  - Analyzed: ITT population - 407 (139 for placebo, 134 for 0.25% and 134 for 0.5% DHEA)
    Safety population – 441 (150 for placebo, 143 for 0.25% and 148 for 0.5% DHEA)
· E2 signature subjects (suspected of concomitant use with estrogen products):
  - Excluded for the PP population analysis set as a major protocol violation.
  - 15 subjects: 7 for placebo, 7 for 0.25% DHEA and 1 for 0.5% DHEA
· Safety:
  - Intravaginal administration of DHEA was well tolerated. There were no serious adverse events, discontinuations or deaths reported. There was no effect on the endometrium.
  - Application site discharge occurred in 1.8% of all subjects (0.7 to 3.5% of subjects per group), was mild to moderate in intensity, and was well tolerated.
· Efficacy results:
  - The effect on the parabasal and superficial cells and vaginal pH was maximal at 2 weeks with a loss of efficacy at later time intervals following change at 2 weeks of the dosing regimen from daily to twice weekly for the next 10 weeks.

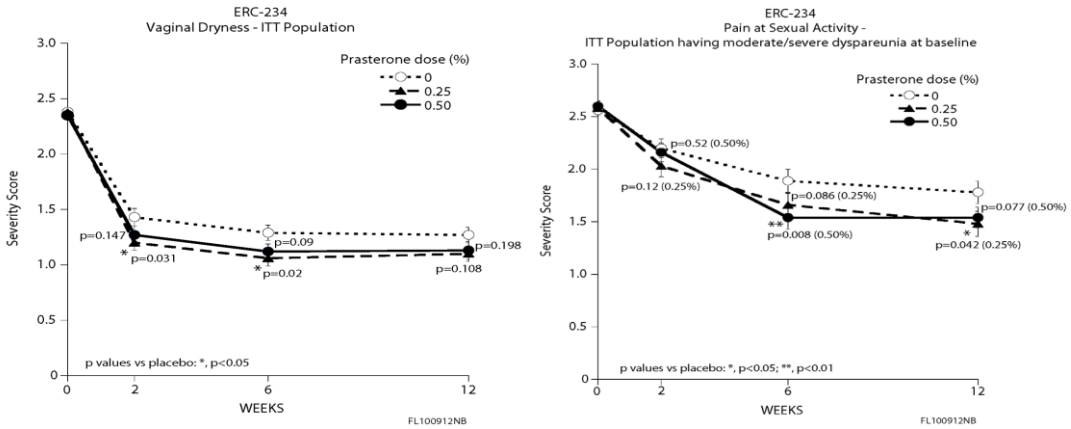


Figure 1. Effect of daily application for 2 weeks followed by twice weekly for 10 weeks of placebo, 3.25mg and 6.5mg prasterone on vaginal dryness and severity score of moderate to severe pain at sexual activity at baseline in the ITT population (means ± SEM; the p values - comparison with placebo for the two doses). [Source: page 98 and 105 in the clinical study report of ERC-234]

· The concentrations of DHEA and its metabolites:

