9 November 2017
EMA/793337/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Intrarosa

International non-proprietary name: prasterone

Procedure No. EMEA/H/C/004138/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

3α-diol-3G	Androstane-3α, 17β-diol 3-glucuronide
3α-diol-17G	Androstane-3α, 17β-diol 17-glucuronide
4-dione	Androstenedione
5-diol	Androst-5-ene-diol-3β, 17β-diol
ADT-G	Androsterone glucuronide
AE	Adverse event
ANCOVA	Analysis of covariance
AR	Androgen receptor
ASCUS	Atypical squamous cells of undetermined significance
ASMF	Active Substance Master File = Drug Master File
BI-RADS	Breast Imaging-Reporting and Data System
BMI	Body mass index
BP	Blood pressure
ca	circa, approximately
CD-spectroscopy	Circular dichroism Spectroscopy
CI	Confidence interval
CND	Canadian
CPP	Critical process parameter
CQA	Critical Quality Attribute
DB	Double-blind
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
DSC	Differential Scanning Calorimetry
DUS	Drug Utilisation Study
E1	Estrone
E1-S	Estrone sulfate
E2	17β-estradiol
EC	European Commission
EP	European Pharmacopoeia
EU	European Union
FDA	Food and Drug Administration
Fr. Ph.	French Pharmacopoeia
FSFI	Female Sexual Function Index
FSH	Follicle stimulating hormone
GC	Gas Chromatography
GC-HS	Gas Chromatography Headspace Solvents
GC-MS/MS	Gas chromatography tandem mass spectrometry
GCP	Good clinical practices
GLP	Good laboratory practices

GMP	Good manufacturing practices
HPV	Human Papillomavirus
ICH	International Conference on Harmonization
INN	International nonproprietary name
IPC	In-process control
ISR	Incurred sample reanalysis
ISS	Integrated summary of safety
ITT	Intent to treat
LC-MS/MS	Liquid chromatography mass spectrometry/mass spectrometry
LDPE	Low density polyethylene
LGSIL	Low-grade squamous intraepithelial lesion
MBS	Most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
MI	Maturation index
Mammo	Mammography
MS	Moderate - Severe
NMR	Nuclear Magnetic Resonance
NS	Not significant
OTC	Over the Counter
OVX	Ovariectomized
Pap	Papanicolaou
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PI	Principal Investigator
PK	Pharmacokinetics
PKWP	Pharmacokinetics Working Party
PP	Per protocol
PT	Preferred-term
PVC	Poly vinyl chloride
PVC/PE	Polyvinylchloride/Polyethylene
QC	Quality control
RH	Relative Humidity
SAE	Serious adverse event
SAS	Statistical analysis system
SD	Standard deviation
SEM	Scanning Electron Microscopy
SEM	Standard error of the mean
SERM	Selective estrogen receptor modulator
SI	System of units
SmPC	Summary of Product Characteristics
SOC	System organ class
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-emergent adverse event

Testo	Testosterone
TTC	Threshold of toxicological concern
TVUS	Transvaginal ultrasound
US	United States
UV	Ultraviolet
VVA	Vulvovaginal atrophy
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Endoceutics Ltd. submitted on 18 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Intrarosa, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 January 2015.

The applicant applied for the following indication (as initially proposed):

"Intrarosa is indicated for the treatment of vulvovaginal atrophy in postmenopausal women."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that prasterone was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance prasterone contained in the above medicinal product to be considered as a new active substance in comparison to prasterone previously authorised in the European Union as Gynodian Depot (prasterone enanthate), DHEA Eljot, Stymen and Biosteron. The applicant claimed that prasterone differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 December 2009 and 22 April 2010. The

Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: Patrick Salmon

- The application was received by the EMA on 18 December 2015.
- The procedure started on 28 January 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 April 2016.
- During the meeting on 26 May 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 August 2016.
- The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GMP inspection at the drug product manufacturer in USA between 20-21 October 2016. The outcome of the inspection carried out was issued on 16 November 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 September 2016.
- During the PRAC meeting on 29 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 13 October 2016, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 22 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 11 January 2017.
- During the PRAC meeting on 12 January 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 26 January 2017, the CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the 2nd CHMP list of outstanding issues on 23 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd list of outstanding issues to all CHMP members on 7 June 2017.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a 3rd list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the 3rd CHMP list of outstanding issues on 9 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 3rd list of outstanding issues to all CHMP members on 30 August 2017.
- During the CHMP meeting on 13 September 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a 4th list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the 4th CHMP list of outstanding issues on 9 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 4th list of outstanding issues to all CHMP members on 26 October 2017.
- During the meeting on 9 November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Intrarosa.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Vulvar and vaginal atrophy (VVA) is a relatively common condition symptomatically affecting approximately 50% of postmenopausal women. It is the consequence of reduced estrogen levels in urogenital and pelvic tissue resulting in a loss of vaginal elasticity, dryness, decreased lubrication with associated irritation, dyspareunia and urinary symptoms.

Vulvovaginal atrophy can occur at any time in a woman's life cycle, although it is more common in the postmenopausal phase, a time of hypoestrogenism. Other causes of a hypoestrogenic state include lactation, various breast cancer treatments, and use of certain medications. In situations other than menopause, VVA may resolve spontaneously when estrogen levels are restored.

2.1.2. Epidemiology

Numerous retrospective studies have evaluated the prevalence of symptoms of VVA. Although these studies differ in type of symptoms elicited, study design, and study population, they provide a range of estimates of VVA prevalence. They all used self-reported symptoms of vaginal dryness to determine the prevalence of VVA. In general, the prevalence ranged from about 4% in the early premenopausal groups to 47% in the late postmenopausal group.

2.1.3. Clinical presentation and diagnosis

The initial symptom is often lack of lubrication during intercourse. Eventually, persistent vaginal dryness may occur. Thinning of the epithelial lining may also cause pruritus, soreness, and a stinging pain in the vaginal and vulvar area, which, in turn, may further contribute to dyspareunia. Vaginal

spotting, due to small tears in the vaginal epithelium, may also occur. Women with VVA may report a thin yellow or grey watery discharge secondary to the rise in pH that accompanies VVA.

2.1.4. Management

Available therapies are either non-hormonal or hormonal treatments.

Non-hormonal treatments:

Current OTC treatments include non-hormonal vaginal moisturizers for VVA symptoms and lubricants for dyspareunia.

Vaginal moisturizers are water based, available as liquids, gels, or pessaries inserted every few days. Vaginal moisturizers can be safely used long term, but they need to be used regularly for optimal effect.

Vaginal lubricants are shorter acting than moisturizers and are applied at the time of sexual activity to reduce dyspareunia. They can be either water or silicone based, with the water-based products being the most widely available. They are applied to the vaginal opening and/or to the penis and often require repeated application during sexual activity. Silicone-based lubricants require application of only a very small amount and last longer. The choice of lubricant may depend on individual preferences and product availability.

Hormonal treatments:

Because the lack of circulating natural estrogens is the primary cause of atrophic vaginitis, the use of estrogen orally, transdermally or vaginally has been shown to be effective in improving symptoms and signs of VVA. Estrogen replacement restores normal pH levels and thickens and re vascularizes the epithelium. Adequate estrogen replacement therapy increases the number of superficial cells, may alleviate existing symptoms or even prevent development of urogenital symptoms if initiated at the time of menopause.

Although vaginal estrogens applied as a cream, vaginal tablets, or a low-dose vaginal ring are systemically absorbed, the rise in serum estrogen levels appears to remain well below premenopausal levels. Nonetheless, this may be of concern to women with a history of breast or other hormonally sensitive cancers.

About the product

Intrarosa is presented as vaginal pessaries containing 6.5 mg of active substance prasterone (DHEA), to be administered in the vagina, with or without the use of an applicator.

The approved indication is the “treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms”.

The product is to be administered once a day, preferably at bed time.

No limited treatment duration is proposed by the Applicant. A careful appraisal of the risks and benefits should be reassessed at least every 6 months and Intrarosa should only be continued as long as the benefit outweighs the risk.

Type of Application and aspects on development

Development program

The clinical efficacy of Intrarosa on the symptoms and signs of vulvovaginal atrophy (VVA) has been evaluated in 6 clinical studies performed in Canada and the USA. Within the 6 studies, there were two pivotal 12-week efficacy studies (ERC-231 and ERC-238) which support the proposed indication. The pivotal efficacy studies were performed in postmenopausal women who have self-identified moderate to severe (MS) dyspareunia (pain at sexual activity) as their most bothersome symptom (MBS) of VVA.

In addition, the clinical programme includes one 7-day PK study (ERC–213), one dose-response study (ERC-210), and one placebo-controlled efficacy study performed with a different (reduced) regimen (ERC-234).

The study ERC–230 was an open-label long term (52 weeks) safety study in which efficacy parameters were only regarded as secondary endpoints.

Compliance with CHMP guidance

There are no specific CHMP guidelines or recommendations for the proposed indication. The US "*Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation*" of January 2003 was considered by the Applicant for the product development.

Compliance with scientific advice

Between 2009 and 2011, Scientific Advices have been given by the following agencies: EMA (initial scientific advice on 2009 and a follow-up on 2010), France, Germany, The Netherland, United-Kingdom, and Sweden. The questions discussed were related to the toxico–pharmacological development and clinical development. These Scientific Advices were granted before the entire clinical development of the drug product was terminated, leading to changes in the clinical programme.

During the different scientific advice discussions, the Applicant was encouraged to consider the conduct of a 3-arm phase III trial with a placebo arm and an active-controlled arm (e.g. intravaginal estradiol considered as the standard treatment). Indeed, comparison to an active treatment was considered as a preferable design than only a placebo-controlled trial, in order to put into perspective the efficacy compared to a "standard" treatment.

No active comparator was included in the study development.

The selection of the 4 co-primary efficacy endpoints was discussed as well as the population to be considered for the primary analysis (ITT).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a pessary for vaginal use containing 6.5 mg of prasterone as active substance.

The other ingredient is hard fat (Adeps solidus).

The product is available in a blister composed of an outer layer of polyvinyl chloride (PVC) and an inner layer of low density polyethylene (LDPE) as described in section 6.5 of the SmPC. The product is supplied with LDPE plastic applicators which are individually wrapped with a plastic film.

2.2.2. Active Substance

General information

The chemical name of prasterone, also known as dehydroepiandrosterone (DHEA), is 3β-Hydroxy-5-androsten-17-one corresponding to the molecular formula $C_{19}H_{28}O_2$. The active substance has a relative molecular mass 288.43 g/mol and the following structure:

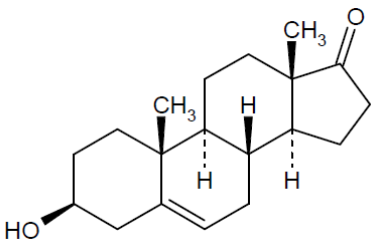

Figure 1: Chemical structure of prasterone.

Prasterone is a steroid, which consists of three six-membered rings (A, B and C) and one five-membered ring (D).

The molecular structure of prasterone has been confirmed by a combination of spectroscopic methods: IR spectroscopy, UV-Vis spectroscopy, CD-spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and X-ray diffraction, following a major objection on the lack of characterization data to unequivocally demonstrate the structure of the molecule that results from the proposed synthesis.

Prasterone exhibits stereoisomerism due to the presence of six chiral centres. These centres originate from the proposed starting material, which proceeds from a natural source and provides a well-defined stereochemistry of the steroidal system (cyclopentane perhydrophenantrene) which remains unchanged during the subsequent chemical transformations leading to the active substance. Enantiomeric purity is controlled routinely by specific optical rotation.

The active substance is a white to yellowish white non hygroscopic powder, practically insoluble in water, soluble in methanol, freely soluble in isopropanol and dichloromethane.

The active substance exhibits polymorphism. Six polymorphs (Forms I, II, III, IV, V and VI), a ¼ hydrate (S1), two polymorphic monohydrates S2 and S3, and a methanol hemisolvate (S4) have been described in literature. In internal investigations, a further monohydrate (S5), a ⅓ hydrate (S unstable acetone solvate (S7) were found. According to X-ray diffraction analysis on prasterone batches manufactured by the proposed manufacturing process, the active substance produced by the proposed manufacturer is mainly composed of one form with traces of a second form. Given that the active substance is solubilized in the excipient during the manufacturing process of the finished product, polymorphism is considered a non-critical quality attribute.

Manufacture, characterisation and process controls

Prasterone is synthesized in three main steps from a well-defined starting material with acceptable specifications, followed by purification and crystallization. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

During the evaluation, a major objection on the proposed starting material was raised since there were concerns regarding the impurity profile of the compound, its proposed specification, the information on

the fate and purge of impurities, and the criticality of the synthetic steps prior to the proposed starting material. These concerns were adequately addressed by the ASMF holder, who provided data on the potential carry-over of impurities and the criticality of the steps prior to the proposed starting material, revised the starting material specification and provided information on the plant species, region/location, harvesting, storage conditions and extractions and solvents used. Based on the additional information provided, the proposed API starting material was accepted.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged into a polyethylene bag which is then sealed and placed into another polyethylene-aluminium laminated bag. The polyethylene-aluminium laminated bag is shipped within a fiber drum, properly labelled, and provided with a plastic seal. The polyethylene complies with Regulations 1935/2004/EC, 2023/2006/EC and 10/2011/EC.

Specification

The active substance specification includes tests for: appearance/description, identification (IR, HPLC), loss on drying (Ph. Eur.), total ash (Ph. Eur.), water content (KF), heavy metals (Ph. Eur. Method C), optical rotation (Ph. Eur.), assay (HPLC), impurities (HPLC), hydroxylamine (UV/Vis), and residual solvents (GC; GC-HS).

The specification of Prasterone complies with the requirements defined in the guidelines ICH Q6A Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances, ICH Q3A Impurities in new drug substances and Q3C Impurities: Guideline for residual solvents. A specification limit for hydroxylamine in line with the French Pharmacopoeia was introduced during the marketing authorisation evaluation as requested by the CHMP.

The two impurities with noted alerting structures are controlled to the TTC level.

The omission of benzene and polymorphism from the active substance specification was adequately justified. Benzene is included in the specifications of the relevant solvents (isopropanol and methanol), and the active substance is solubilised in the excipient, so polymorphism is not a critical quality attribute (CQA).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three commercial scale of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 60 months under long term conditions at 25 ± 2°C / 60 ± 5 % RH and for up to 6 months under accelerated conditions at 40 ± 2°C / 75 ± 5 % RH according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification (IR), start of melting, end of melting, specific optical rotation, loss on drying, water content, impurities and assay. The specifications limits and analytical procedures for the parameters tested during stability are identical to those employed by the ASMF holder for release testing.

The stability results presented are all within the proposed specifications. Although a slight increase in loss on drying and water content was observed, both under long term and accelerated conditions, all results complied with the specifications. No trends were observed in any of the other tests. Photostability testing following the ICH guideline Q1B was performed on one batch. This study indicated that the active substance is photolabile.

In addition, a forced degradation study under high temperature, high humidity, acidic and alkali conditions, oxidative condition, exposure to light was performed on five batches. Samples were tested for appearance, assay, specific impurities and unknown impurities. High degradation was observed upon exposure to high temperatures (above 80°C) or oxidation. Prasterone, both solid and in aqueous suspension, showed degradation under the light influence.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a pessary for vaginal use containing 6.5 mg of prasterone as active substance. The pessary is approximately 28 mm long and 8.6 mm in diameter at its widest end.

The pessaries are packaged in sealed PVC/PE blisters.

The pessary is administered using the finger or a vaginal applicator made with LDPE and 1% of white colorant. The applicant provided a self-declaration for Class I device that the applicator meets the provisions of Council Directive 93/42/EEC as amended by 2007/47/EC. The applicators are individually wrapped with a plastic film.

The qualitative composition of Intrarosa is presented in Table 1 below.

Table 1. Qualitative composition of Intrarosa.

Component and Quality Standard (and Grade, if applicable)	**Function**
Prasterone, in house	Drug Substance
Hard Fat, EP	Base

The finished product is composed of prasterone active substance and hard fat excipient, EP. The active substance is dissolved in the melted hard fat during the manufacturing of the pessaries. Therefore, particle size and polymorphism of the active substance are not critical.

The physical characteristics of the active substance after re-solidification step were examined by X-Ray Powder Diffraction (XRPD), differential scanning calorimetry (DSC) and Scanning Electron Microscopy (SEM), demonstrating that prasterone is completely solubilized in the excipient.

As mentioned above, the only excipient in the formulation is hard fat, a compendial (EP) mixture of fatty acid esters. Its melting point is in the range of 33.5–35.5°C, which allows having solid pessaries at room temperature that melt rapidly when introduced into the vaginal cavity at 37°C permitting the release of the active substance. This is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The only excipient is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The same qualitative composition and container closure system were used for the manufacture of the finished product at all sites during all clinical studies; the only difference was the batch size. Different strengths were manufactured to support pre-clinical and clinical studies: 0% (placebo), 0.25% (3.25 mg), 0.5% (6.5 mg), 1% (13 mg) and 1.8% (23.4 mg) prasterone. Based on the results from these studies, the 0.5% (6.5 mg) strength was selected for commercialization.

Following a major objection on the rationale for the choice of the dissolution method and its discriminatory nature, the applicant provided a historical summary of the dissolution method regarding dissolution apparatus (paddle versus flow-through cell), paddle speed effect, effect of medium (pH), sink conditions and SLS concentration. In addition, the discriminating ability of the proposed QC dissolution method was demonstrated using different batches of pessaries manufactured with different grades of hard fat and different amounts of prasterone (from 0.5% to 1.8%) in hard fat . The data presented addressed the concerns and the proposed quality control (QC) dissolution method was considered acceptable.

Since initial development, the manufacturing process had been scaled up two times and transferred to four different manufacturing facilities. Prior to manufacturing clinical trial batches, the manufacturing process was optimized. The primary focus of the study was on the three interdependent variables that impact converting the sealed product dosage form from its liquid phase to its solid phase (product temperature, cooling temperature, and machine speed). Based on the results of these experiments the temperatures/settings to manufacture clinical supplies were defined.

The impact of critical process parameters (CPPs) on the product critical quality attributes (CQAs) was evaluated.

Two manufacturing sites are proposed for marketing. In order to support the pre-approval manufacturing site transfer from one site to the other, appropriate validation batches and profile comparison was performed between the two sites. The primary packaging is PVC/PE blister. The polyethylene lamina, which is the drug contact surface, conforms to Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. As mentioned above, the product is administered using the finger or a CE marked vaginal applicator that is made of LDPE material and a white colorant (approximately 1%).

The applicators should be re-used during one week and then discarded (2 back-up applicators are included, if needed). A study was conducted to identify the best suitable cleaning procedure and to demonstrate that this cleaning procedure results in a sufficient reduction of the micro-organisms. The cleaning procedure is described in section 4.2 of the SmPC.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: melting the hard fat, adding and dissolving the prasterone active substance, filling the PVC/PE formed cavities, cooling and sealing alveoli, packaging strips in a carton box.

The applicant did not define critical steps and relevant operating process parameters in the original submission, which resulted in a major objection. This information was added during the procedure and the concerns were satisfactorily addressed.

The in-process controls comprise: clarity of solution (of the active substance dissolved in the excipient), appearance and weigh of the pessaries and molds seal. The in-process controls are adequate for this pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies. Process validation data from three commercial scale batches manufactured at each of the proposed manufacturing sites according to the production protocol and validation plan were presented. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specification includes appropriate tests for this kind of dosage form: description, identification (HPLC, UV), melting temperature (Ph. Eur.), assay (HPLC), impurities (HPLC), content uniformity (Ph. Eur.), average weight, dissolution (Ph. Eur.), microbial limit tests: TAMC, yeast and molds, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans*.

The limits of known and unknown impurities were established in accordance with ICH Q3B and the total impurities limit was established to cover the limits of individual known impurities which are known metabolites of DHEA.

The dissolution specification was defined to cover the dissolution behavior observed in the stability studies, which was evaluated and concluded to have no impact on the *in vivo* effect of the drug product in women.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for eighteen batches of different strengths used in first clinical studies, as well as three commercial scale batches from each of the proposed manufacturing sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial scale batches of finished product produced by each of the proposed finished product manufacturers stored under long term and intermediate conditions for 36 months at 5°C ± 3°C, 25 ºC / 60% RH and 30°C /75% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of Intrarosa are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive data from four additional batches from another manufacturer used during development were also provided. The only difference of these batches is that they were filled in larger blisters, instead of the smaller size used of the commercial blisters, which represent a worst case condition.

Samples were tested for appearance, package integrity, melting range, assay, impurities, dissolution and microbial tests. The analytical procedures used are stability indicating.

All test results were within the specification limits except assay at 30°C / 75% RH which droped below the proposed specification at 36 months. However, this condition at 36 months is not used to support the proposed storage conditions in the EU.

All other parameters were stable under the conditions and showed no trend during storage except for dissolution of samples stored at 5°C, 25°C / 60% RH and 30°C / 75% RH which showed slight deceleration in dissolution over time due to known partial and progressing crystallisation of the hard fat during storage.

Under accelerated conditions, 40°C/75% RH out of specification results were observed for appearance after 6 months storage and for assay for some batches. No change of dissolution behaviour occured with samples stored at 40°C/75% RH because the pessaries are completely molten during this arm of the study and no hard fat crystallization can therefore develop.

The photostability of the finished product was assessed in line with ICH Q1B “Guideline Photostability Testing of New Drug Substances and Product” on one batch. Unprotected vaginal pessaries exposed to light stress exhibited increased levels of degradation products as well as decrease of the assay and dissolution, with out of specification results; whereas dark controls and pessaries protected in the commercial primary packaging showed comparable results within the specifications. Therefore, the finished product is not stable when exposed to light (as per ICH photostability conditions) outside of its primary packaging, but the proposed commercial primary packaging is suitable for light protection.

Based on the results presented, the proposed shelf-life is of 36 months. The drug product can also be stored refrigerated at 5°C (optional).

Forced degradation studies were also conducted as part of the validation of the analytical HPLC method for assay. Samples were exposed to temperature (200°C for 1h), base (1N NaOH, 24h), acid (1N HCl, 24h), and oxidation (30% H_2O_2, 24h). Major oxidative compounds were observed after exposure of the active substance and finished product to thermal conditions.

Based on available stability data, the proposed shelf-life of three years with the special storage condition “Store below 30°C. Do not freeze.” as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Although there were several major objections during the procedure, namely on the selection of the starting material, control of hydroxylamine in the active substance specification, choice and discriminatory nature of the QC dissolution method and omission of critical steps and operating process parameters from the finished product manufacturing process description, these were satisfactorily addressed during the evaluation procedure. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these

in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Five non-clinical studies have been submitted in support of the application; the Applicant has indicated that these are GLP-compliant. All other non-clinical evidence has been derived from the published literature; the GLP status could not be verified from these publications.

The pharmacology part of the dossier is only based on scientific publications.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacology data are limited to in vivo studies in OVX rat model, no in vitro data have been submitted.

A 2-week study has been performed by the Applicant in the OVX rat model with intravaginal administration of prasterone (DHEA) as pessaries using the same formulation used in clinical (Study URMA-r-70-05).

Three doses of DHEA have been tested in this study: 0.33, 0.66 and 1 mg/pessary. The efficacy endpoints were only limited to histological assessment without measurement of the vaginal epithelial thickness. No vaginal smears were performed and no active estrogen comparator was included in the design of the study. Results are only reported in the context of a publication (Berger et al, 2008) with limited details. Based on morphological assessment, the vehicle appears to produce an effect of its own with no significant differences between DHEA treated animals and placebo after 2 weeks. Sex steroid expression was used by the Applicant to assess the extent of androgenic and estrogenic response. However, given the high expression in all groups it is not possible to evaluate and interpret these data.

Other pharmacodynamic data in the OVX rat model are available from 2 published studies investigating the effects of percutaneous administration or vaginal application of DHEA up to 9 and 3 months, respectively. In these studies, efficacy criteria were also limited to histological assessment and vaginal weight. Vaginal epithelial thickness was only determined in the 9-month study performed with a higher dose of 80 mg/kg in which DHEA increased thickness of the vaginal epithelium.

In all studies, DHEA administration caused mucification and vacuolization typical of an androgenic effect.

Secondary pharmacodynamic studies

The effects of intravaginal DHEA administration on the uterus and mammary gland have been investigated in the context of the primary pharmacodynamics studies conducted in OVX rats.

In the 2-week study performed with intravaginal administration as pessaries (Study URMA-r-70-05), no significant morphological effects attributable to DHEA treatment were observed in the uterus and mammary gland. A small non-significant increase in AR expression was recorded in the two higher DHEA dose-groups.

In a 12-month study performed with DHEA applied on the dorsal skin (Sourla, Martel et al 1998), a dose of 30 mg stimulated lobuloalveolar and ductal growth.

The applicant has not performed receptor binding screening. Literature data suggest that DHEA could bind to some receptors and/or ion channels at exposure levels, which are not clinically relevant.

Safety pharmacology programme

No safety pharmacology data have been provided regarding potential effects of systemic availability of exogenous DHEA on the peripheral, central and autonomic nervous systems, respiratory and/or cardiovascular systems. The Applicant justifies this lack given the mode of administration.

Pharmacodynamic drug interactions

No specific studies have been provided, but the applicant has reviewed the pharmacological effect of DHEA in combination with the anti-estrogens and SERMs (EM-800 and acolbifene) or anti-androgens (Flutamide). These did not reveal any concerns for the proposed use and no further data were requested.

2.3.3. Pharmacokinetics

No specific ADME studies have been performed. The submitted data are from scientific publications. The serum levels of DHEA and some of its metabolites have been determined in the repeat-dose toxicity studies performed by oral route in rats and monkeys.

Method of analysis

Validated GC-MS and LC-MS/MS methods were used to quantify DHEA and its metabolites in repeat dose toxicity studies in rats and monkeys and in the PD/PK study performed in OVX rats. The stability in rat and monkey serum under analysis and storage conditions has been investigated. Long term stability in monkey serum at -80°C for ADT-G, 3α-diol-3G and 3α-diol-17G was not assessed.

Absorption

Pharmacokinetic data following single intravaginal administration are available in the context of the primary pharmacodynamics study performed in the OVX rats (Study URMA-r-70-05). The serum levels of DHEA and some of its metabolites: DHEA-S, 5-DIOL, 4-DIONE, TESTO, DHT, E2 and E1 have been determined up to 4 hours. A systemic exposure to DHEA was clearly demonstrated with a rapid absorption.

Distribution

No specific data have been provided.

Metabolism

The metabolic fate of DHEA is well characterized. However, there are significant inter-species differences regarding patterns/rate of DHEA transformation to androgenic or estrogenic hormones.

Excretion

No specific data have been provided.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were not conducted.

Repeat dose toxicity

Pivotal repeat dose toxicity studies have not been performed via intravaginal route, which is the intended route of administration in clinical. Repeat-dose toxicity studies have been performed in rats and monkeys via the oral route up to 26 weeks and 52 weeks, respectively. The oral route was selected by the Applicant to permit high exposure multiples relative to humans. This approach was discussed and agreed during the scientific advice given by the EMA. However, the performed repeat dose toxicity studies were not specifically designed to assess the safety profile of DHEA as a single compound.

In female monkeys treated with DHEA alone, no adverse effects were observed on any parameters evaluated at both doses. At the highest dose tested of 10 mg/kg, the exposure to DHEA and DHEA-S was 7,8 and 3,4 fold compared to human exposure.

In female rats exposed to DHEA as a single compound, lower serum bilirubin concentrations, higher serum alkaline phosphatase and higher liver weights were observed at 100 mg/kg without histological changes. Minimal to slight squamous metaplasia of the glandular epithelium was observed in some animal (3-4 per group) at both doses. At the lowest dose tested of 10 mg/kg, the exposure to DHEA and DHEA-S was 2,5 and 1 fold compared to human exposure.

Genotoxicity and Carcinogenicity

Prasterone did not reveal a genotoxic potential in a standard battery of genotoxicity. A carcinogenicity study was not conducted. The applicant has provided adequate justification utilising available knowledge regarding the potential impact of DHEA-derived hormones on carcinogenic risk. However, as outlined during the scientific advice, given the route of administration there is a concern for local carcinogenic effects since DHEA is converted locally into androgens and estrogens, a local carcinogenic effect cannot be excluded (please refer to discussion on abnormal Pap smears (MedDRA term: cervical dysplasia) in the clinical section of this assessment report).

Reproduction Toxicity

No specific studies were performed, which is agreed because of the indication.

Local Tolerance

A non-clinical study investigating the local tolerance in the vagina was not performed. However, clinical data on local tolerance were obtained from women treated with prasterone pessaries up to 52 weeks as well as from women who received placebo pessaries containing the excipient up to 12 weeks; no further non-clinical data were requested.

2.3.5. Ecotoxicity / environmental risk assessment

The Log Kow has been determined experimentally and is ‹ 4,5.

The PECsw is above the trigger value of 0.01 µg/L. Therefore a phase II environmental fate and effects analysis would in principle be required. The Applicant has not performed specific studies as described in the Guideline and used available data on the European Chemical website.

As DHEA can be considered as a pro-drug and is nearly fully metabolized, additional studies are not necessary.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Pharmacodynamics studies submitted in support of this application are limited to scientific publications.

The applicant claims that DHEA is converted intracellularly into active sex steroids in the vagina, and thus the active steroids exert their effects locally on the vagina. However, the actual formation of these active steroids in the vagina has not been clearly demonstrated.

Only one study was performed in OVX rat via intravaginal administration. This study was a 2-week PD/PK performed by the applicant (Study URMA-r-70-05). However, results are only available in the context of a publication. Based on morphological assessment, the vehicle appears to produce an effect of its own with no significant differences between DHEA treated animals and placebo after 2 weeks. No significant morphological effects attributable to DHEA treatment were observed in the uterus and mammary gland.

In relation to secondary pharmacodynamics, the applicant has not performed receptor binding screening. Literature data suggest that DHEA could bind to some receptors and/or ion channels at exposure levels, which are not clinically relevant.

Safety pharmacology data have not been provided. This lack is acceptable given the limited bioavailability demonstrated in clinical studies.

Pharmacokinetics

Validated methods were used to quantify DHEA and its metabolites in repeat dose toxicity studies.

The metabolic fate of DHEA appears well elucidated. Considering the significant inter-species differences highlighted by the applicant in relation to endogenous DHEA levels, additional non-human characterisation of DHEA metabolism would likely be of little value. Specific distribution or excretion studies were not under taken by the applicant.

As evaluated in vitro using pooled human liver microsomes, up to the highest tested drug concentration (IC50 > 10 µM), co-incubation with DHEA did not affect the activities of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4, thus indicating that drug-drug interactions due to inhibition of these enzymes by DHEA is unlikely. Specific CYP450 induction studies were not performed. However, this lack is justified.

Toxicology

The toxicology of DHEA was evaluated in two long-term repeat-dose toxicity studies conducted under GLP conditions in rats and monkeys. DHEA was given orally in these studies to permit sufficiently high exposure multiples relative to humans, since such high exposures were not possible to achieve using the intended intravaginal route in animal models. However, these studies were not specifically designed to study the safety profile of DHEA as single compound. The species were selected according to previous studies performed with acolbifene and estradiol. Moreover, only two doses of DHEA have been tested in the repeat-dose toxicity studies performed in both species, whereas three doses are generally recommended.

Reproductive and developmental toxicity have not been conducted, which is agreed given the clinical indication.

DHEA was not genotoxic in a standard battery and formal carcinogenicity studies were not conducted.

As agreed during the scientific advice, local or systemic rodent long term carcinogenicity studies are not necessary nor appropriate and were not performed by the Applicant. The Applicant claims that the increase of DHEA and its metabolites observed is in the normal ranges of post-menopausal women and has no clinical significance, and thus a carcinogenic risk is unlikely. However, given the route of administration there is a concern for local carcinogenic effects since DHEA is supposed to be converted locally into androgens and estrogens. A local carcinogenic effect at the cervix or via diffusion to the endometrium cannot be excluded and clinical data are limited. This issue has been included in the risk management plan.

2.3.7. Conclusion on the non-clinical aspects

There are no unresolved issues from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The following table summarizes the studies performed during the clinical development of prasterone in the claimed indication “treatment of vaginal atrophy in postmenopausal women”.

Table 2: Summary of studies performed for the clinical development

Study ID	No of centers	Design	Posology	Study objective	Subj / arm randomized/ completed	Duration	Gender, median age	Diagnosis Incl criteria	Primary endpoint
ERC-213 **(Ph I PK study)**	1	Random, DB, placebo controlled	Placebo, DHEA: 6.5, 13 and 23.4 mg	DHEA and metabolites serum level. PK parameters	40 in total 10/10 each arm	7 days	F Median age: 62	Postmenopausal women with vaginal atrophy	PK parameters
ERC-210 (Ph II) Dose – response study	8	Random, DB, placebo controlled	Placebo, DHEA: 3.25 mg, 6.5 mg and 13 mg	Dose - response	54/48 53/48 56/52 54/51	12 weeks	F Median age: 58	Postmenopausal women with vaginal atrophy	4 co- primary (vaginal maturation index*, vaginal pH, improvement in MBS)
ERC–231 (Ph III pivotal).	33	Random, DB, placebo controlled	Placebo, DHEA: 3.25 mg and 6.5 mg	Confirm efficacy on symptoms and signs of VA	81/72 87/74 87/76	12 weeks	F Median age: 59	Postmenopausal women with VVA, dyspareunia as MBS	4 co- primary (vaginal maturation index*, vaginal pH and dyspareunia)
ERC–238 (Ph III, pivotal).	38	Random, DB, placebo controlled	Placebo, DHEA: 6.5 mg	Confirm efficacy on dyspareunia as MBS	182/171 376/356	12 weeks	F Median age: 59	Postmenopausal women with VVA, dyspareunia as MBS	4 co- primary (vaginal maturation index*, vaginal pH and dyspareunia)
ERC–234 (Ph III).	42	Random, DB, placebo controlled	Placebo, DHEA: 3.25 mg and 6.5 mg	Confirm efficacy on vaginal dryness. **Different regimen**	152/130 148/128 150/125	12 weeks	F Median age: 58	Postmenopausal women with VVA, dryness as MBS	4 co- primary (vaginal maturation index*, vaginal pH and vaginal dryness)
ERC–230 (Ph III long term safety)	41	Open-label	DHEA: 6.5 mg	Long-term safety	521/435	52 weeks	F Median age: 58	Postmenopausal women with VVA symptom(s) (mild to severe)	Safety parameters

*: percentage of superficial cells and parabasal cells

2.4.2. Pharmacokinetics

One study, Study ERC-213, was performed to evaluate an eventual absorption of DHEA and systemic exposure. This study was performed in 2006 to assess efficacy, safety and PK of prasterone administered intra-vaginally. It included 40 subjects, 10 for each treatment groups. Subjects received a placebo, or 0.5% prasterone pessaries (strength intended for commercialisation), or 1% prasterone pessaries, or 1.8% prasterone pessaries, once daily for seven days. PK data were available at Day 1 and Day 7.

Lack of ISR (incurred sample reanalysis) was incompletely justified (as compared to the PKWP Q and A recommendations), but further explanations provided by the applicant are considered sufficient. Data excluded from the PK analysis set were properly justified.

Compared to placebo, the AUC0-24 of DHEA increased:

* 2.68 fold, 3.06 fold and 5.05 fold at Day 1 for 0.5%, 1% and 1.8%, respectively,

* 2.26 fold, 3.07 fold and 4.61 fold at Day 7 for 0.5%, 1% and 1.8%, respectively.

Discussion on average serum level comparisons (AUC0-24 / 24 hours) was much less pertinent and was not pursued further. Based on comparisons of AUC0-24, a systemic passage of DHEA cannot be excluded. However, the following elements must be taken into account:

* The small sample size (10 subjects per strength investigated),

* A very large inter-individual variability found in literature,

* A parallel design that allows only for an indirect comparison of a treated subject versus a placebo subject. A crossover design would have allowed for individual comparison of DHEA with each subject as their own reference,

The applicant`s main argument is that the DHEA serum concentrations after administration of 0.5% prasterone pessaries are in the same range as those in post-menopausal women in literature (*Labrie, Bélanger et al, The journal of steroid biochemistry and molecular biology, vol. 99, p 182-188, June 2006*). But this does not account for the higher DHEA serum concentrations after the 1.8% prasterone pessaries. It is to be noted that the literature data comes from the same research team that performed study ERC-213. Sampling time and analytical methods were provided by the applicant further to CHMP request, but the age range in the referenced literature (55-65 years) differs from that in study ERC-213 (44-72 years; median age: 62 years), making comparison of those concentrations problematic.

Study ERC-230 and the safety (ISS) report provided additional data for serum DHEA and metabolites. The applicant was asked for an additional table summarizing those exposures and the comparative descriptive statistics attached to it. The applicant's answer was incomplete, as they did not separate the effects of different weeks. However, when comparing this additional table with the summary of data presented in the initial submission, several changes from baseline become statistically significant once Study ERC-234 was taken off. Additionally, the changes from baseline for placebo are never statistically significant, asserting that variability does not prevent comparison of data.

Table 3: Post-baseline concentrations / baseline concentrations individual ratios of serum DHEA and metabolites with 6.5 mg prasterone dose (data from studies ERC-210; ERC-230 (up to week 52); ERC-231 and ERC-238).

	Prasterone 3.25 mg	**Prasterone 6.5 mg**	**Prasterone 13 mg**

	(N=139)		(N=1048)		(N=64)	
	Change	**p**	**Change**	**p**	**Change**	**p**
E1	+ 12%	0.0465	+ 22%	P<0.0001	+ 43 %	<0.0001
E2	+ 17 %	0.2534	+ 31%	P<0.0001	+ 62%	<0.0001
DHEA	+29 %	0.0024	+66%	P<0.0001	+ 133 %	<0.0001
Testo	+ 12 %	0.0367	+ 26%	P<0.0001	+ 70 %	<0.0001
DHT	+ 25%	0.0003	+ 50%	P<0.0001	+106%	<0.0001

In the state of knowledge described by those data, it can be concluded that there is a statistically significant increase of exposure in DHEA, E1, testosterone and other analytes for all the different strengths of DHEA tested.