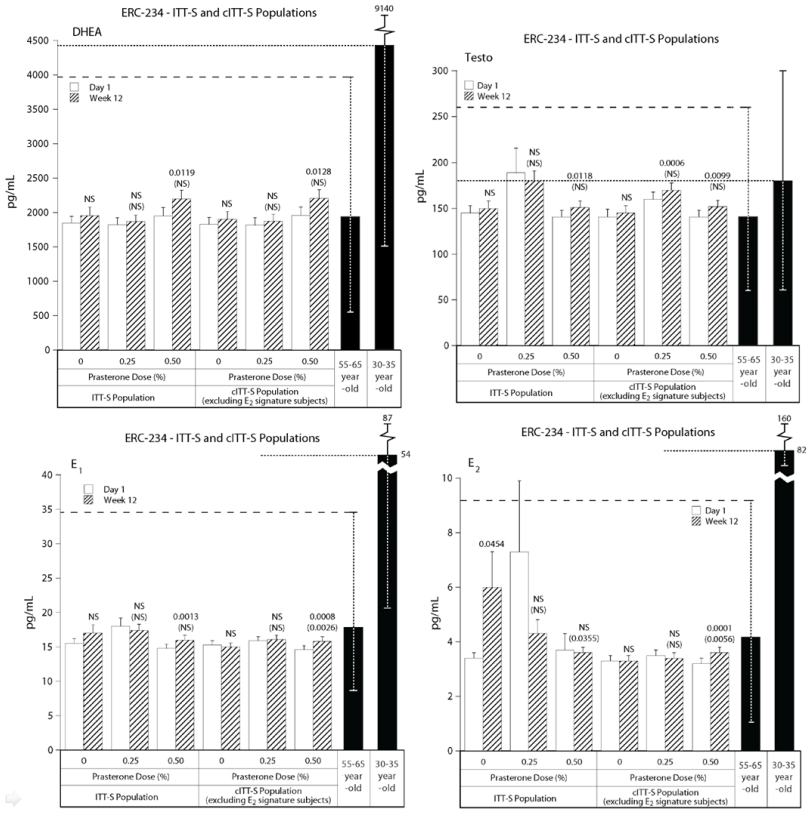


Figure 2. Mean serum trough concentrations of DHEA, testosterone (TESTO), E1 and E2 on Day 1 and 12 weeks following daily vaginal administration of placebo, 3.25mg and 6.5mg prasterone in postmenopausal women [means ± SEM; p values - comparisons with baseline and placebo; serum steroid concentrations measured in normal 55-65 years old postmenopausal women (n=377) and 30-35 years old premenopausal women (n=47) as reference as means and 5th and 95th centiles (dashed lines). [Source: page 180 to 203 in the clinical study report of ERC-234]

Sponsor's conclusion:

· While both doses, 0.25% and 0.50% of DHEA, administered daily for 2 weeks followed by twice weekly for 10 weeks have shown highly statistically significant effects on the decrease in the percentage (%) of parabasal cells, the increase in the % of superficial cells and the decrease in vaginal pH, the improvement of MBS vaginal dryness did not reach statistical significance at 12 weeks following 10 weeks of biweekly treatment after 2 weeks of daily administration.

· A clear loss of efficacy was observed when the dosing regimen was changed from daily to twice weekly at 2 weeks.

· Despite the loss of efficacy of the twice weekly dosing regimen in the majority of the population, over 25% of subjects were responders to all four co-primary endpoints, including dryness, as well as pain at sexual activity.

Reviewer's comments:

· Treatments with 3.25mg and 6.5mg prasterone, administered daily for 2 weeks followed by twice weekly for 10 weeks, did not reach statistical significance on the improvement of vaginal dryness at 12 weeks even though they had statistically significant effects on the vaginal cell maturation and pH.

- The results of vaginal cell maturation and pH may imply that twice weekly regimen may result in a lack of efficacy for the symptoms due to VVA.
- While twice weekly regimen with 3.25 mg prasterone did not significantly increase the rough concentrations of DHEA and its metabolites, treatment with 6.5 mg prasterone significantly increased them at 12 weeks compared to that that at baseline.

❖ Study ERC-238

Title: Intravaginal Prasterone (DHEA) against vulvovaginal atrophy associated with menopause (Placebo controlled, double blind and randomized phase 3 study)

Objectives:
- The primary objective:
  - To confirm the efficacy of intravaginal DHEA on moderate to severe pain at sexual activity as most bothersome symptom of VVA due to menopause.
  - To collect further data on subjects exposed to intravaginal DHEA at the dose or dose range believed to be efficacious
- The secondary objective:
  - To examine the tolerance to intravaginal administration of DHEA
  - To investigate a possible influence of treatment on the male partner
  - To evaluate the efficacy on the other two symptoms of VVA
  - To evaluate the efficacy on arousal/lubrication, subjective arousal, desire, satisfaction and orgasm by the female sexual function index (FSFI) questionnaire.
  - To obtain information on the usability of the applicator used to insert the medication.