During the procedure, the Applicant was asked to compare the observed increases in systemic exposure at week 52 to an independent reliable public source/guidelines presenting normal postmenopausal ranges that are commonly used in clinical practice. Results showed that the increase of DHEA & related metabolites levels observed during the clinical trials with a dose of 6.5 mg of prasterone was indeed statistically significant compared to the baseline (and to placebo) but this increase remains within normal post-menopausal steroid concentration ranges (as per usual observations and guidelines).

Finally, there are additional safety signs that point to systemic exposure (please refer to the discussion on safety regarding TEAE related to androgenic and estrogenic exposure).

Pharmacokinetic interaction studies

The potential of dehydroepiandrosterone to act as a direct inhibitor of human cytochrome P450 isoforms (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) was evaluated *in vitro* using pooled human liver microsomes. In addition, 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 pre-incubation with NADPH-supplemented human liver microsomes with those of obtained after co-incubation.

Based on the results, drug-drug interactions through inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 by dehydroepiandrosterone are unlikely.

2.4.3. Pharmacodynamics

Mechanism of action

The pharmacological effects of dehydroepiandrosterone (DHEA; prasterone) on the vagina were evaluated by the Applicant in R&D studies performed in virgin female rats following intravaginal administration of DHEA by pessaries or topical application on the vaginal mucosa as well as following percutaneous application of DHEA on the skin which is similar to the vaginal mucosa. At daily doses of 0.33 mg, 0.66 mg or 1 mg DHEA/pessary in ovariectomized animals for two weeks, the objective was to induce local beneficial effects in the vagina without significant systemic action. The results show that the morphological effects of DHEA on the vaginal mucosa were observed at the lowest dose used (0.33 mg DHEA/pessary) and consisted mainly of a typical androgenic effect of epithelial mucification. No

change in morphological features related to cell proliferation was observed at any DHEA dose used (up to 1 mg DHEA/pessary) on the uterus, mammary gland and skin. Immunohistochemistry for androgen, estrogen alpha and progesterone receptors did not reveal any significant systemic effects in the uterus, mammary gland and skin except some suggestion of increased androgen receptor labeling in mammary gland and skin at the highest DHEA dose. The data obtained from this preclinical study shows that intravaginal DHEA can exert beneficial effects limited to the vagina. Two other studies performed in rats following topical application of DHEA on the vaginal mucosa and on the skin have also demonstrated the beneficial effects of DHEA on the vagina.

No specific clinical studies of phase I were performed to clarify the pharmacological effect of DHEA on the human vagina. The Applicant hypothesis and conclusions with regard to the DHEA mechanism of action repose on results obtained at pre-clinical level from studies performed in female rat.

The mechanism of action of DHEA administered intravaginally is based on the hypothesis of intracrinology. This hypothesis - proposed by the Applicant - suggests that DHEA, an inactive compound by itself, is converted in peripheral tissues (vaginal cells) under the action of specific enzymes into sex steroids and then inactivated locally thus avoiding an increase of systemic exposure to sex steroids. However, a clear proof of this concept (intracrinology) is neither sustained by dedicated studies in the dossier nor confirmed by data of the literature (if we exclude all the published articles related to the submitted dossier). In addition, increase in systemic exposure of DHEA metabolite after treatment with prasterone is observed (see PK section of the report).

Primary and Secondary pharmacology

Regarding primary pharmacology, no specific phase I or phase II study was performed by the Applicant to elucidate the DHEA primary pharmacology. Data are obtained from the phase III studies (in particular pharmacodynamics parameters of efficacy and values of serum sex steroid after intravaginal exposure to DHEA).

The concept of intracrinology proposed by the Applicant suggests that steroid-forming and steroid-inactivating enzymes expressed in peripheral tissues permit to each cell to synthesize a small amount of androgens and/or estrogens in order to meet the local physiological needs, without affecting the other tissues of the organism. However, a systemic increase in serum sex steroids, further to administration to DHEA intravaginally, cannot be excluded (see PK section and increase in DHEA AUC after vaginal exposure).

In conclusion, a proof of the intracrinology concept (conversion of DHEA to active metabolites inside the vaginal cells and local action) is not provided in the dossier. No formal phase I or phase II studies were performed. Clarification of DHEA pharmacodynamics is based on analysis of DHEA effect on vaginal mucosa (increase in superficial cells and decrease in parabasal cells).

Treatment with prasterone is associated with systemic exposure as an increase in serum levels of DHEA metabolites is observed (see PK section above for more details). When compared to the extended literature data, the increase of DHEA & related metabolites levels observed during the clinical trials with a dose of 6.5 mg of prasterone was indeed statistically significant compared to the baseline (and to placebo) but this increase remains within normal post-menopausal steroids concentration ranges (as per usual observations and guidelines).

2.4.4. Discussion on clinical pharmacology

The pharmacodynamic effects of the vaginal DHEA observed in the phase II PK study ERC-213 consist of a change in vaginal maturation index (increase in percentage of superficial cells, decrease in

percentage of parabasal cells) and vaginal pH. However, the mechanism of action of DHEA administered intravaginally is not fully elucidated.

DHEA (prasterone) is an endogenous steroid secreted by the adrenal cortex having no intrinsic estrogenic or androgenic activity. It is an inactive precursor of testosterone and oestradiol. Serum DHEA and DHEA-S progressively decrease from the age of 30-50 years with a 60% decrease at menopause. The Applicant suggests that intravaginal DHEA provides the appropriate levels of androgens and/or oestrogens delivered exclusively in specific tissues by 'intracrine' mechanisms, while avoiding systemic effects of the active sex steroids. Based on the Applicant hypothesis, oestradiol would contribute to an increase in superficial cells, while androgens strengthen the other two layers of the vaginal wall. The "Intracrinology" concept proposed by the Applicant to clarify the mechanism of action is based on the hypothesis that steroid-forming and steroid-inactivating enzymes expressed in peripheral tissues permit to each cell to synthesize a small amount of androgens and/or estrogens in order to meet the local physiological needs, without affecting the other tissues of the organism. However, it is unclear to what extent DHEA is metabolised to estradiol and testosterone.

In addition, the "intracrinology" concept is supposed to exclude increase in sex steroid serum levels after administration of vaginal DHEA. However, from the PK study ERC–213, increases were observed in AUC (0 - 24 hours) of DHEA of 127%, 207% and 361% over control at 6.5 mg, 13 mg and 23.4 mg doses of DHEA, respectively. Similar increases of the AUC (0-24 hours) for all other steroids were observed on Day 1 and Day 7.

The applicant has compared the estrogen levels of Intrarosa pessaries to Vagifem 25 micrograms estradiol containing vaginal tablets and Premarin 0.625 mg conjugated estrogens containing vaginal cream. Due to the relatively high oestrogen exposure, the use of the Vagifem 25 micrograms dose has been mostly abandoned and the Premarin cream is not approved anymore. Therefore, the selected comparators are not supported. At day 120 of the procedure the company was asked to compare the systemic estradiol and oestrone levels of Intrarosa pessaries to literature data on Vagifem 10 micrograms, which is commonly used for vaginal atrophy. Results of this comparison were provided by the Applicant and data showed that the levels of estradiol, estrone & estrone sulphate after 12 weeks treatment with prasterone are comparable to treatment with 10 µg of vaginal estradiol (Vagifem).

The percent aromatization of DHEA to estradiol and oestrone positively correlates with body weight. At day 120 of the procedure, the Applicant was requested to discuss whether obesity and subsequently aromatization of the androgens could have an effect on serum levels of estradiol and oestrone metabolites. The Applicant has presented the change in co-primary endpoint from baseline in subjects based on their BMI. There is no difference in change of primary efficacy endpoint. The Applicant has also presented a subgroup analysis & forest plot assessing the effect of BMI on the co-primary endpoints and noticeable treatment effect differences between investigated subgroups were not found.

2.4.5. Conclusions on clinical pharmacology

The intracrinology concept proposed by the Applicant to explain the mechanism of action is based on the hypothesis that steroid-forming and steroid-inactivating enzymes expressed in peripheral tissues permit to each cell to synthesize a small amount of androgens and/or oestrogens in order to meet the local physiological needs, without affecting the other tissues of the organism. However, PK data showed a statistically significant increase in serum levels (compared to baseline) of DHEA and its metabolites, sustaining systemic exposure after intravaginal administration of DHEA but further comparison with independent reliable public sources/guidelines presenting normal postmenopausal ranges that are commonly used in clinical practice led to the conclusion that those increases were actually within normal post-menopausal ranges.

Clinical safety consequences on long term cannot be excluded.

2.5. Clinical efficacy

2.5.1. Dose response study

Dose – response study (ERC–210)

Design and objectives

This dose-response study was a placebo-controlled, double-blind randomized study conducted in Canada and US to evaluate the effectiveness of vaginal suppositories (pessaries) at four different DHEA concentrations on the symptoms and signs of vaginal atrophy.

The primary objective was to determine the dose-response of vaginal mucosa parameters to the local action of DHEA in postmenopausal women with vaginal atrophy. Secondary objective was to investigate the effect of DHEA on sexual dysfunction and libido.

The treatment groups were placebo and 3 DHEA doses: 0.25% (3.25 mg), 0.5% (6.5 mg) or 1.0% (13 mg).

The study included postmenopausal women from 40 to 75 years old with vulvovaginal atrophy (low vaginal maturation index and vaginal pH over 5). They should have self-identified at least one moderate to severe clinical symptom related to VVA (vaginal dryness, irritation or vaginal pain during intercourse).

No baseline information about frequency of intercourse in study participants was available.

Following randomization, two-hundred eighteen (218) evaluable participants (54-56 subjects per arm) were to be treated daily for 12 weeks.

The Applicant considered this study as a phase III study; however, given the limited population size and the study objective, it should be considered as a phase II dose-response (supportive) study.

Endpoints:

There were four co-primary endpoints consisting of three pharmacodynamics parameters (decrease in parabasal cells, increase in superficial cells, change in vaginal pH) and one clinical parameter (change in severity score of the vaginal clinical symptom self-assessed at 12 weeks via a questionnaire).

Change in parabasal and superficial cell percentage was assessed using a 100-cell count to classify cells as superficial (S), intermediate (I) and parabasal (P) squamous cell types. Vaginal pH was measured by applying a pH indicator strip directly to the lateral wall of the vagina with a forceps.

As secondary endpoints, sexual function as well as quality of life were evaluated at screening, day 1 and weeks 4, 8 and 12 by the MENQOL, ASF, PGWB and SC questionnaires.

The primary time point for analysis was the 12-week assessment. The change from baseline to each post-baseline assessment was calculated and used for statistical analysis for the comparison of each DHEA dose group to placebo; additionally, the significance of the change from baseline within each treatment group was also statistically assessed.

Statistics:

The dose-response analysis was carried out for each co-primary endpoints in the ITT population consisting in subjects presenting with a moderate to severe dyspareunia as the most bothersome

symptom. This is the population of interest for the targeted indication. No dose-response analysis was performed in the per-protocol population. The statistical analysis was mainly based upon an analysis of variance adjusted on endpoint's baseline, testing for the overall heterogeneity of the 4 treatment groups (including the placebo), followed by pairwise comparisons between each DHEA group and the placebo group. Adjustment for multiple testing was ensured by the Bonferroni type-1 error correction, taking into account the number of comparisons (x3) between DHEA doses and the placebo, but not the number of co-primary endpoints involved. It did not weakened though authors' conclusion, most of p-values associated DHEA vs placebo comparisons (3x4) in the primary analysis, being lower than 0.005.

Results

Study participants are white subjects, mean age of 58 years old, mean BMI of 26. No European subject was included. Proportion of subjects with prior HRT treatment is balanced in the groups. It should be confirmed that a proper wash-out procedure was respected for these subjects.

Efficacy data: At the time interval of 2 weeks of treatment, no change was observed in the placebo group in the *percentage of parabasal* cells. In all DHEA groups, the following decreases were observed:

28.6 ± 4.95 from 56.9 ± 5.54 to 28.3 ± 4.34 with the lowest dose of 3.25 mg

37.1 ± 4.55 (from 58.8 ± 5.37 to 21.6 ± 3.47) with the dose of 6.5 mg and

36.0 ± 4.91 (from 48.9 ± 5.46 to 12.9 ± 2.81) with the dose of 13 mg.

At the standard duration of 12 weeks of treatment, decreases of 39.8 ± 5.33 ($p<0.0001$), 45.9 ± 5.31 ($p<0.0001$) and 44.5 ± 5.19 ($p<0.0001$) were observed in the percentage of parabasal cells with the 3.25 mg, 6.5 mg and 13 mg DHEA doses, respectively, while no change was observed on this parameter in the placebo group.

Regarding the *superficial cells*, their percentage increased in a statistically significant manner at 2 weeks in the groups 6.5 mg and 13 mg, but not in the DHEA group of 3.25 mg.

At 12 weeks, increases of 4.3 ± 0.96 (from 0.7 ± 0.26 to 5.0 ± 0.90, $p<0.0001$), 6.8 ± 1.29 (from 0.5 ± 0.16 to 7.2 ± 1.29, $p<0.0001$) and 5.8 ± 1.13 (from 0.9 ± 0.24 to 6.7 ± 1.16 $p<0.0001$) were measured in the 3.25 mg, 6.5 mg and 13 mg of DHEA groups, respectively. No change was observed in the placebo group.

Of note, the change in parabasal and superficial cell percentage was assessed by one cytopathologist blinded to the treatment regimen. There was no double assessment of this count performed to confirm the outcome. Thus, the reproducibility of the assessment is questionable.

A statistically significant decrease was observed on the *vaginal pH* since 2 weeks ($p<0.001$) in the 3 DHEA groups. At week 12 vaginal pH decreased by 1.1 ± 0.12 ($p<0.0001$) pH unit from 6.5 ± 0.09 units, by 1.3 ± 0.13 ($p<0.0001$) from 6.6 ± 0.07 pH units, and by 1.4 ± 0.13 ($p<0.0001$) from 6.3 ± 0.09 pH units in the 0.25%, 0.50% and 1.0% DHEA-treated groups, respectively, while no change was observed in the placebo group.

Regarding the 4th co-primary endpoint, after 2 weeks of treatment, there was a significant change (decrease) observed in the severity score of most bothersome symptom regardless the type of symptom (vaginal dryness, dyspareunia, irritation/itching) in all the treatment groups including placebo (decrease of 0.4, 0.6, 0.6 and 0.8 points versus baseline with the placebo, 3.25 mg, 6.5 mg and 13 mg, respectively).

Table 4: Analysis of most bothersome symptom at week 12. Change from Baseline (ITT population) (study ERC–210)

Analysis of Most Bothersome Symptom - Change From Baseline (ITT Population)

Visit Stat	Group A 0% (N=54)	Group B 0.25% (N=54)	Group C 0.5% (N=56)	Group D 1.0% (N=54)	P-Value[2] A vs B	A vs C	A vs D
Week 12							
N	53	51	55	52	0.0023	<.0001	0.0001
Mean	-0.6	-1.2	-1.5	-1.3			
Std Dev	0.95	1.01	1.07	1.00			
Std Err	0.13	0.14	0.14	0.14			
Median	0.0	-1.0	-2.0	-1.0			
Minimum	-3.0	-3.0	-3.0	-3.0			
Maximum	1.0	1.0	0.0	1.0			
P=value[1]	<0.0001	<0.0001	<0.0001	<0.0001			

This decrease appears to be more time dependent than dose dependent. At week 12, the size effect on the clinical symptom (severity score) was larger in all DHEA treatment groups (decrease of 0.6, 1.2, 1.5 and 1.3 points with the placebo, 3.25, 6.5 and 13 mg, respectively).

Overall, this dose-finding study is supposed to identify the lowest effective dose having the most acceptable safety pattern. Results showed that at the standard 12-week time interval, for all co-primary endpoints, a clear difference in responses between the 3 DHEA arms was observed versus the placebo arm, but no clear trend to higher response with higher dose was observed when considering only the 3 DHEA doses.

There was no placebo effect at any time point on the PD parameters (parabasal and superficial cells, vaginal pH) while a clear placebo effect was observed at all the time points on the clinical symptom.

There was no major difference in the safety pattern between the treatment groups.

Based on the lack of marked difference between the doses 6.5 and 13 mg regarding the efficacy parameters, the dose of 13 mg was ruled out for the rest of the clinical studies.

2.5.2. Main studies

The phase 3 programme consisted of two 12 weeks pivotal studies with similar design and objectives (ERC-231 and ERC–238). In addition, there were 2 supportive studies: one efficacy/safety study using a reduced regimen (ERC–234) and one open-label long term safety study conducted for 52 weeks (ERC-230).

Pivotal study ERC–231: DHEA against Vaginal Atrophy (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal DHEA).

- **Study participants**

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

Inclusion criteria

Postmenopausal women (non hysterectomized or hysterectomized) must satisfy either;

- No menses for at least one year for non hysterectomized women, or
- Follicle stimulating hormone (FSH) levels > 40 IU/L (within 60 days prior to Day 1) in women with no menses >6 months but <12 months, or hysterectomized women who were premenopausal at the time of hysterectomy, or
- Six months (of screening visit) or more following bilateral oophorectomy.

Women who have self-identified at baseline pain at sexual activity as moderate to severe and as the most bothersome vaginal atrophy symptom:

Women should identify dyspareunia as the most bothersome to her at baseline. The change of this symptom will be followed and will serve to evaluate the effect of treatment as a co-primary objective.

Women between 40 and 75 years of age.

Women having ≤ 5% of superficial cells on vaginal smear at baseline.

Women having a vaginal pH above 5 at baseline.

Normal mammogram (American College of Radiology BI-RADS 1 or 2) within 9 months of study start (Day 1).

Normal breast examination.

A normal Pap smear (which includes inflammatory changes) within the last 12 months (of) for both non-hysterectomized and hysterectomized women following specimens collection as described in exclusion criteria.

Willing to participate in the study and sign an informed consent.

No former or present narcotic addiction or alcoholism.

For non-hysterectomized women, willing to have endometrial biopsy at baseline and end of study.

Exclusion criteria

Undiagnosed abnormal genital bleeding.

Previous diagnosis of cancer, except skin cancer (non melanoma).

Active or history of thromboembolic disease (thromboembolic event following an accident, a surgery or immobilization is acceptable).

Significant metabolic or endocrine disease.

Uncontrolled diabetes mellitus

Use of estrogen alone injectable drug therapy or progestin implant within 6 months prior to study entry Use of estrogen pellet or progestin injectable drug within six months prior to study entry.

Oral estrogen, progestin or DHEA exposure or intrauterine progestin therapy in the eight weeks prior to baseline assessments

Vaginal hormonal products (rings, creams, gels or tablets) or transdermal estrogen alone or estrogen/progestin products in the 8 weeks prior to baseline assessments

Subjects can washout as follows, but the questionnaire on vaginal atrophy as well as the evaluation of cell maturation and pH must be answered or evaluated after the required washout period:

- At least an eight-week washout period for prior oral estrogen, DHEA and/or progestin therapy.
- At least an eight-week washout period for prior transdermal hormone therapy.
- At least an eight-week washout period for locally delivered hormone replacement therapy for vaginal dryness (rings, creams, gels or tablets).
- Eight-weeks or longer for prior intrauterine progestin therapy.
- At least 6 months for prior estrogen pellet therapy or progestin injectable drug therapy.
- Six months or longer for prior progestin implants and estrogen alone injectable drug therapy.

Cardiac failure or manifest coronary heart disease.

Hypertension equal to or above 140/90 mm Hg.

Confirmed clinically significant depression (not controlled by standard therapy) or confirmed history of severe psychiatric disturbance.

The administration of any investigational drug within 30 days of screening visit.

Previous treatment with androgens or anabolic steroids within 3 months prior to screening visit.

Clinically significant abnormal serum biochemistry, urinalysis or hematology.

Baseline cervical cytology showing atypia of squamous cells of undetermined significance (ASCUS) or worse. Since ASCUS can be due to atrophy, a subject with ASCUS without history of abnormal Pap within the last two years and a negative HPV test can be enrolled.

Palpable fibroids, or Grade 2 uterine prolapse (when the cervix reaches labia minora) by gynecologic exam.

Coagulation disorders or on anticoagulant drug therapy.

Endometrial hyperplasia (simple or complex hyperplasia with or without atypia), cancer or endometrial histology showing proliferative, secretory or menstrual type characteristics at histologic evaluation of endometrial biopsy performed at screening

Subjects who suffer from vulvar lichen sclerosis.

- **Treatments**

This was a Phase III, placebo-controlled, double-blind and randomized study to confirm the efficacy of daily intravaginal administration of a 0.25% (3.25 mg) DHEA and 0.50% (6.5 mg) DHEA suppositories for 12 weeks compared to placebo in postmenopausal women. Women were randomized between 3 treatment arms in a 1:1:1 ratio. The study was divided into two phases, namely a screening period of 4 to 6 weeks followed by a treatment period of 12 weeks.

Women were instructed to apply one intravaginal ovule (suppository, pessary) containing placebo (0 %), 0.25% (3.25 mg) prasterone or 0.50% (6.5 mg) prasterone daily before bedtime (usually evening) during 12 weeks.

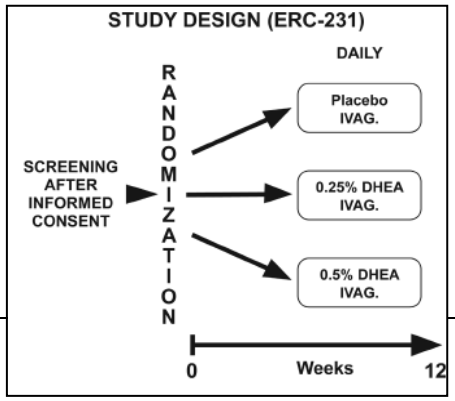

Figure 2: Study design ERC-231

Clinical study ERC-210 had shown highly significant effects at the three doses used, namely daily intravaginal administration of 0.25%, 0.50% and 1.0% prasterone with no clear difference between the 0.50% and 1.0% doses on dyspareunia. It was thus decided to compare the 0.50% and 0.25% prasterone doses with placebo, thus being well below the 1.0% (13 mg) prasterone dose shown to maintain serum estradiol and testosterone below the threshold of biological activity.

- **Objectives**

Primary objective was to confirm the efficacy of daily intravaginal administration of DHEA on the symptoms and signs of vaginal atrophy in postmenopausal women suffering from moderate to severe pain at sexual activity (dyspareunia) as their MBS of VVA at baseline.

Secondary objectives were 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 as well as to examine the tolerance to local administration of DHEA.

- **Outcomes / endpoints**

In agreement with the FDA guidelines, the four co-primary endpoints compared to placebo are:

1. A statistically significant decrease in percentage of parabasal cells.

2. A statistically significant increase in percentage of superficial cells.

3. A statistically significant decrease in vaginal pH.

4. A statistically significant improvement of moderate to severe dyspareunia self-identified by subjects as the most bothersome VVA symptom to her at screening and at baseline (Day 1).

Self-assessment of the other symptoms of vulvar and vaginal atrophy associated with menopause were evaluated by a questionnaire but were not co-primary objectives:

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

Secondary efficacy variables included: dryness and irritation as symptoms of vaginal atrophy, observations at vaginal examination related to local tolerance to DHEA (vaginal secretions, vaginal epithelial integrity, vaginal epithelial surface thickness, vaginal color, menopause-specific quality of life questionnaire (MENQOL), Female Sexual Function Index (FSFI), and safety variables, vital signs.

In order to confirm that all sex steroids remained within the normal postmenopausal range following intravaginal administration of prasterone, serum concentrations of DHEA and its main metabolites (namely dehydroepiandrosterone sulfate (DHEA-S), testosterone (Testo), dihydrotestosterone (DHT), androstenedione (4-dione), androst-5-ene-3β,17β-diol (5-diol), estrone (E1), 17β-estradiol (E2), estrone sulfate (E1-S), androsterone glucuronide (ADT-G) and androstane-3α, 17β-diol 3- and 17-glucuronide (3α-diol-3G and 3α-diol-17G)) were determined at baseline and at Week 12 (or at discontinuation visit, if applicable).

Table 5: Schedule of the procedure (study ERC-231)

Tests and procedures	Screening (4-6 weeks)	Days	Weeks		Discontinuation visit or early end of study
		1	6[a]	12[b]	
Informed Consent	X				
Medical History	X				
Check Inclusion Criteria	X	X			
Check Exclusion Criteria	X	X			
Physical Examination	X			X	X
Gynecological Examination	X	X[d]	X[d]	X[d]	X[d]
Vaginal Cell Maturation (central lab)	X	X	X	X	X
Vaginal pH	X	X	X	X	X
Papanicolaou Smear (central lab)	X[c]				
Mammography	X[e]				
Hematology (central lab)	X	X		X	X
Blood chemistry (central lab)	X[g]	X[g]		X[g]	X[g]
Urinalysis (central lab)	X	X		X	X
DHEA + Steroids (central lab)		X		X	X
Vital signs	X	X	X	X	X
Height and Body Weight	X			X[f]	X[f]
Vaginal Atrophy Symptoms Questionnaire	X	X	X	X	X
Tolerability +AEs		X	X	X	X
Concomitant Medications	X	X	X	X	X
Protocol Compliance Questionnaire	X	X	X	X	X
Verification of Diary Compliance			X	X	X
Female Sexual Function Index Questionnaire (FSFI)	X	X	X	X	X
Dispense/Collect Study Medication		X	X	X	X
Dispense/Collect Diary Card for Study Medication		X	X	X	X
Endometrial Biopsy (central lab)	X			X	

X = to be completed
a = ± 7 days
b = 12-week visits must be done on schedule or up to 7 days earlier
c = if not done during the last 12 months (prior Day 1)
d = to evaluate the aspect of the mucosa
e = if not done during the last 9 months (prior to Day 1)
f = body weight only
g = under 8 hours of fasting conditions

- **Statistical Methods and sample size**

Statistical analyses were performed at the two-sided significance level of 0.025 unless otherwise stated. The categories for summarization for the analysis of data from baseline through Week 12 consist of the placebo, the 0.25% DHEA and the 0.50% DHEA treatment groups. The co-primary objectives analyzed are the changes in % of parabasal and superficial cells, vaginal pH and severity score of pain at sexual activity (dyspareunia).

Sample size calculations for the 4 co-primary endpoints were based on the results of study ERC-210, where statistical significance was seen for all DHEA treatment groups (0.25%, 0.50% and 1.0% intravaginal ovule) compared to placebo for change from baseline to 12 weeks. The population of women used in this analysis consisted of those who satisfied the entry criterion of having moderate to

severe vaginal pain at intercourse as the MBS, at both the screening and baseline visits. The 0-3 scores (in increasing severity) were analyzed as continuous data.

Sample sizes per group would provide power of 95% for a t-test at a 2-sided significance level (alpha-level) of 0.025 for each co-primary endpoint, to detect similar differences in the current study between the DHEA 0.50% and DHEA 0.25% treatment groups and placebo. Therefore, the maximum sample size over all 4 co-primary endpoints of 60 would be required per arm; to be conservative, and to provide increased safety data, a sample size of 70 subjects was planned to be enrolled in each DHEA arm and 70 in the placebo arm (accounting for drop-outs).

Efficacy analyses were performed primarily on the Intent to Treat population (all subjects who have received at least one dose of study drug with a baseline (Day 1) evaluation meeting the entry criteria), with additional secondary analysis done on the Per-Protocol population. Safety analyses were performed on the Safety population (subjects who receive any amount of study treatment). Demographics and baseline characteristics were summarized and presented by treatment groups.

The primary time point for analysis and data presentation is the 12-week assessment, with additional secondary presentations of the data at 6 weeks. The change from baseline (Day 1) to post-baseline assessments as well as differences from placebo was used for analysis. Analyses of differences between DHEA 0.25%, DHEA 0.50% and Placebo were performed using an analysis of covariance with baseline as the covariate. All available safety data were used for analysis. For adverse events and laboratory data, standard methods of analysis were used.

- **Randomisation**

The randomization was done centrally. Treatment codes were generated using a permuted block design utilizing PROC PLAN of SAS. Blocks of 3 women were generated to ensure a balanced allocation to the three treatment arms by investigational site, with each block sequence randomly allocated. Treatment allocation follows the sequence configuration within each block with codes A, B and C denoting Placebo, 0.25% DHEA and 0.50% DHEA, respectively. This translates to a random allocation within each block with a 1:1:1 ratio for the 3 treatment arms.

- **Blinding**

One (1) set of sealed envelopes identified with the medication number and containing information about the treatment (Placebo or DHEA containing medication) for each particular subject was prepared. The DHEA concentration (0.25% or 0.50%) was not documented on the form F-UCPO0230 (EndoCeutics Code Breaking Notification Sheet). This set was kept at the trial site (during the entire trial period) and the randomization list was kept by the Sponsor. The trial site envelopes were returned to the Sponsor at study close-out using the form F-URC027.

Results of the study ERC-231:

- **Participants flow:**

464 subjects were screened and 255 were enrolled and randomized to this study. 222 subjects have completed the study. Among the 33 subjects who prematurely discontinued from study treatment, 15 subjects discontinued early as they did not meet the inclusion criteria (vaginal maturation index, vaginal pH and/or vulvovaginal atrophy symptom).

The ITT population (all subjects who have received at least one dose of study drug (based on diary) with a baseline (Day 1) evaluation meeting the entry criteria) is the primary analysis population of efficacy analyses and includes a total of 237 subjects with 77, 79 and 81 subjects in the placebo, 0.25% and 0.50% prasterone groups, respectively. The ITT population is composed of postmenopausal women aged 58.84 ± 0.38 years (mean ± standard error of the mean (SEM)) and includes 93% of

White Caucasian, 5% of Black or African American, 1% Asian and 1% other race while the ethnicity of 94% of this population is not Hispanic or Latino. In this population, 63% had an hysterectomy and 33% had undergone an ovariectomy prior to the study.

The Per Protocol (PP) Population consists of a subset of 204 subjects of the ITT population that completed the study through the time points of 12 weeks with no major protocol violations considered to compromise efficacy data. Subjects in this population have received at least 90% of the required number of applications of study treatment, based on the subject diary data. The PP population is a supportive population for efficacy data analysis.

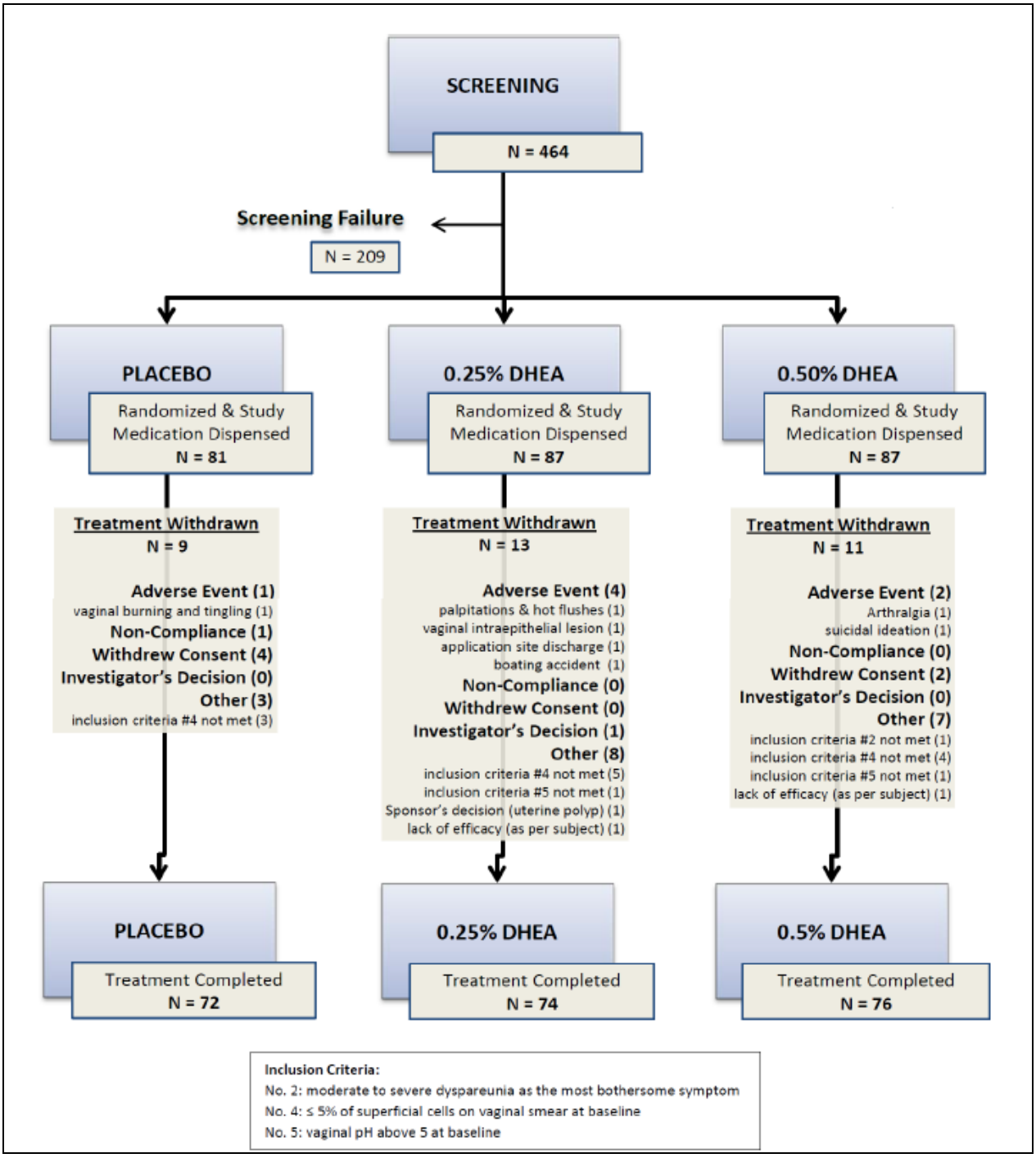

Figure 3: ERC-231 subjects disposition chart

- **Recruitment**

The first subject first visit was on 30 November 2010 and the last subject last visit was on 29 July 2011. The end of the study date was 30 January 2014.

- **Conduct of the study**

Protocol deviation

There were a similar number of subjects with protocol deviations in each treatment group (8 – 9 subjects per group). These deviations did not affect the integrity of the study data. The following table summarizes subjects with major protocol deviation.

Table 6: Number of subjects with major protocol deviation (ERC–231)

Protocol deviation Category	Placebo	0.25% DHEA	0.50% DHEA	Total
Number of subjects randomized	81	87	87	255
Number of subjects (%) with a major deviation:				
Inclusion criteria 2: subjects did not identify moderate to severe dyspareunia as MBS	0	2 (2.3)	1 (1.1)	3 (1.2)
Inclusion criteria 5: subjects did not have vaginal pH above 5.0	0	1 (1.1)	1 (1.1)	2 (0.8)
Exclusion criteria 2: subject with a history of cancer	1 (1.2)	0	0	1 (0.4)
Exclusion criteria 19: subject with an endometrial polyp at Screening	1 (1.2)	0	0	1 (0.4)
Exclusion criteria 20: subject with active *lichen sclerosis*	0	0	1 (1.1)	1 (0.4)
Subjects took prohibited intravaginal product or medication	3 (3.7)	2 (2.3)	1 (1.1)	6 (2.4)

Three subjects were excluded from the ITT and PP analyses because they were enrolled in the study despite the fact that they did not meet Inclusion Criteria No. 2 (VVA) while two subjects were excluded from the ITT and PP analyses because they were enrolled in the study despite the fact that they did not meet Inclusion Criteria No. 5 (vaginal pH>5.0).

The following deviations to inclusion/exclusion criteria and excluded concomitant treatments were not considered significant enough to warrant exclusion:

Exclusion criterion No. 2: One subject (14-001) enrolled in the study had a prior history of melanoma. The site was instructed to terminate this subject but the subject could not be reached before she completed the study. The subject was included in the ITT and PP analyses.

Exclusion criterion No.19: Contrary to Exclusion Criteria No. 19, subject 15-014 (placebo) was randomized despite the presence of an endometrial polyp at Screening. The subject was withdrawn from the study and included in the ITT analysis.

Exclusion criterion No.20: Vulvar *lichen sclerosis* was added as an exclusion criterion in the 07 March 2011 version of the protocol. Subject 14-012 (0.50% DHEA) was enrolled in the study with active *lichen sclerosis* five days after the effective date of the protocol amendment. This may have brought a bias to the self-assessment of symptoms given the similarity of some symptoms like itching and irritation. It had no impact on subject safety. The subject was included in all statistical analysis (PP, ITT and Safety).

Prohibited concomitant treatments

Six subjects took an intravaginal product (antifungal medication or equivalent) during the study: subject 04-004 (placebo) took clotrimazole on Days 66 and 67, subject 05-025 (placebo) took miconazole 5 days prior to Day 1, subject 09-002 (0.50% DHEA) took miconazole cream at Week 12, subject 18-011 (placebo) took clotrimazole on Days 79 to 81 and subject 01-011 (0.25% DHEA) took petroleum jelly on Day 46. These deviations were not considered significant. Subject 12-006 (0.25% DHEA) was withdrawn from the study and included only in the safety analysis. Subjects 01-011, 09-002 and 18-011 took the intravaginal products 48 hrs of a scheduled study visit so the MI, vaginal pH and vaginal observations data collected at those visits were considered invalid and they were replaced with the corresponding data from the previous visit in accordance with the SAP.

Premature emergency unblindings at the study site:

There were no premature unblindings in this study.