Study Design:
- Multi-center, randomized, double-blind, placebo-controlled study with two arms
- Clinical trial sites: 36 sites in the U.S. and Canada
- The planned subject number: 483 postmenopausal women (322 for DHEA and 161 for placebo)
- Subjects: postmenopausal women (≤5% of superficial cells on vaginal smear, a vaginal pH above 5 and self-identified moderate to severe pain at sexual activity as VVA symptom)
  - Treatments: the vaginal inserts daily for 12 weeks of placebo or 6.5 mg prasterone (0.5% DHEA)
- Efficacy evaluation
  - Primary endpoints: change in pain at sexual activity and changes in % of parabasal cells, % of superficial cells, and vaginal pH.
  - Secondary endpoints: arousal/lubrication, subjective arousal, desire, satisfaction and orgasm
- Safety evaluation
  - Reported adverse events, vital signs, physical examinations, hematology and coagulation, blood chemistry, urinalysis and endometrial biopsy of the non-hysterectomized subjects
  - Questionnaire survey of the male partners who had intercourse for the last 2 months
- Measurements of DHEA and its metabolites
  - Blood collection: at baseline before dosing and weeks 12

Results:
- Study Population
  - Enrolled: 558 (376 for DHEA and 182 for placebo)
  - Analyzed: ITT population - 482 (325 for DHEA and 157 for placebo)
    Safety population – 554 (374 for DHEA and 180 for placebo)
- Male partner population: 34 for placebo and 66 for DHEA

- E2 signature subjects:
  - Excluded for the corrected ITT, PP and corrected safety analysis set as a major protocol violation.
  - 18 subjects: 12 for DHEA and 6 for placebo group
- Efficacy results:

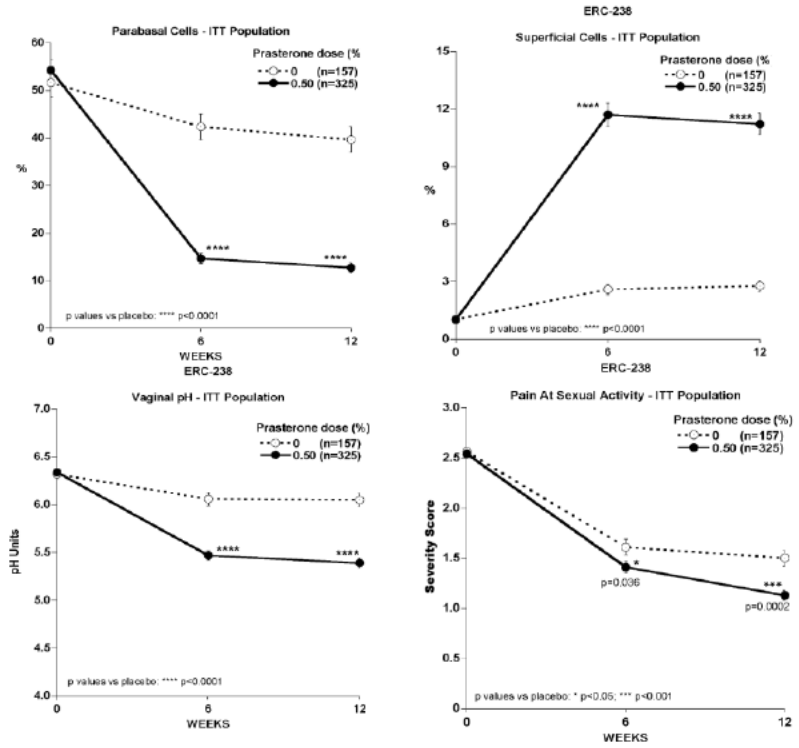


Figure 1. Effect of daily intravaginal application of placebo and 6.5 mg prasterone for 6 and 12 weeks on the percentage of vaginal parabasal and superficial cells, vaginal pH and the pain at sexual activity in the ITT population (means ± SEM; the p values - comparisons with placebo). [Source: page 89 to 102 in the study report of ERC-238]

- The concentrations of DHEA and its metabolites:

Table 1. Mean trough serum concentrations of DHEA, testosterone, E1 and E2 on Day (baseline) and 12 weeks following daily administration of 6.5 mg prasterone vagi insert in postmenopausal women (Reanalysis by the reviewer using the dataset).

	Population(N)	Baseline (mean± S.D.)	12 weeks (mean± S.D.)	% change from baseline
DHEA (ng/mL)	ITT-S (300)	1.80±1.63	2.69±1.95**	49% ↑
	cITT-S (295)	1.80±1.64	2.71±1.96**	51% ↑
Testosterone (pg/mL)	ITT-S (293)	150.6±98.7	183.5±107.9**	22% ↑
	cITT-S (289)	150.1±99.2	183.4±108.4**	22% ↑
E1 (pg/mL)	ITT-S (295)	15.32±12.49	19.11±27.38*	25% ↑
	cITT-S (290)	14.57±9.83	18.64±26.87*	28% ↑
E2 (pg/mL)	ITT-S (293)	3.39±8.71	3.41±2.53	< 1% ↑
	cITT-S (288)	2.72±1.72	3.26±2.02**	20% ↑

ITT-S = Intent-to-treat population having measurements at both baseline and 12 weeks; cITT-S = excluding subjects with a serum estrogen signature; * $p < 0.05$ and ** $p < 0.0001$ for comparisons with baseline

- Safety:

- Intravaginal administration of DHEA was well tolerated. There was no difference in the adverse events between the placebo and 6.5 mg prasterone groups.
- Application site discharge occurred in 5.6 to 6.1% of subjects per group, was mild to moderate in intensity, and was generally well tolerated with only two subjects discontinuing treatment for that reason.
- Daily administration of 6.5 mg prasterone vaginal insert for 12 weeks had no effect on the endometrium.
- There was no adverse event reported from 66 male partners whose women partner was on the treatment of DHEA insert.

Sponsor's conclusion:

· Intravaginal DHEA significantly improved vaginal pH, superficial and basal/parabasal epithelial cell counts, and relieved dyspareunia. Moderate to severe vaginal dryness accompanied dyspareunia in 84% of women and was similarly improved by DHEA treatment.
· Parallel and highly significant beneficial effects of DHEA were also observed on vaginal secretions, epithelial integrity, epithelium thickness and vaginal color as well as on the six domains of the FSFI, thus confirming the previous benefits of intravaginal DHEA on female sexual function.
· All serum sex steroids related with DHEA remained well within the normal postmenopausal values.
· Application site discharge due to melting of the vehicle reported in about 5% of subjects is the only adverse event which can be reasonably attributed to the drug.
· Male partners were highly satisfied with the improved sexual situation and no adverse reaction was reported.
· Overall, DHEA acting by a strictly local formation of sex steroids followed by their local inactivation in the vagina shows clinically and statistically significant beneficial effects on all recognized subjective and objective elements of VVA and dyspareunia compared to placebo.

Reviewer's comments:

· Daily treatment with 6.5 mg prasterone vaginal insert for 12 weeks showed significant changes in vaginal cell maturation and pH and improvement in the pain at sexual activity compared to the placebo group.
· Application site discharge was the most common drug-related adverse event in two groups. Other reported adverse events were not different between two groups.
· There was no adverse event reported voluntarily from the male partners who participated in the questionnaire survey. However, all questions given to the participants were related with the satisfaction before and after women's use of prasterone vaginal insert. This evaluation is deficient to address a safety issue in the exposed partners.
· The trough concentrations of DHEA, testosterone and E1 in the group with 6.5 mg prasterone increased significantly at 12 weeks compared to that at baseline. The trough concentration of testosterone was statically different between baseline and 12 weeks in both populations, ITT-S and cITT-S. While the mean concentration of E2 increased significantly after treatment for 12 weeks in the cITT-S population, it appeared to be comparable between baseline and 12 weeks in the ITT-S population. This result may imply that the concentrations of DHEA and its metabolites measured in cITT population excluding the E2 signature subjects seem to reflect the actual change in systemic exposure to them following administration of DHEA vaginal insert. In addition, the cITT population also exhibited much lower interindividudal variability for E2 at baseline, which suggests that the higher baseline in the ITT population was due to other potential exogenous sources.
· The patients with hepatic or renal impairment were not restricted from participating in the study. There were subjects whose laboratory findings at screening and Day 1 indicated an abnormality in renal or hepatic function. However, the proportions of subjects showing ALT and AST higher than 2-fold of their upper limit of normal range (ULN) at screening were only approximately 1.5% and 0.4% out of