- **Baseline data**

Demographic characteristics:

The demographics and baseline characteristics of the subjects enrolled in the different treatment groups were similar. The study population consisted mainly of White Caucasian non-Hispanic women. The proportion of White Caucasian women ranged from 86% (Placebo) to 95% (0.50% DHEA) per group. Black or African American women were the second most represented race with 3% (0.50% DHEA) to 11% (Placebo) of the women in each treatment group. Non-Hispanic women made up 90% (0.50% DHEA) to 99% (Placebo) of the women in each treatment group. Overall, the average age of the women enrolled in the study was 58.55 years with a median age of 59 and a range of 40 to 75 years. Similar age distributions were observed in all three treatment groups. On average, the women measured 160.75 cm and weighed 67.49 kg with a BMI of 26.08.

The women assigned to the different treatment groups had similar reproductive histories. An average of 14.47 years (13.88 [Placebo] to 15.47 [0.25% DHEA]) had elapsed between their last menses and their participation in this study. Menstrual cycles ceased naturally in approximately half the population (48% [Placebo] to 50% [0.25% DHEA]). The average age at which the women had their last menstrual period ranged from 47.42 [Placebo] to 49.05 [0.25% DHEA] years in women who had a natural menopause and from 38.68 [0.50% DHEA] to 42.69 [Placebo] in women who had a surgical menopause.

- **Numbers analysed**

Overall, data corresponding to 237 subjects was analysed in the ITT set. Of them, 77 correspond to placebo group and 160 to DHEA groups.

Table 7: Number of subjects included in the different analysis sets in each treatment group and overall

Analysis Set	Placebo	0.25% DHEA	0.50% DHEA	Overall
Intent-to-treat (ITT)	77	79	81	237
Corrected ITT	75	77	80	232
Per-Protocol (PP)	65	69	70	204
Safety	80	86	87	253
Corrected Safety	78	84	85	247

- **Outcomes and estimations**

Vaginal Atrophy:

Effect on parabasal cells: There was no effect of placebo on the percentage of parabasal cells in women from the ITT population treated with daily intravaginal placebo at week 12 of the treatment. Regarding DHEA groups;

➔ The 3.25 mg prasterone decreased the % of parabasal cells from 65.72 ± 4.56% at baseline to 31.76 ± 3.78% at 6 weeks ($p<0.0001$ over placebo) and 28.43±3.62% at 12 weeks ($p<0.0001$ vs placebo).

➔ The 6.5 mg decreased the % of parabasal cells from 65.05 ± 4.63% at baseline to 26.31 ± 3.38% ($p<0.0001$ versus placebo) at 6 weeks and 17.65 ± 2.87% at 12 weeks ($p<0.0001$ vs placebo).

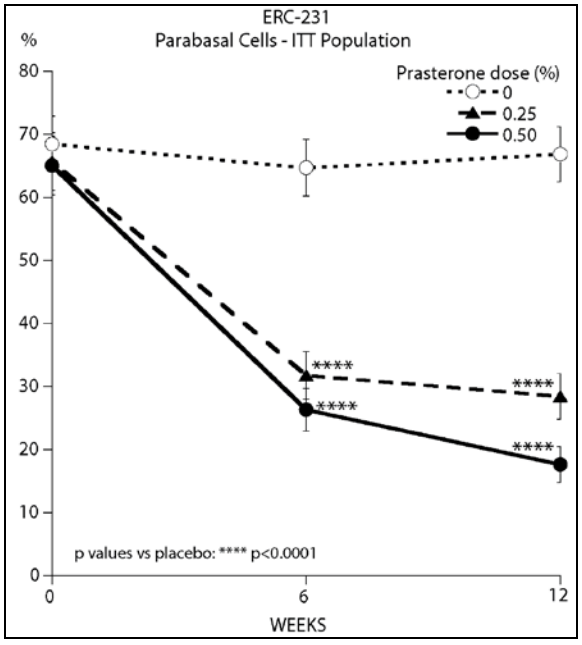

Figure 4: Effect of prasterone on % of parabasal cells at 6 and 12 weeks (ITT, ERC–231)

Five women of the ITT population had a pattern of sex steroids typical of women having taken estrogens (a situation most likely associated with a bias in the VVA data). An additional analysis of co-primary endpoints and VVA symptoms was performed where these 5 subjects were excluded from the

ITT population analysis (corrected ITT population, cITT). Results showed no significant change versus initial ITT population.

Effect on superficial cells: There was a slight increase in the % of superficial cells in the ITT placebo group of 77 women from 0.73 ± 0.15% at baseline to 1.13 ± 0.24% (p=0.028 versus baseline) and 1.64 ± 0.33% (p=0.004 versus baseline) at 6 and 12 weeks, respectively.

Regarding DHEA groups;

- ➔ In the group of 79 women ITT population who received daily 3.25 mg prasterone, the % of superficial cells increased from 0.68 ± 0.13% at baseline to 4.33 ± 0.50 (p<0.0001 versus placebo) and 5.43 ± 0.57% (p<0.0001 versus placebo) at 6 and 12 weeks, respectively.
- ➔ In the ITT group of 81 women who received a daily dose of 6.5 mg prasterone, the % of superficial cells increased from 0.68 ± 0.12% at baseline to 5.11 ± 0.57% (p<0.0001 versus placebo) and 6.30 ± 0.59% (p<0.0001 versus placebo) at 6 and 12 weeks, respectively.

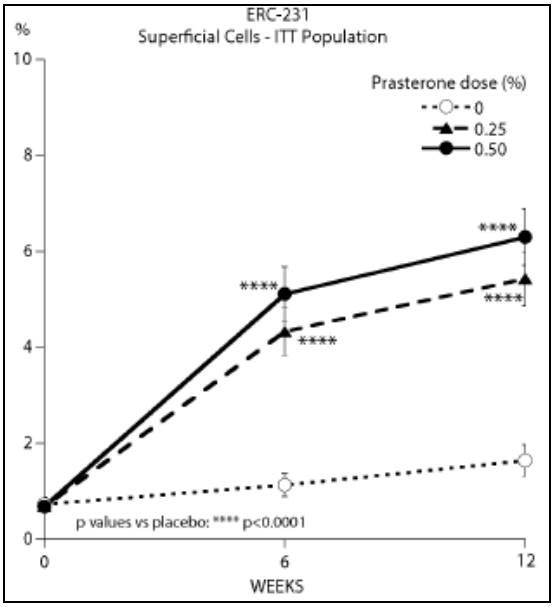

Figure 5: Effect of prasterone on superficial cells at 6 and 12 weeks (ITT, ERC– 231)

Table 8: Change from baseline to end-of-treatment for percentage of superficial and parabasal cells (ERC-231)

	0.25% DHEA	0.50% DHEA	Placebo
Superficial Cells			
N	79	81	77
Baseline	0.68	0.68	0.73
Week 12	5.43	6.30	1.64
Mean Change	4.75	5.62	0.91
SD	5.15	5.49	2.69
Difference from Placebo[a]	3.84	4.71	
P-value[b]	<0.0001	<0.0001	
Parabasal Cells			
N	79	81	77
Baseline	65.72	65.05	68.48
Week 12	28.43	17.65	66.86
Mean Change	-37.29	-47.40	-1.62
SD	37.00	42.50	28.22
Difference from Placebo[a]	-35.67	-45.77	
P-value[b]	<0.0001	<0.0001	

Abbreviations: DHEA=dehydroepiandrosterone; N=number of subjects; SD=standard deviation
[a] Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean).
[b] ANCOVA test with treatment group as the main factor and baseline value as the covariate.

Similarly, in the group of 77 women of the corrected ITT population who received daily 3.25 mg, the % of superficial cells increased from 0.68 ± 0.14% at baseline to 4.42 ± 0.51 ($p<0.0001$ versus placebo) and 5.51 ± 0.58% ($p<0.0001$ versus placebo) at 6 and 12 weeks, respectively. On the other hand, for the cITT group of 80 women who received a daily intravaginal dose of 6.5 mg (0.50%) prasterone, the % of superficial cells increased from 0.69 ± 0.12% at baseline to 5.15 ± 0.58% ($p<0.0001$ versus placebo) and 6.26 ± 0.60% ($p<0.0001$ versus placebo) at 6 and 12 weeks, respectively.

Effect on vaginal pH: A slight decrease was observed in the placebo group.

Regarding the DHEA groups;

- ➔ with 3.25 mg prasterone, the pH decreased from 6.48 ± 0.07 pH units at baseline to 5.81 ± 0.10 ($p=0.0008$ vs placebo) and 5.70 ± 0.11 ($p<0.0001$ versus placebo) at 6 and 12 weeks, respectively.
- ➔ with 6.5 mg prasterone, the pH decreased from 6.47 ± 0.07 at baseline to 5.52 ± 0.10 ($p<0.0001$ vs placebo) at 6 weeks and then to 5.43 ± 0.10 ($p<0.0001$ versus placebo) at 12 weeks.

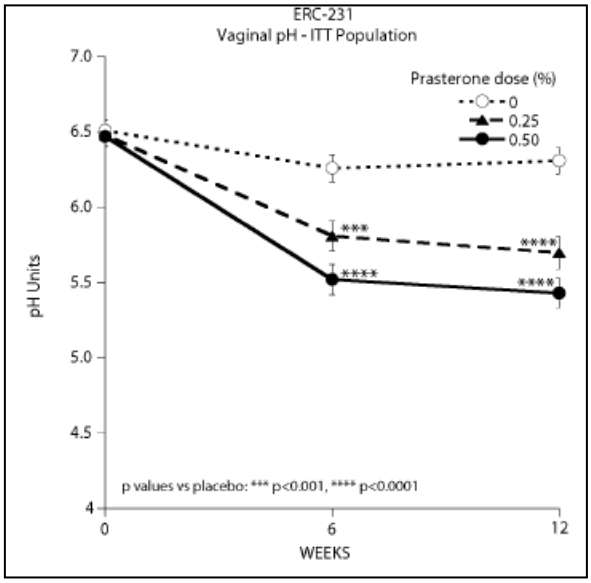

Figure 6: Effect of prasterone on vaginal pH (ITT, study ERC–231)

When the 5 women who had a pattern of sex steroids typical of women having taken estrogens were excluded from the analysis (cITT), the pH decreased, in women treated with the dose of 3.25 mg, from 6.48 ± 0.07 pH at baseline to 5.81 ± 0.10 (p=0.0001 versus placebo) and 5.70 ± 0.11 (p<0.0001 versus placebo) at 6 and 12 weeks, respectively. In the group of women treated daily with 6.5 mg, the pH decreased from 6.46 ± 0.07 at baseline to 5.52 ± 0.10 (p<0.0001 versus placebo) at 6 weeks and then to 5.45 ± 0.10 (p<0.0001 versus placebo) at 12 weeks.

Effect on dyspareunia: Women were enrolled on the basis of having pain at sexual activity considered as most bothersome symptom. The self-reported symptom score takes the following values: none, mild, moderate or severe to be analyzed using values of 0, 1, 2 or 3, respectively. All subjects must have this symptom at screening and Day 1 graded as 2 or 3.

In the placebo group, there was a decrease in the severity score of dyspareunia from 2.58 at baseline to 1.87 and 1.71 at 6 and 12 weeks, respectively (p<0.0001 versus baseline at both time intervals).

- ➔ At the 3.25 mg dose, the severity score of dyspareunia decreased from 2.56 at baseline to 1.86 (NS versus placebo) and 1.54 (NS versus placebo) at 6 and 12 weeks, respectively.
- ➔ At the 6.5 mg dose, the severity score of dyspareunia decreased from 2.63 ± 0.05 at baseline to 1.63 ± 0.13 (p=0.066 versus placebo) and 1.36 ± 0.12 (p=0.013 versus placebo) at 6 and 12 weeks, respectively. An improvement of 0.40 severity score unit was thus observed or a 46% improvement over placebo (p=0.013 versus placebo).

When the 5 women who had a pattern of sex steroids typical of women having taken estrogens were excluded (cITT), the severity score of dyspareunia in women (n=80) treated with 6.5 mg decreased from 2.63 ± 0.05 units at baseline to 1.64 ± 0.13 (p=0.0389 versus placebo) at 6 weeks and to 1.36 ± 0.12 (p=0.0069 versus placebo) at 12 weeks, thus showing lower p values (than in the ITT population analysis) at both 6 and 12 weeks due to the smaller improvement in the placebo group in the cITT analysis. In fact, by excluding 2 women showing a signature of estrogen intake from the ITT placebo group, the severity score decreased from 2.59 ± 0.06 units at baseline to 1.92 ± 0.12 and 1.76 ± 0.11 at 6 and 12 weeks, respectively (p<0.0001 versus baseline) at both time intervals. Thus, the severity score improved by 0.44 unit following treatment with 0.50% DHEA for a 53% increase over placebo (p=0.007 over placebo).

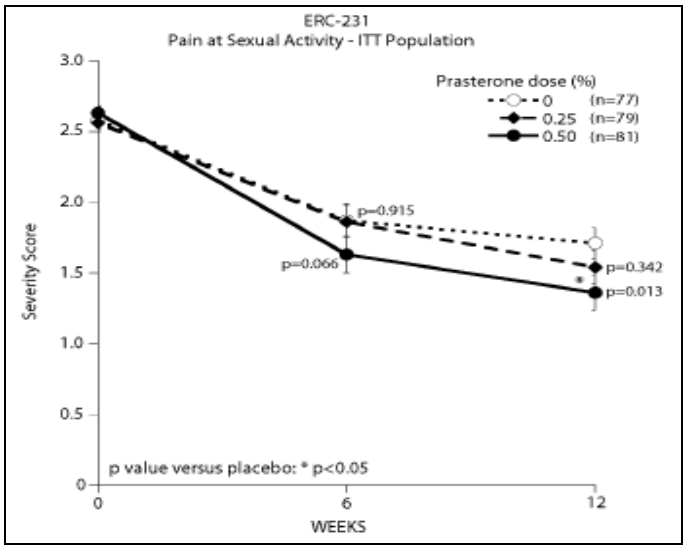

Figure 7: Effect of prasterone on pain at sexual activity (ITT, study ERC-231)

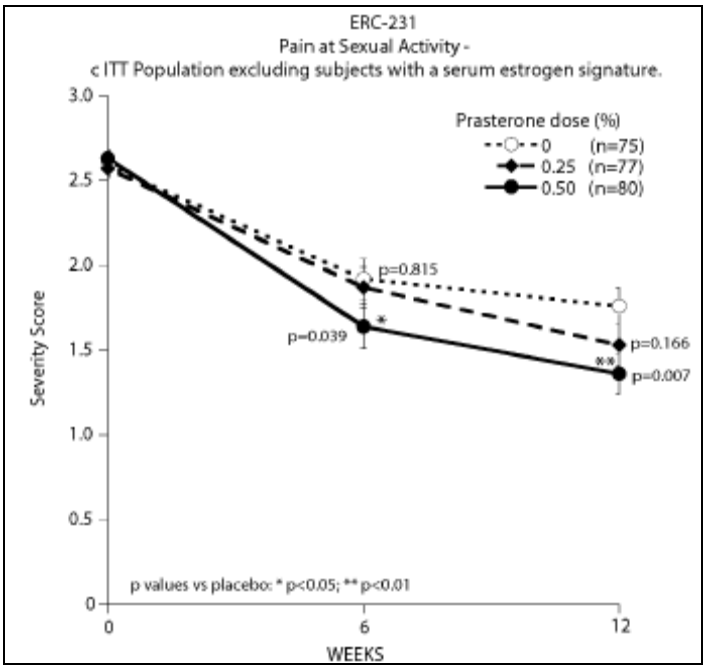

Figure 8: Effect of prasterone on pain at sexual activity on corrected ITT population (cITT, study ERC-231)

- **Ancillary analyses**

Self-assessment of the other symptoms of vulvar and vaginal atrophy associated with menopause were evaluated by a severity score questionnaire but were not co-primary objectives:

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

In the ITT population of 237 women who had pain at sexual activity as moderate to severe and VVA, 192 women also had MS vaginal dryness at baseline.

The following figure shows that regarding **vaginal dryness**, the decrease in DHEA groups became statistically significant (versus placebo) at week 12 of the study.

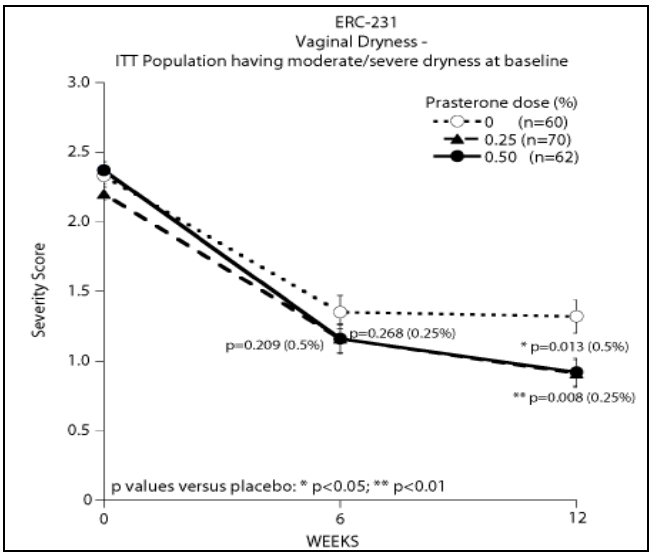

Figure 9: Effect of prasterone on vaginal dryness (ERC-231)

Regarding **irritation / itching**, the number of women in the ITT population who had moderate to severe irritation/itching at baseline was small (23 in the placebo group and 25 at each dose of prasterone). At 12 weeks, in the ITT population the differences from placebo have shown p values of 0.091 and 0.198, respectively, for the 0.25% and 0.50% doses at prasterone.

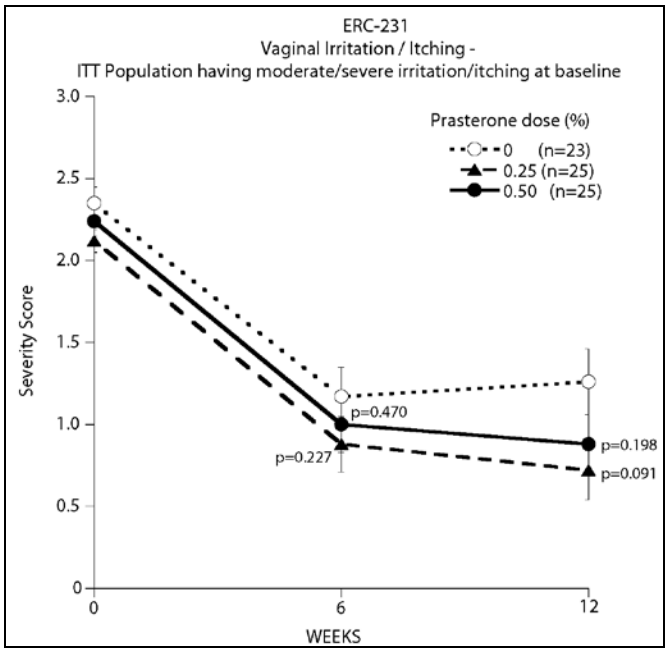

Figure 10: Effect of prasterone on irritation / itching

At each visit (baseline, 6 weeks and 12 weeks), the physician performed a vaginal examination with speculum to evaluate the severity of the four main signs of VVA (severity evaluated as none, mild,

moderate or severe and using the values 1, 2, 3 or 4 respectively, to calculate responses). These signs are vaginal secretions, vaginal epithelial integrity, vaginal epithelial surface thickness and vaginal color.