study population, respectively. Approximately 1.2% (7 subjects) of study population had abnormality of total bilirubin at screening. There were two subjects who had serum creatinine higher than 1.5-fold of its ULN. It may suggest that this study did not enroll a sufficient number of subjects to address safety of prasterone vaginal insert in patients with renal or hepatic impairment.

❖ Study ERC-230

Title: DHEA against vaginal atrophy – Safety study of 12 months

Objectives:

· The primary objective: assessment of the long-term safety of intravaginal DHEA.
· The secondary objective:
  - The long-term effect of intravaginal prasterone on the symptoms and signs of vaginal atrophy by evaluating the changes in % parabasal and superficial cells, vaginal pH and self-assessment of symptoms of VVA associated with menopause.
  - Tolerance to prasterone assessed by vaginal examination.
  - The efficacy on arousal/lubrication, subjective arousal, desire, pain at sexual activity, satisfaction and orgasm

Study Design:

· Multi-center, open-label study
· Clinical trial sites: 41 sites in the U.S. and Canada
· The planned number of subjects: 350 postmenopausal women
· Subjects: postmenopausal women (non-hysterectomized) between 40 and 75 years of age with a symptom of VVA
· Treatments: daily administration of 6.5mg prasterone (0.5% DHEA) vaginal insert for 12 months
· Efficacy evaluation
  - Changes from baseline in % of parabasal cells, % of superficial cells, vaginal pH, self-assessment of symptoms of VVA/ subjective arousal, desire, pain at sexual activity, satisfaction and orgasm
· Safety evaluation
  - Adverse event (AE), clinical laboratory tests (hematology and coagulation, blood chemistry, urinalysis, lipid profile), physical examination (including vital signs and gynecological examination), Papanicolaou smear, mammography, and endometrial biopsy
· Measurements of DHEA and its metabolites
  - Blood collection: at baseline before dosing and weeks 12, 26 and 52

Results:

· Study Population
  - Enrolled: 530
  - Analyzed: Safety population – 521 (435 subjects completed the 52-week study)
    Efficacy population – 487
· E2 signature subjects (n=28): excluded from the PP population set as a major protocol violation
· Safety:
  - DHEA vaginal insert was well tolerated following intravaginal administration at daily dose of 0.5% DHEA for up to 52 weeks.
  - Systemic adverse events were infrequent and most of these were not drug-related.
  - One subject was diagnosed with breast cancer following an abnormal week 52 mammogram. The Investigator considers that this serious AE was possibly related to the study drug, but the Sponsor considers that the available evidence does not support a drug effect. The serum concentrations of

estrogens following treatment with DHEA vaginal insert were not different significantly from the baseline and other subjects (Table 1).

Table 1. The serum concentration of DHEA and estrogen concentrations in subject 230-02-061

	Day 1 (baseline)	Week 12	Week 26	Week 52
DHEA (ng/mL)	1.39	3.09	2.29	3.83
E1 (pg/mL)	18.3	20.7	23.3	17.9
E2 (pg/mL)	4.4	4.5	5.7	5.0
Estrone sulfate (pg/mL)	254	279	242	200

- Following prolonged intravaginal administration of DHEA, all endometrial biopsies samples showed atrophic or inactive endometrium. Women (n=43) who did not have an evaluable biopsy sample at discontinuation or at 52 weeks had no clinically significant change in endometrial thickness.
- Application site discharge occurred in 14% of subjects, was mild to moderate in intensity, and was generally well tolerated. Four subjects discontinued the study because of this AE.

· Efficacy results:
- Clinically and statistically significant beneficial effects of treatment with daily intravaginal 0.5% DHEA were observed in comparison to baseline on vaginal cell maturation and pH as well as on the improvement of VVA symptoms.
- DHEA had benefits of comparable amplitude and followed a similar time course of action for moderate or severe dyspareunia, vaginal dryness and irritation/itching.
- Highly significant effects were observed on desire, arousal, lubrication, orgasm, satisfaction and pain, as well as in the total FSFI score at 52 weeks in comparison to baseline.

· The concentrations of DHEA and its metabolites:

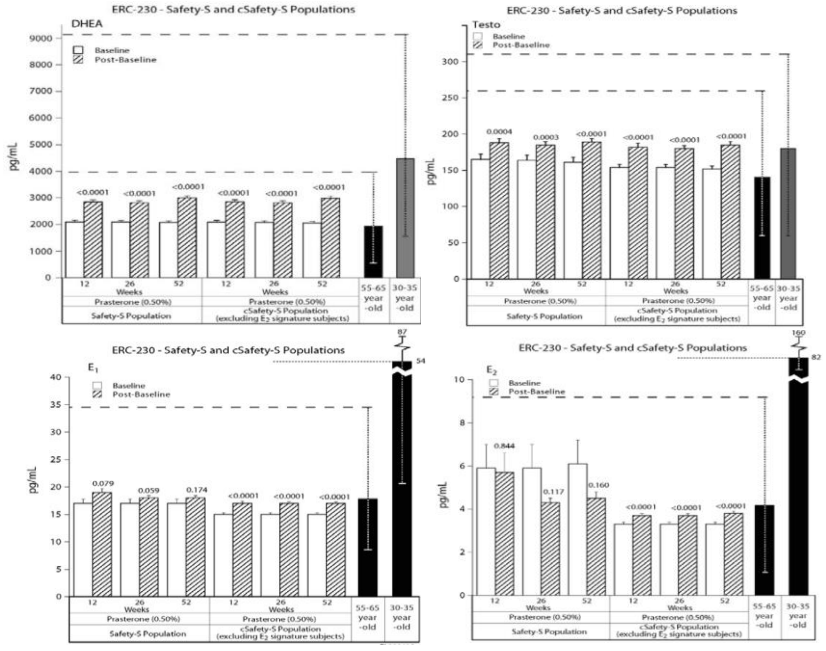


Figure 1. Mean trough serum concentrations of DHEA, testosterone (TESTO), E1 and E2 at 12, 26 and 52 weeks following daily vaginal administration of 6.5mg prasterone in postmenopausal women (means ± SEM; p values - comparisons with baseline and with placebo; serum steroid concentrations measured in normal 55-65 years old postmenopausal women (n=377) and 30-35 years old premenopausal women (n=47) as reference as means and 5th and 95th centiles (dashed lines) (Labrie et al, 2008 and 2013). [Source: page 195 to 221 in the study report of ERC-238]

Sponsor's conclusion:

- DHEA was well tolerated following intravaginal administration at a dose of 0.50% (6.5 mg) per day for up to 52 weeks. Systemic adverse events were infrequent and all of these were not drug-related. The only drug-related AE, as assessed by the Sponsor, was application site discharge.
- Following prolonged intravaginal administration of DHEA, all endometrial biopsies samples have shown atrophic or inactive endometrium and, in women with no biopsy specimen, no clinically significant change in endometrial thickness was observed.
- The Sponsor concluded that the case with breast tumor cannot be attributed to DHEA because (1) breast tumors evolve over a much longer time period before reaching such a stage, (2) DHEA inhibits breast tumor growth in numerous breast cancer models, and (3) this woman's serum steroid concentrations did not vary significantly and remained well within the normal postmenopausal range during the study.
- Compared to baseline, clinically and statistically significant beneficial effects of treatment with daily intravaginal 0.50% (6.5 mg) prasterone were observed on the % of parabasal cells, % of superficial cells and vaginal pH. Parallel beneficial effects were observed on dyspareunia, vaginal dryness and irritation/itching.