For **vaginal secretions**, the difference from placebo was already significant for both doses of prasterone at 6 weeks. At 12 weeks, in the placebo group, the standard time interval, the score decreased from 2.78 ± 0.08 at baseline to 2.36 ± 0.08 ($p<0.0001$ versus baseline) at 12 weeks (15.1% difference). For the 0.25% dose, the score decreased from 2.81 ± 0.07 at baseline to 2.10 ± 0.09 at Week 12 ($p=0.016$ versus placebo, 25.3% difference) while in the group receiving 0.50% prasterone, the severity score decreased from 2.83 ± 0.08 at baseline to 1.95 ± 0.08 ($p=0.0002$ versus placebo, 31% decrease) at 12 weeks

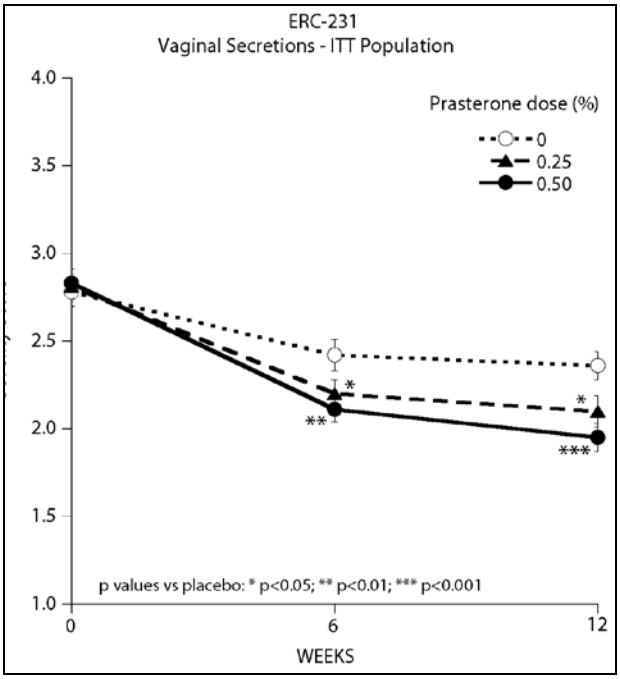

Figure 11: Effect of prasterone on vaginal secretions (ERC-231)

For vaginal epithelial integrity, at Week 12 for the placebo group (n=77), the severity score improved from 2.58 ± 0.09 at baseline to 2.13 ± 0.09 at 12 weeks ($p<0.0001$ versus baseline, 17.4%). In the group of women receiving daily 0.25% prasterone intravaginally, the severity score decreased from 2.57 ± 0.10 at baseline to 1.92 ± 0.09 at 12 weeks ($p=0.076$ versus placebo, 25.3% change). However, in the group of women treated with the daily 0.50% dose, the severity score decreased from 2.57 ± 0.10 at baseline to 1.69 ± 0.09 at 12 weeks ($p=0.0001$ versus placebo, 34.2% change).

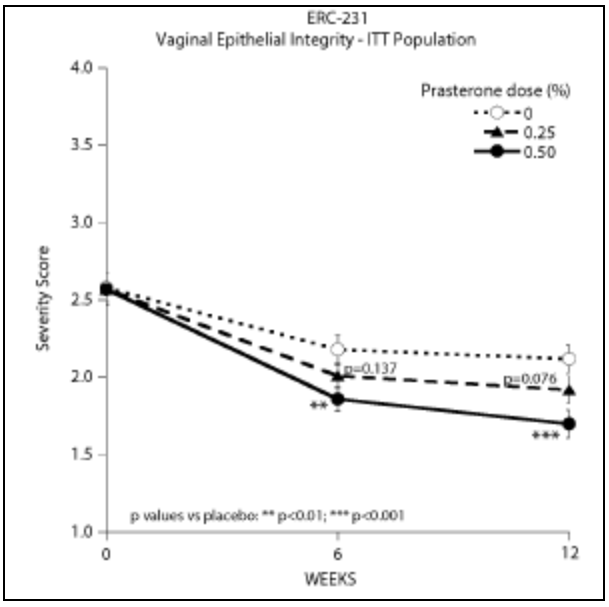

Figure 12: Effect of prasterone on vaginal epithelial integrity (ERC–231)

As a complementary estimate by Investigators blinded to the treatment received, the **epithelium surface thickness** has shown an improvement of the severity score from 2.91 ± 0.07 at baseline to 2.57 ± 0.08 at 12 weeks (p<0.0001 versus baseline, -11.7%) in the placebo group. In the group of women who received 0.25% prasterone (n=79), the severity score of vaginal epithelial integrity decreased from 2.90 ± 0.08 at baseline to 2.32 ± 0.09 at Week 12 (p=0.0153 versus placebo, -20.0%) while the score decreased from 2.89 ± 0.07 at baseline to 2.14 ± 0.08 at Week 12 in the group of women who received 0.50% prasterone (p<0.0001 versus placebo, -25.9%).

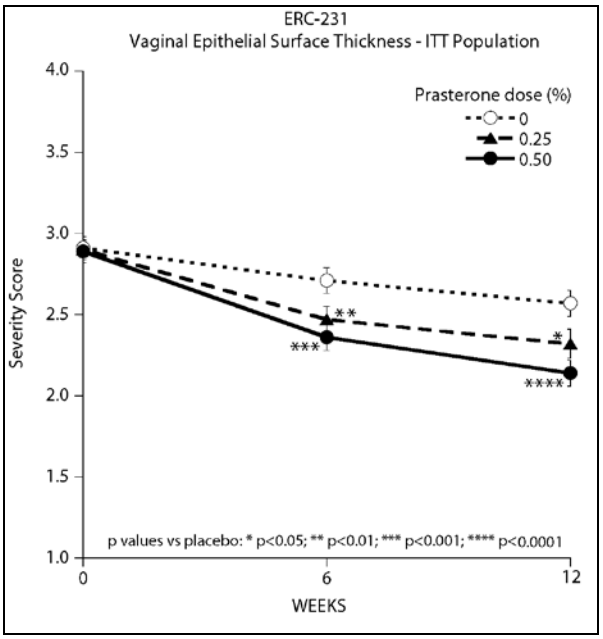

Figure 13: effect of prasterone on vaginal epithelium surface thickness (ERC–231)

Concerning **vaginal color** in the placebo group, the score decreased from 2.82 ± 0.08 at baseline to 2.56 ± 0.08 at 12 weeks (p=0.0003 versus baseline, 9.2% decrease). For the 79 women who received 0.25% prasterone, the score related to vaginal color decreased from 2.94 ± 0.08 at baseline to 2.27 ±

0.10 at 12 weeks for a 22.8% decrease (p=0.0017 versus placebo). On the other hand, a 30.3% decrease in the severity score (p<0.0001 versus placebo) was observed in the group of women receiving a daily dose of 0.50% prasterone with values decreasing from 2.94 ± 0.08 to 2.05 ± 0.09.

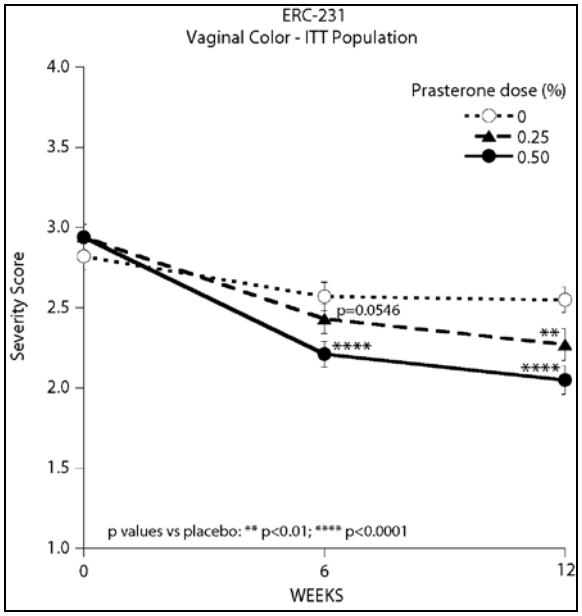

Figure 14: Effect of prasterone on vaginal color (ERC–231)

Study ERC–238: Intravaginal prasterone (DHEA) against vulvovaginal atrophy associated with menopause: a placebo controlled double blind and randomized phase III study.

Methods:

- **Study participants**

The subject population was postmenopausal women (non-hysterectomized or hysterectomized), between 40 and 80 years of age, having ≤5% of superficial cells on vaginal smear, a vaginal pH above 5 and having self-identified moderate to severe vaginal pain associated with sexual activity (dyspareunia) as their MBS of VVA at baseline (Day 1).

Inclusion criteria

1. Postmenopausal women (non hysterectomized or hysterectomized) must satisfy either a or b or c:

   a) No menses for at least one year for non hysterectomized women, or

   b) Follicle stimulating hormone (FSH) levels >40 IU/L or>postmenopausal value of the laboratory where the FSH assay is performed in women with no menses >6 months but <12 months, or in hysterectomized women who were premenopausal at the time of hysterectomy, or

   c) Six months or more of Day 1 visit following bilateral oophorectomy with or without hysterectomy.

2. Women who have self-identified at screening and baseline (Day 1) pain at sexual activity as moderate to severe and as the most bothersome VVA symptom (based on the Vaginal Atrophy Symptoms Questionnaire (VASQ)).

3. Women between 40 and 80 years of age.

4. Women having ≤ 5% of superficial cells on vaginal smear at screening and baseline (Day 1).

5. Women having a vaginal pH above 5 at screening and baseline (Day 1).

6. Women who currently have intercourse or other sexual activity (masturbation, etc.) at least once a month (with or without a partner), or who had intercourse or other sexual activity at least once a month in the past but later decreased sexual activity due to excessive pain or vaginal dryness.

7. Normal mammogram (American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS)) category 1 or 2 within 9 months of study start (Day 1).

8. Normal breast examination.

9. A normal Pap smear (which includes inflammatory changes) within the last 12 months (of Day 1) for both non-hysterectomized and hysterectomized women following specimens collection as described in the protocol (see exclusion criteria No. 14).

10. Willing to participate in the study and sign an informed consent.

11. No former or present narcotic addiction or alcoholism.

12. For non-hysterectomized women, willing to have endometrial biopsy during the screening period to exclude endometrial pathology.

Exclusion criteria

1. Previous enrollment in EndoCeutics studies performed with intravaginal DHEA (ERC-210, ERC-213, ERC-230, ERC-231 or ERC-234).

2. Previous diagnosis of cancer, except skin cancer (non melanoma).

3. Active or history of thromboembolic disease (thromboembolic event following an accident, a surgery or immobilization is not an exclusion criterion).

4. Clinically significant metabolic or endocrine disease (including diabetes mellitus) not controlled by medication.

5. Use of estrogen alone injectable drug therapy or progestin implant within 6 months prior to study entry (screening visit).

6. Use of estrogen pellet or progestin injectable drug within six months prior to study entry (screening visit).

7. Oral estrogen, progestin or DHEA exposure or intrauterine progestin therapy in the eight weeks prior to baseline assessments (screening visit).

8. Vaginal hormonal products (rings, creams, gels or tablets) or transdermal estrogen alone or estrogen/progestin products in the 8 weeks prior to baseline assessments (screening visit).

9. Previous treatment with androgens or anabolic steroids within 6 months prior to screening visit.

10. Natural oral estrogenic products in the 4 weeks prior to baseline assessments (screening visit) whether intended or not for the relief of symptoms of VVA and/or hot flushes.

Regarding exclusion criteria no. 5 to 10, subjects can washout as indicated below, but the questionnaire on VVA as well as the evaluation of cell maturation and pH must be answered or evaluated after the required washout period:

- At least a eight-week washout period for prior oral estrogen, DHEA and/or progestin therapy.
- At least a eight-week washout period for prior transdermal hormone therapy.

- At least a eight-week washout period for locally delivered hormone replacement therapy for vaginal dryness (rings, creams, gels or tablets).
- Eight weeks or longer for prior intrauterine progestin therapy.
- At least 6 months for prior estrogen pellet therapy or progestin injectable drug therapy.
- Six months or longer for prior progestin implants and estrogen alone injectable drug therapy.
- Six months or longer for previous treatment with androgens or anabolic steroids.
- Four weeks or longer for prior natural oral “estrogenic” products.

11. Confirmed clinically significant depression (not controlled by standard therapy) or confirmed history of severe psychiatric disturbance.

12. The administration of any investigational drug within 30 days of screening visit.

13. Clinically significant abnormal serum biochemistry, urinalysis or hematology.

14. Baseline cervical cytology showing atypia of squamous cells of undetermined significance (ASC-US) or worse. Since ASC-US can be due to atrophy, a subject with ASC-US without history of abnormal Pap within the last two years and a negative Human papillomavirus (HPV) test could be enrolled.

15. Palpable fibroids, or Grade 2 uterine prolapse (when the cervix reaches labia minora) by gynecologic exam.

16. Endometrial hyperplasia (simple or complex hyperplasia with or without atypia), cancer or endometrial histology showing proliferative, secretory or menstrual type characteristics at histologic evaluation of endometrial biopsy performed at screening.

17. Subjects who suffer from vulvar lichen sclerosis.

18. Endometrial polyps.

19. Subjects who had endometrial ablation.

- **Treatments**

Clinical phase III study ERC-231 has compared the effect of 0.25% (3.25 mg) and 0.50% (6.5 mg) prasterone doses with placebo. The co-primary endpoints for analysis in that study were the change from baseline to Week 12 in pain at sexual activity (dyspareunia) as MBS at baseline, percentage of parabasal and superficial cells, and vaginal pH. In ERC-231, with the 3.25 mg (0.25%) dose of prasterone, statistical significance was not reached over placebo for one co-primary endpoint, namely dyspareunia, thus indicating that the appropriate prasterone dose was 6.5 mg (0.50%).

The confirmatory efficacy study ERC-238 was then performed with the selected 6.5 mg (0.50%) prasterone dose.

Women were randomized in a 2:1 ratio between the 0.50% DHEA and placebo DHEA groups as follows:

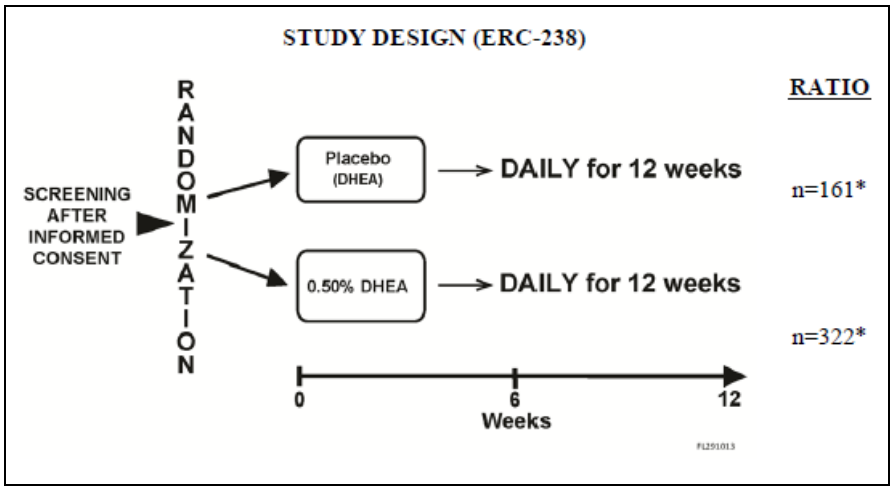

Figure 15: Study design ERC-238

- **Objectives**

Primary objectives

To confirm the efficacy of intravaginal DHEA on moderate to severe (MS) pain at sexual activity (dyspareunia) as most bothersome symptom (MBS) of VVA due to menopause and to collect further data on subjects exposed to intravaginal DHEA at the dose or dose range believed to be efficacious in order to meet the ICH E1 guideline requirement so that the "total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500."

Secondary objectives

- Examine the tolerance to intravaginal administration of DHEA;
- Investigate a possible influence of treatment on the male partner;
- Evaluate the efficacy on the other two symptoms of VVA (dryness and irritation/itching);
- Evaluate the efficacy on arousal/lubrication, subjective arousal, desire, satisfaction and orgasm by the Female Sexual Function Index (FSFI) questionnaire according to the indicated priority design;
- Obtain information on the usability of the applicator used to insert the medication.

- **Outcomes / endpoints:**

The four co-primary endpoints compared to placebo are:

- A statistically significant decrease in percentage of parabasal cells;
- A statistically significant increase in percentage of superficial cells;
- A statistically significant decrease in vaginal pH; and
- A statistically significant improvement of moderate to severe dyspareunia self-identified by subjects as the most bothersome VVA symptom to her at screening and at baseline (Day 1).

Secondary efficacy endpoints:

Self-assessment of the other symptoms of VVA associated with menopause were evaluated by a questionnaire but were not co-primary objectives:

- Vaginal dryness (none, mild, moderate or severe); and

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

Other secondary efficacy variables included: observations at vaginal examinations, local tolerance, Female Sexual Function Index (FSFI).

Table 9: Schedule of the procedures (study ERC–238).

Tests and procedures	Screening (up to 8 weeks*)	Day 1	Weeks		Discontinuation visit or early end of study	30-Day[b] follow-up phone call
			6[a]	12[a]		
Informed Consent	X					
Medical History	X					
Check Inclusion Criteria	X	X				
Check Exclusion Criteria	X	X				
Physical Examination	X			X	X	
Gynecological Examination	X	X[c]	X[c]	X[c]	X[c]	
Vaginal Cell Maturation (central lab)	X	X	X	X	X	
Vaginal pH	X	X	X	X	X	
Papanicolaou Smear (central lab)	X[d]					
Mammography	X[e]					
Endometrial Biopsy (central lab)	X[f]					
Hematology (central lab)	X	X		X	X	
Blood chemistry (central lab)	X[g]	X[g]		X[g]	X[g]	
Urinalysis (central lab)	X	X		X	X	
DHEA + Steroids (central lab)		X		X	X	
Vital signs	X	X	X	X	X	
Height and Body Weight	X			X[h]	X[h]	
Vaginal Atrophy Symptoms Questionnaire	X	X	X	X	X	
Female Sexual Function Index Questionnaire (FSFI)	X	X	X	X	X[i]	
Questionnaire on Usability of the Applicator				X	X	
Tolerability +AEs	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	
Protocol Compliance Questionnaire	X	X	X	X	X	
Verification of Diary Compliance			X	X	X	
Dispense/Collect Study Medication		X	X	X	X	
Dispense/Collect Diary Card for Study Medication		X	X	X	X	
MALE PARTNER (if he agrees)						
Informed Consent of Male Partner + Phone Call[j]	X					
Questionnaire of Male Partner + Possibility of Phone Call at Week 12[k]	X			X[k]		

*: following notification to protocol (see Section 7)
X = to be completed
a = ± 7 days
b = up to 7 days later
c = to evaluate the aspect of the mucosa
d = if not done during the last 12 months (prior to Day 1)
e = if not done during the last 9 months (prior to Day 1)
f = after verification of inclusion/exclusion criteria (especially MBS symptom and pH) to avoid unnecessary invasive procedure
g = under 8 hours of fasting condition
h = body weight only
i = if at least 6 weeks of treatment
j = to give information on informed consent form and male partner questionnaire
k = a phone call to get additional information will be made to the male partner if "worse" or "much worse" is answered at question 6 of the questionnaire at Week 12 evaluation

- **Statistical methods and sample size**

Sample size calculation was based on the results from study ERC-231 using values of DHEA 0.50% versus placebo.