Reviewer's comments:

- There was no serious drug-related AE following treatment of 6.5mg prasterone vaginal insert for 12 months for one case of breast cancer. The change in the serum concentrations of estrogens in this patient appeared to be not different from the baseline and other subjects.
- The beneficial effect on the vaginal cell maturation and pH and pain at sexual activity maintain steadily during treatment period of 12 months.
- One subject who was diagnosed with breast carcinoma had a previous history of breast disease before the study, but it was not found in the screening. The serum concentrations of estrogens following treatment with DHEA vaginal insert were not different significantly from the baseline and other subjects. While a relationship with treatment of DHEA vaginal insert in the case with breast cancer (230-02-061) was not excluded, the serum concentrations of estrogens following treatment with DHEA vaginal insert does not appear to support a relationship between exposure to estrogen and occurrence of breast cancer.
- In the cITT population, the trough concentrations of DHEA and its metabolites increased significantly at 12, 26, and 52 weeks compared to that that at baseline, but there was no significant difference among them.

❖ Study PH-38062

Title: Determination of the inhibitory potency of dehydroepiandrosterone (DHEA) towards human CYP isoforms i*n vitro*

Experimental design:

The potential of DHEA to act as a direct inhibitor of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 was evaluated *in vitro* using pooled human liver microsomes. The potential of DHEA to act as a time-dependent inhibitor of CYP3A4 was evaluated by comparing the inhibitory potential of DHEA after 30 min preincubation with NADPH-supplemented human liver microsomes with those of obtained after coincubation.

Table 1. Incubation condition using human microsomes

CYP	Substrate (concentration)	Standard inhibitor	Tested concentration of DHEA
1A2	Phenacetin (45 µM)	Furafylline	0.3, 0.6, 1.3, 2.5, 5 and

2A6	Coumarin (2.0 μM)	Tranylcypromine	10 mcgM
2B6	Bupropion (100 μM)	Ticlopidine	
2C8	Amodiaquine (2 μM)	Montelukast	
2C9	Diclofenac (4 μM)	Sulfaphenazole	
2C19	Mephenytoin (50 μM)	Benzyl- phenobarbital	
2D6	Dextromethorphan (5 μM)	Fluoxetine	
2E1	Chlorzoaxazone (50 μM)	4-Methylpyrazole	
3A4	Midazolam (2.5 μM)	Ketoconazole	
	with preincubation (2.5 μM)	Mibefradil	
3A4	Testosterone (50 μM)	Ketoconazole	
	with preincubation (50 μM)	Mibefradil	

Results:
No direct-acting inhibitory potency of DHEA on biotransformation reactions catalyzed by CYP1A2 (phenacetin O-deethylation), CYP2A6 (coumarin 7-hydroxylation), CYP2B6 (bupropion hydroxylation), CYP2C8 (amodiaquine N-deethylation), CYP2C9 (diclofenac 4'-hydroxylation), CYP2C19 (mephenytoin 4'-hydroxylation, CYP2D6 (dextromethorphan O-demethylation), and CYP2E1 (chlorzoxazone 6-hydroxylation) and CYP3A4 (midazolam 1'-hydroxylation, testosterone 6β-hydroxylation) was observed up to 10 μM of DHEA.
Preincubation (30 min) of DHEA with NADPH-supplemented human liver microsomes did not affect midazolam 1'-hydroxylation activity (93% after preincubation *vs*. 89% after coincubation) and testosterone 6β-hydroxylation activity (82% after preincubation *vs*. 80% after coincubation) in the presence of 10 μM DHEA, giving no hints for time dependent inhibition of CYP3A4

Sponsor's conclusion:
· Drug-drug interactions through inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 by dehydroepiandrosterone (DHEA, BAY 86-5314) are unlikely.

Reviewer's comments:
· The experimental condition appears appropriate to assess an inhibitory potential of DHEA on CYP isoforms.
· The results showed no inhibitory potential of DHEA up to 10 mcgM on the tested CYP. Following daily administration of 6.5 mg prasterone vaginal insert for 7 days, the mean C_{max} was 5.97ng/mL or 0.02 mcgM. This suggests that in vivo CYP-mediated drug-drug interaction is unlikely to occur at the proposed therapeutic dose of prasterone vaginal insert.

4.4 References

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/s/

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10/21/2016

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