The sample size which would be the maximum required for all 4 efficacy parameters for the DHEA to placebo comparison at a 2:1 ratio of DHEA:placebo would be 274 and 137, respectively, based on the endpoint of dyspareunia in the DHEA and placebo groups. An allowance of 15% for not completing the

study was added, resulting in n=322:161 for the DHEA:placebo groups. The sample size of 322 DHEA-treated subjects also permitted to achieve the total number of 1500 subjects exposed to intravaginal DHEA across all studies, as requested by the ICH E1 guideline. The power for pH, superficial cells and parabasal cells would be > 99.99%, therefore the overall power for all 4 endpoints (calculated as the product of the power for each of the 4 endpoints) would be > 97%.

The sample size required to detect these same differences between DHEA and placebo in the current study ERC-238, at a one-sided alpha-level of 0.025 and power of 97.7%, are provided in the table below.

Table 10: Power calculation based on ERC–231 (change from baseline to week 12).

Parameter	Statistic	Placebo	0.50% DHEA
Parabasal cells	N	77	81
	Mean	-1.62	-47.40
	SD	28.22	42.50
	Difference from placebo		-45.77
	Power	>99.99%	
pH	N	77	81
	Mean	-0.21	-1.04
	SD	0.69	1.00
	Difference from placebo		-0.83
	Power	>99.99%	
Superficial cells	N	77	81
	Mean	0.91	5.62
	SD	2.69	5.49
	Difference from placebo		4.71
	Power	>99.99%	
Vaginal pain at sexual activity	N	77	81
	Mean	-0.87	-1.27
	SD	0.95	0.99
	Difference from placebo		-0.40
	Power	>97.7%	

alpha-level is one-sided 0.025 for all statistical tests
power is >97% for vaginal pain, pH, superficial cells and parabasal cells
* Margin as a percentage of treatment effect versus placebo

- **Randomisation**

The randomization was done centrally. Treatment codes were generated using a permuted block design utilizing PROC PLAN of Statistical Analysis System (SAS). Taking into account the 2:1 ratio between the DHEA group (group B) and the placebo group (group A), in order to keep the blind at each investigational site, two different lots of DHEA were used and were identified as B1 and B2. Blocks of 3 women (A, B1 and B2) were then generated to ensure a balanced allocation by investigational site between the treatment arms DHEA and placebo, in the corresponding 2:1 ratio, with each block sequence randomly allocated.

- **Blinding**

One (1) sealed envelope identified with the medication number and containing information about the treatment (Placebo or DHEA containing medication) for each particular subject was prepared. The envelope was kept at the trial site (during the entire trial period) and the randomization list was kept

by the Sponsor. The trial site envelopes were returned to the Sponsor at the end of the study using the appropriate form.

The blind has not been broken for any subject during the course of this study.

Results:

- **Participants flow**

A total of 1226 postmenopausal women were screened and 558 subjects were enrolled and randomized to this study in a 2:1 ratio. A total of 527 subjects (94%) have completed the study (DHEA = 356 and Placebo = 171).

The intent-to-treat (ITT) population, which consists of all subjects who have received at least one dose of study drug (based on the diary card) with a baseline (Day 1) evaluation meeting the study entry criteria, is the primary analysis population of efficacy analyses and includes a total of 482 subjects with 157 and 325 women in the placebo and 0.50% DHEA (prasterone) groups, respectively.

The Per Protocol (PP) Population consists of a subset of 373 subjects (DHEA = 254 and Placebo = 119) of the ITT population that completed the study through the time point of 12 weeks with no major protocol violations considered to compromise efficacy data. Subjects in this population have received at least 90% of the required number of applications of study treatment, based on the subject diary data and they have valid data entry at Week 12 for the 4 co-primary efficacy endpoints (superficial and parabasal cells, pH and pain at sexual activity).

Table 11: Subject disposition of the study ERC-238

Parameter	Placebo Group A	0.50% DHEA Group B	Overall
Total Screened Subjects			1226
Screen Failure Subjects			668
Randomized (1)	182	376	558
Safety Population (2)	180	374	554
Intent-to-Treat (ITT) Population (3)	157	325	482
Per-Protocol (PP) Population (4)	119	254	373
Completed Study N (%)(5)			
No	11 (6)	20 (5)	31 (6)
Yes	171 (94)	356 (95)	527 (94)
Reason for Discontinuation N (%)			
Adverse Event	5 (45)	5 (25)	10 (32)
Disease Progression	0	0	0
Non-Compliance	1 (9)	1 (5)	2 (6)
Lost to Follow-up	2 (18)	3 (15)	5 (16)
Patient Withdrew Consent	2 (18)	8 (40)	10 (32)
Investigator's Decision	0	1 (5)	1 (3)
Death	0	0	0
Other	1 (9)	2 (10)	3 (10)

- **Recruitment**

The first subject first visit was on 11 February 2014 and the last subject last visit was on 6 January 2015.

- **Conduct of the study**

Protocol deviation

In the placebo and the 0.50% DHEA groups, there were respectively 11 (6.0%) and 35 (9.3%) subjects with major protocol deviations. These deviations did not affect the integrity of the study data.

Table 12: Number of the subjects with major protocol deviations (ERC-238)

Protocol Deviation Category	Placebo	0.50% DHEA	Total
Number of subjects randomized	182	376	558
Number of subjects (%) with a major deviation			
Deviations to Inclusion Criteria			
Inclusion Criteria No.1b: Subject is premenopausal or FSH was not determined	2 (1.1)	0	2 (0.4)
Inclusion Criteria No.2: subjects did not identify moderate to severe dyspareunia as MBS	1 (0.5)	1 (0.3)	2 (0.4)
Inclusion Criteria No.11: no former or present alcoholism	0	1 (0.3)	1 (0.2)
Deviations to Exclusion Criteria			
Exclusion Criteria No.2: subject with a previous diagnosis of cancer	1 (0.5)	0	1 (0.2)
Exclusion Criteria No.4: subjects with clinically significant metabolic or endocrine disease not controlled by medication	0	6 (1.6)	6 (1.1)
Exclusion Criteria No.7: oral estrogen, progestin or DHEA exposure therapy in the 8 weeks prior to baseline assessments	1 (0.5)	0	1 (0.2)
Exclusion Criteria No.8: vaginal hormonal products in the 8 weeks prior to baseline assessments	1 (0.5)	1 (0.3)	2 (0.4)
Exclusion Criteria No.11: confirmed clinically significant depression not controlled by standard therapy	0	1 (0.3)	1 (0.2)
Exclusion Criteria No.13: subjects with clinically significant abnormal urinalysis at Screening	0	2 (0.5)	2 (0.4)
Exclusion Criteria No.14: subject randomized with an ASCUS on Pap test done at Screening	0	1 (0.3)	1 (0.2)
Exclusion Criteria No.16: subjects randomized with an endometrial biopsy report of "tissue insufficient for diagnosis" or abnormal endometrial histology	0	4 (1.1)	4 (0.7)
Subjects Took Prohibited Intravaginal Product or Medication	2 (1.1)	4 (1.1)	6 (1.1)

Prohibited Concomitant Treatments

Six subjects took intravaginal products after Day 1:

Four subjects took vaginal lubricants.

One subject used Monistat Cream to treat a vaginal yeast infection.

Another subject used Terazol 0.4% intra-vaginal cream to treat a vaginitis.

These deviations were not considered to have impact on study data because they were used punctually and not within 48 hours of any scheduled visit and study procedures.

- **Baseline data**

Demographic characteristics:

The demographics and baseline characteristics of the subjects enrolled in the two treatment groups were similar.

Table 13: Overview of demographics and baseline characteristics (ERC–238)

Parameter	Placebo	0.50% DHEA	Total
Number of subjects (%)	180 (100)	374 (100)	554 (100)
Race (Number of subjects, %)			
White Caucasian	163 (91)	338 (90)	501 (90)
Black or African American	13 (7)	28 (7)	41 (7)
Asian	2 (1)	4 (1)	6 (1)
American Indian or Alaskan Native	0	1 (0)	1 (0)
Native Hawaiian or Other Pacific Islander	0	1 (0)	1 (0)
Other	2 (1)	2 (1)	4 (1)
Ethnicity (Number of subjects, %)			
Not Hispanic or Latino	166 (92)	330 (88)	496 (90)
Hispanic or Latino	14 (8)	44 (12)	58 (10)
Age (years)			
Mean	59.6	59.5	59.5
Median	59.0	59.0	59.0
Range (Min - Max)	47 - 75	40 - 80	40 - 80
Anthropometric measurements (mean)			
Height (cm)	161.7	161.0	161.2
Weight (kg)	67.8	69.2	68.7
Body Mass Index (kg/m^2)	26.0	26.7	26.4
Reproductive history			
Years since last menses (mean)	13.4	14.1	13.9
Cause of last menses			
Natural (%)	120 (67)	237 (63)	357 (64)
Surgical (%)	60 (33)	137 (37)	197 (36)
Age (years) at last menses (mean)			
All women	46.2	45.4	45.6
Natural menopause	48.9	48.6	48.7
Surgical menopause	40.6	39.8	40.0
Hysterectomy (%)	36	39	38
Ovariectomy			
Any ovariectomy (%)	24	27	26
Bilateral ovariectomy (%)	17	19	19
Previous hormone replacement therapy (%)	42	42	42
Baseline medical history			
Any medical history abnormality (%)	100	100	100
Any physical exam abnormality (%)	14	14	14
Any vital sign abnormality (%)	4	6	6

- **Numbers analysed**

The ITT population set contains data from 157 subjects exposed to the placebo and 325 subjects exposed to DHEA 6.5 mg. The treatment duration was 12 weeks.

- **Outcomes and estimation**

Primary efficacy variables:

Effect on parabasal cells: There was a slight effect of intravaginal placebo on the percentage of parabasal cells. At baseline, percentage of parabasal cells was 51.66 ± 3.00%, and decreased to:

- 42.35 ± 2.73% ($p<0.0001$ versus baseline) at week 6
- 39.68 ± 2.68% ($p<0.0001$ versus baseline) at week 12

With the daily 6.5 mg (0.50%) intravaginal prasterone, the % of parabasal cells decreased from 54.25 ± 2.14% at baseline to:

- 14.72 ± 1.09% ($p<0.0001$ versus placebo) at 6 weeks
- 12.74 ± 1.02% ($p<0.0001$ versus placebo) at 12 weeks

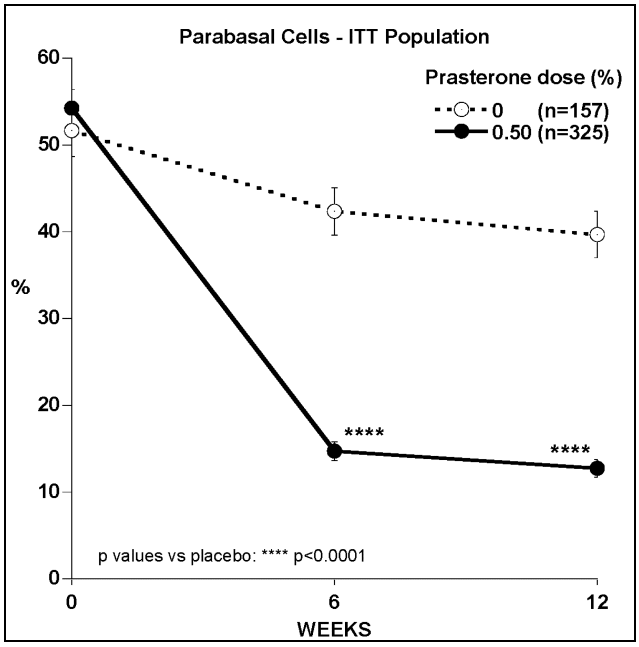

Figure 16: Effect of prasterone on percentage of parabasal cells (ERC-238)

Effect on superficial cells: Percentage of superficial cells increased slightly in the ITT placebo group of 157 women from 1.04 ± 0.11% at baseline to:

- 2.60 ± 0.27% (p<0.0001 versus baseline) at week 6
- 2.78 ± 0.27% (p<0.0001 versus baseline) at week 12

In the group who received daily 6.5 mg prasterone, the % of superficial cells increased from 1.02 ± 0.08% at baseline to:

- 11.71 ± 0.61% (p<0.0001 versus placebo) at week 6
- 11.22 ± 0.56% (p<0.0001 versus placebo) at week 12

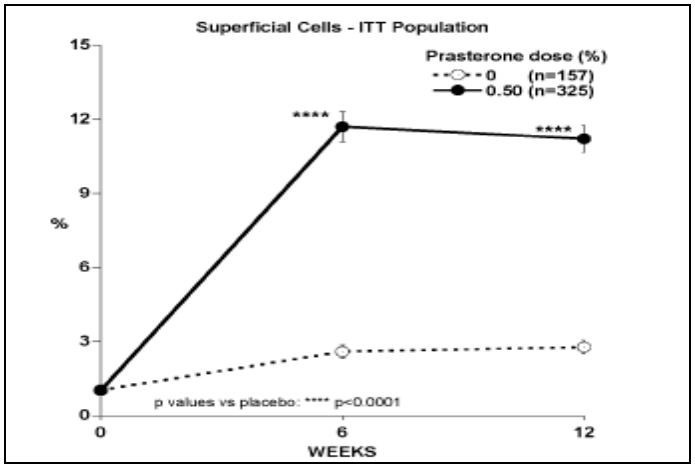

Figure 17: Effect of prasterone on percentage of superficial cells (ERC-238)

Table 14: Change from Baseline to end-of-treatment for percentages of parabasal and superficial cells (ERC–238)

	0.50% DHEA	Placebo
Superficial Cells		
N	325	157
Baseline	1.02	1.04
Week 12	11.22	2.78
Mean Change	10.20	1.75
SD	10.35	3.33
Difference from Placebo[a]	8.46	
P-value[b]	<0.0001	
Parabasal Cells		
N	325	157
Baseline	54.25	51.66
Week 12	12.74	39.68
Mean Change	-41.51	-11.98
SD	36.26	29.58
Difference from Placebo[a]	-29.53	
P-value[b]	<0.0001	

Abbreviations: DHEA=dehydroepiandrosterone; N=number of subjects; SD=standard deviation
[a] Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean).
[b] ANCOVA test with treatment group as the main factor and baseline value as the covariate.

Effect on vaginal pH: A relatively small decrease was observed in the placebo group. Vagina pH decreased from 6.32 ± 0.05 pH units at baseline to:

- 6.06 ± 0.07 (p<0.0001 versus baseline) at 6 weeks
- 6.05 ± 0.07 (p<0.0001 versus baseline) at 12 weeks

In the dose group of 6.5 mg prasterone, the pH decreased from 6.34 ± 0.04 at baseline to:

- 5.47 ± 0.05 (p<0.0001 versus placebo) at 6 weeks
- 5.39 ± 0.05 (p<0.0001 versus placebo) at 12 weeks

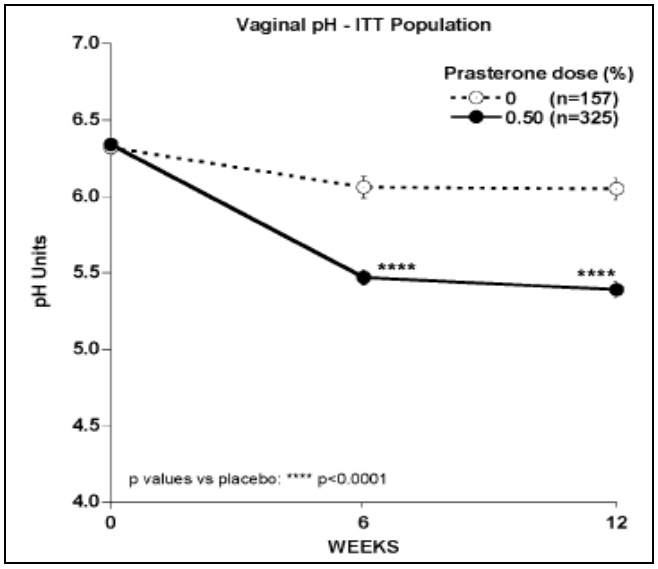

Figure 18: Effect of prasterone on vaginal pH (ERC–238)

Effect on dyspareunia (as MBS): In the ITT placebo group, (N=157), the severity score of dyspareunia decreased from 2.56 ± 0.04 units at baseline to 1.61 ± 0.08 at 6 weeks and 1.50 ± 0.08 unit at 6 and 12 weeks, (p<0.0001 versus baseline at both time intervals).

With the daily 6.5 mg (0.50%) prasterone dose (N=325), the severity score of dyspareunia decreased from 2.54 ± 0.03 units at baseline to:

- 1.41 ± 0.06 (p=0.036 versus placebo) at 6 weeks
- 1.13 ± 0.05 (p=0.0002 versus placebo) at 12 weeks

An improvement of 0.35 point in the severity score unit was thus observed or a 33% improvement over placebo (p=0.0002 versus placebo).

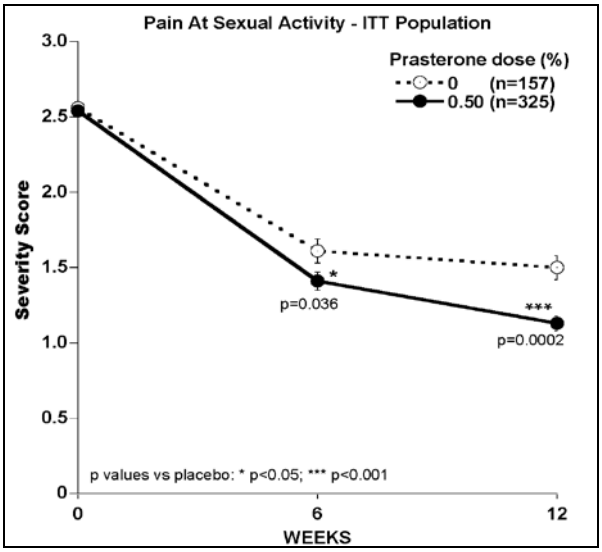

Figure 19: Effect of prasterone on pain at sexual activity (ERC–238)

Table 15: Change from baseline to end-of-treatment for dyspareunia (ITT population; Study ERC-238)

	0.50% DHEA	Placebo
Pain at Sexual Activity		
N	325	157
Baseline	2.54	2.56
Week 12	1.13	1.50
Mean Change	-1.42	-1.06
SD	1.00	1.02
Difference from Placebo[a]	-0.35	
P-value[b]	0.0002	

Abbreviations: DHEA=dehydroepiandrosterone; N=number of subjects; SD=standard deviation
[a] Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean).
[b] ANCOVA test with treatment group as the main factor and baseline value as the covariate.

It was expected, based on inclusion criterion no. 6, that subjects would have sexual activity at least once during the 12-week treatment and evaluation period. However, it has happened that 14 and 20 women in the placebo and DHEA groups, respectively, have not engaged in sexual activity after Day 1. In order to examine unbiased data for the co-primary endpoint dyspareunia, an additional analysis was performed on a modified ITT (mITT) composed of women from the ITT population who had post-baseline sexual activity at least once before evaluation of dyspareunia. Data obtained from the mITT population were very similar to those of the ITT population, with an improvement of dyspareunia following DHEA treatment (N=305) of 0.34 severity score unit over placebo (N=143; p=0.0003 versus placebo).

Secondary efficacy variables

Moderate to severe vaginal dryness

The severity score of vaginal dryness in the ITT population decreased from 2.30 ± 0.04 units at baseline in the placebo group to:

- 1.13 ± 0.08 at 6 weeks, (p<0.0001 vs baseline)
- 1.13 ± 0.08 unit at 12 weeks (p<0.0001 versus baseline)

In women treated with daily 6.5 mg prasterone group the severity score of vaginal dryness decreased from 2.30 ± 0.03 units at baseline to:

- 1.05 ± 0.05 (p=0.3984 versus placebo) at 6 weeks
- 0.86 ± 0.05 unit (p=0.004 versus placebo) at 12 weeks

The improvement over placebo was 0.27 severity score unit at 12 weeks or 23% (p=0.004 versus placebo), an effect similar to that observed on MBS dyspareunia in the same ITT population where the improvement of MBS dyspareunia was 0.35 severity score unit or 33% over placebo (p=0.0002 versus placebo).

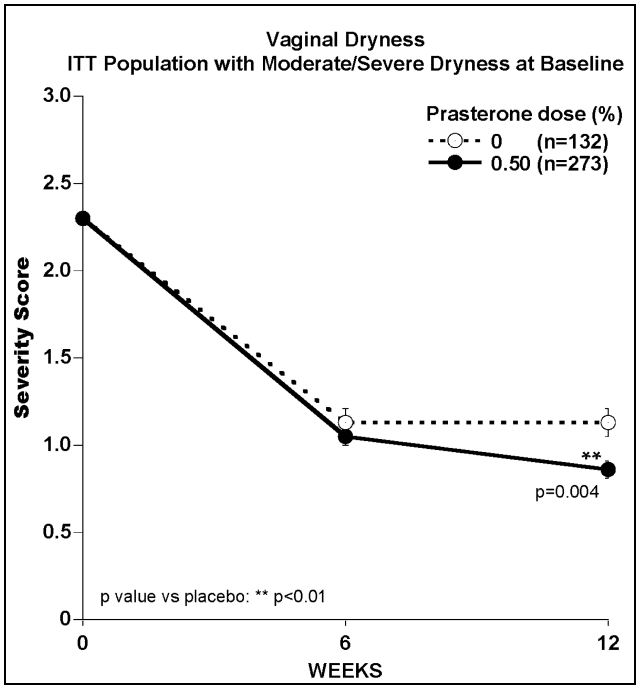

Figure 20: Effect of prasterone on vaginal dryness (ERC–238)

Table 16: Change from baseline to end-of-treatment for vaginal dryness (ERC-238)

	0.50% DHEA	Placebo
Vaginal Dryness		
N	273	132
Baseline	2.30	2.30
Week 12	0.86	1.13
Mean Change	-1.44	-1.17
SD	0.93	0.99
Difference from Placebo[a]	-0.27	
P-value[b]	0.004	

Abbreviations: DHEA=dehydroepiandrosterone; N=number of subjects; SD=standard deviation
[a] Difference from placebo = DHEA (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean).
[b] ANCOVA test with treatment group as the main factor and baseline value as the covariate.

Other efficacy findings*:*

The FSFI questionnaire was filled at baseline, Week 6 and Week 12. The FSFI domain desire increased over placebo by 0.24 unit (+49.0%, p=0.0105), arousal by 0.42 unit (+56.8%, p=0.0022), lubrication by 0.57 unit (+36.1%, p=0.0005), orgasm by 0.32 unit (+33.0%, p=0.047), satisfaction by 0.44 unit (+48.3%, p=0.0012) and pain at sexual activity by 0.62 unit (+39.2%, p=0.001). The total FSFI score, on the other hand, has shown a superiority of 2.59 units in the DHEA group over placebo or a 41.3% greater change than placebo (p=0.0006) over placebo. The present data on the FSFI show a 33.0% (orgasm, p=0.047) to 56.8% (arousal, p=0.0022) increase over placebo in all the six domains of the FSFI, thus confirming the previous benefits of intravaginal DHEA on female sexual dysfunction by an action exerted exclusively at the level of the vagina.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application (ERC–231 and ERC–238). These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17: Summary of efficacy for trials

Title: DHEA Against Vaginal Atrophy (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal DHEA)		
Study identifier	**ERC-231**	
Design	Placebo-controlled, double-blind, randomized phase III study of 3-month treatment	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks N/A N/A
Hypothesis	Superiority (comparison to placebo)	
Treatments groups	Placebo	12 weeks of treatment. 81 subjects randomized

Title: **DHEA Against Vaginal Atrophy (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal DHEA)**			
Study identifier	**ERC-231**		
	DHEA 3.25 mg		12 weeks of treatment. 87 subjects randomized.
	DHEA 6.5 mg		12 weeks of treatment. 87 subjects randomized.
Endpoints and definitions	4 Co-Primary endpoints	Change in vaginal maturation index (vaginal smear) change in vaginal pH, change in dyspareunia	Decrease vs baseline in % of parabasal cells Increase vs baseline in % of superficial cell Decrease vs baseline in vaginal pH Improvement in dyspareunia considered as most bothersome symptom of VVA
	Key Secondary endpoints	Vaginal dryness vaginal irritation or itching	Change in vaginal dryness severity score Change in vulvar irritation/itching severity score
	Other Secondary endpoint	Effect on arousal/lubrication, desire, satisfaction and orgasm Local tolerance	Improvement in corresponding severity scores using a questionnaire (FSFI). Self-assessment by the subjects. Vaginal observations at gynaecological examination.
Database lock	Last subject last visit: January 29th, 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population after 12 weeks of treatment			
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**DHEA 3.25 mg**	**DHEA 6.5 mg**
	Number of subjects	N = 77	N = 79	N = 81
	Decrease in % of parabasal cells (vs baseline)	-1.62	-37.29	-47.40
	SD	28.22	37.00	42.50
	Increase in % of superficial cells (vs baseline)	+ 0.91	+ 4.75	+ 5.62
	SD	2.69	5.15	5.49
	Decrease in pH value (vs baseline) SD	-0.21 0.69	-0.77 0.90	-1.04 1.00

Title: **DHEA Against Vaginal Atrophy (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal DHEA)**				
Study identifier	**ERC-231**			
	Decrease in dyspareunia severity score (vs baseline) SD	-0.87 0.95	-1.01 1.02	-1.27 0.99
Effect estimate per comparison	Co-Primary endpoint	Comparison groups	DHEA 3.25 mg, DHEA 6.5 mg compared to placebo	
		Difference in change between 3.25 mg DHEA and placebo	% Parabasal cells : -35.67 % Superficial cells: +3.84 pH:-0.57 Dyspareunia score: -0.14	
		Difference in change between DHEA 6.5 mg and placebo	%Parabasal cells: -45.77 %Superficial cells: +4.71 pH:-0.83 Dyspareunia score: -0.40	
		P value	<0.0001 For dyspareunia: = NS (3.25 mg) = 0.013 (6.5 mg)	
Notes	A clear placebo effect on dyspareunia was observed at week 12. The clinical relevance of the DHEA effect over placebo is unknown.			

Title: **Intravaginal Prasterone (DHEA) Against Vulvovaginal Atrophy Associated With Menopause (Placebo-Controlled, Double-Blind and Randomized Phase III Study)**			
Study identifier	**ERC-238**		
Design	Placebo-controlled, double-blind, randomized phase III study of 3-month treatment		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks N/A N/A	
Hypothesis	Superiority (comparison to placebo)		
Treatments groups	Placebo	12 weeks of treatment. 157 subjects randomized	
	DHEA 6.5 mg	12 weeks of treatment. 325 subjects randomized.	
Endpoints and definitions	4 Co-Primary endpoints	Change in vaginal maturation index (vaginal smear)	Decrease vs baseline in % of parabasal cells Increase vs baseline in % of superficial cell
		Change in vaginal pH,	Decrease vs baseline in vaginal pH
		Change in dyspareunia	Improvement in dyspareunia considered as most bothersome symptom of VVA

Title: Intravaginal Prasterone (DHEA) Against Vulvovaginal Atrophy Associated With Menopause (Placebo-Controlled, Double-Blind and Randomized Phase III Study)			
Study identifier	**ERC-238**		
	Key Secondary endpoints	Vaginal dryness Vaginal irritation or itching	Change in vaginal dryness severity score Change in vulvar irritation/itching severity score
	Other Secondary endpoint	Effect on arousal/lubrication, desire, satisfaction and orgasm Local tolerance	Improvement in corresponding severity scores using a questionnaire (FSFI). Self-assessment by the subjects. Vaginal observations at gynaecological examination.
Database lock	Last subject last visit: January 6th, 2015		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population after 12 weeks of treatment			
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**		**DHEA 6.5 mg**
	Number of subjects	N = 157		N = 325
	Decrease in % of parabasal cells (vs baseline)	-11.98		-41.51
	SD	29.58		36.26
	Increase in % of superficial cells (vs baseline)	+ 1.75		+ 10.20
	SD	3.33		10.35
	Decrease in pH value (vs baseline) SD	-0.27 0.74		-0.94 0.94
	Decrease in dyspareunia severity score (vs baseline) SD	-1.06 1.02		-1.42 1.00
Effect estimate per comparison	Co-Primary endpoint	Comparison groups		DHEA 6.5 mg compared to placebo
		Difference in change between DHEA 6.5 mg and placebo		%Parabasal cells: - 29.53 %Superficial cells: + 8.46 pH:- 0.67 Dyspareunia score: - 0.35

Title: Intravaginal Prasterone (DHEA) Against Vulvovaginal Atrophy Associated With Menopause (Placebo-Controlled, Double-Blind and Randomized Phase III Study)			
Study identifier	**ERC-238**		
		p-value	<0.0001 For dyspareunia = 0.0002
Notes	The placebo effect at week 12 was more important than expected in particular on the PD endpoints. A clear placebo effect on dyspareunia was observed at week 12. The clinical relevance of the DHEA effect over placebo is unknown. Overall, the results are comparable to those obtained with the ERC-231		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

In this application, the target population is postmenopausal women with VVA. No clinical studies were performed in special population. Based on the inclusion criteria of the phase III clinical studies, subjects enrolled are postmenopausal women with VVA aged from 40 and 75-80 years old. This represents a large population of postmenopausal women. Inside this population, no difference is made with regard to any specific age range.

The following subgroup analyses (Forest plots) were requested at day 120 of the procedure for the 4 co-primary endpoints: Canada and USA, BMI =< 25 and BMI > 25, Age =< 55 and age > 55, duration of menopause (1-2 y, 2-5y and >5y). Results show no noticeable treatment effect differences between investigated subgroups, except for the duration of menopause. It seems that women with 1-2y menopause could benefit more of prasterone compared to other subgroups (3-5y, >=6y); however, this discrepancy could also be explained by the small size of the 1-2y subgroup (33 subjects vs 86 in 3-5y and 521 in >=6y) rather than a true interaction effect across subgroups.

Supportive study(ies)

Study ERC-234 was a phase III efficacy and safety study where two doses of DHEA were compared to placebo using an administration regimen different from the pivotal studies ERC-231 and ERC-238. Indeed, in this study, treatment was administrated intravaginally once daily during 2 weeks then biweekly during 10 weeks and time points for assessment of efficacy variables were week 2, 6 and 12.

Decrease in dyspareunia severity score was the clinical co-primary endpoint in the mentioned pivotal studies ERC-231 and 238, while the decrease in vaginal dryness severity score was the clinical co-primary endpoint in this study ERC-234 considered as supportive.

Apart from these two differences, the study design and inclusion/exclusion criteria were similar to the pivotal studies ERC-231 and 238. Here also, the study was conducted in Canada and USA and no European subjects were included. Thus, the extrapolation of the findings to European population is questionable given the cultural dimension of menopause and sexual activities.

No active control group (local oestrogens) was included in the study design. Comparison was performed versus placebo.

15 women of the ITT population had a pattern of sex steroids typical of women having taken estrogens (a situation most likely associated with a bias in the data). These subjects were excluded from the corrected ITT population set. Analysis of efficacy endpoints was performed on ITT and corrected ITT population including 132 subjects who received placebo, 127 subjects who received DHEA 3.25 mg and 133 who received DHEA 6.5 mg.

Results showed that the effect on PD parameters (percentage of parabasal cells, superficial cells and vaginal pH) was maximal at 2 weeks with a loss in efficacy at further time intervals. This is due to the reduced regimen after 2 weeks of daily administration.

With regard to vaginal dryness considered as the most bothersome symptom in this study (clinical co-primary endpoint), with 3.25 mg DHEA, the severity score in ITT population decreased from 2.37 ± 0.04 at baseline to 1.06 ± 0.07 at 6 weeks (p=0.02 versus placebo) and then increased slightly to 1.10 ± 0.07 (p=0.108 versus placebo) at 12 weeks. In the 6.5 mg DHEA, the severity score decreased from a value of 2.35 ± 0.04 at baseline to 1.12 ± 0.07 (p=0.090 versus placebo) at 6 weeks and then to 1.13 ± 0.08 (p=0.198 versus placebo) at 12 weeks.

In conclusion based on this supportive study outcome, the reduced regimen (twice weekly; 3.25 mg and 6.5 mg) is associated with a loss in efficacy on all co primary endpoints, with results on vaginal dryness at week 12 being not statistically different from placebo. Thus, this reduced regimen was ruled out.

Study ERC–230 was a phase III multi-center open label safety study of 52 weeks performed to assess the long term safety of intravaginal 6.5 mg DHEA.

This study was performed in USA and Canada. The study was divided into 2 phases, namely a screening period up to 6 weeks followed by a treatment period of 12 months. Subject population to be studied was postmenopausal women (non-hysterectomized), between 40 and 75 years of age having self-identified at least mild to severe vaginal dryness or vaginal or vulvar irritation, or vaginal pain at sexual activity. Overall, 530 subjects were enrolled and a total of 487 women were part of the population for evaluation of efficacy. Efficacy variables were part of the secondary objectives. Analysis of efficacy outcomes showed that the effect on MS dyspareunia, MS vaginal dryness and MS irritation/itching is the same whether each MS symptom is considered MBS or not MBS by the women. Limited improvement in the severity scores of dyspareunia, vaginal dryness and irritation/itching is observed when daily intravaginal administration of 0.50% prasterone is extended from 12 weeks to 52 weeks. In fact, 19.4%, 15.1% and 6.5% of the 52-week effect was obtained for MS dyspareunia, MS vaginal dryness and MS irritation/itching between Week 12 and Week 52 of treatment.

The similar and parallel effects of prasterone treatment on dyspareunia, dryness and irritation/itching strongly suggest that prasterone is acting directly on the cause(s) of VVA itself while the changes observed on the symptoms are secondary to the improvement of the VVA pathology.

In conclusion, from this long term non comparative open-label safety study, analysis of efficacy outcomes as secondary endpoints showed an improvement versus baseline in each efficacy criteria until week 26 of the treatment and a maintenance of this effect from week 26 to week 52 of the treatment. In other words, there is no loss on efficacy after 26 weeks of treatment.

No additional conclusion can be drawn from this long term study with regard to efficacy parameters.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical study (ERC–210)

The primary objective was to determine the dose-response of vaginal mucosa parameters to the local action of DHEA in postmenopausal women with vaginal atrophy. The treatment groups were placebo and 3 DHEA doses: 0.25% (3.25 mg), 0.5% (6.5 mg) or 1.0% (13 mg). The Applicant considered this study as a phase III study. However, given the limited population size and the study objective, it should be considered as a phase II dose-response (supportive) study.

There were four co-primary endpoints consisting of three pharmacodynamics parameters (decrease in parabasal cells, increase in superficial cells, change in vaginal pH) and one clinical parameter (change in severity score of the vaginal clinical symptom self-assessed at 12 weeks via a questionnaire). Change in parabasal and superficial cell percentage was assessed using a 100-cell count to classify cells as superficial (S), intermediate (I) and parabasal (P) squamous cell types. Vaginal pH was measured by applying a pH indicator strip directly to the lateral wall of the vagina with a forceps.

As secondary endpoints, sexual function as well as quality of life were evaluated at screening, day 1 and weeks 4, 8 and 12 by the MENQOL, ASF, PGWB and SC questionnaires.

The primary time point for analysis was the 12-week assessment. The change from baseline to each post-baseline assessment was calculated and used for statistical analysis for the comparison of each DHEA dose group to placebo; additionally, the significance of the change from baseline within each treatment group was also statistically assessed.

Efficacy data and additional analyses (ERC–210)

This dose-finding study was intended to identify the lowest effective dose having the most acceptable safety pattern. Results showed that at the standard 12-week time interval, for all co-primary endpoints, a clear difference in responses between the 3 DHEA arms was observed versus the placebo arm, but no clear trend to higher response with higher dose was observed when considering only the 3 DHEA doses.

In this study there was no placebo effect at any time point on the PD parameters (parabasal and superficial cells, vaginal pH) while a clear placebo effect was observed at all the time points on the clinical symptoms.

Based on the lack of marked difference between the doses 6.5 and 13 mg regarding the efficacy parameters, the dose of 13 mg was ruled out for the rest of the clinical studies.

Design and conduct of clinical study (Pivotal study ERC-231)

This was a double-blind placebo-controlled randomized study to confirm the efficacy of daily intravaginal administration of a 0.25% (3.25 mg) DHEA and 0.50% (6.5 mg) DHEA vaginal suppositories (pessaries) for 12 weeks compared to placebo in postmenopausal women.

Although local oestrogens are considered as a “standard” treatment of VVA in postmenopausal women, DHEA was only compared to placebo and no active comparator group was included. The lack of such comparator was not justified with robust arguments. Indeed, the use of active comparator group was recommended during SA discussion at EMA and at national level. Instead, the Applicant provided further to day 120 of the procedure an indirect comparison between prasterone, Vagifem 10 µg and conjugated estrogens (vaginal administration) and comparison showed a trend to comparable efficacy.

No safety data are available. On PK level, an increase was noted in serum E2 levels after 83 days treatment of 4.64 and 9.41 pg/ml, respectively, for the 10 µg and 25 µg estradiol doses (Vagifem). Regarding the change in mean Estradiol, Estrone & Estrone-sulphate in the treatment groups in the principal studies (prasterone): Estradiol mean levels were 4.2 pg/ml range for the 0.5% (6.5 mg) prasterone dose. Mean Estrone levels increased by 1.9 pg/ml to 19 pg/ml after 12 weeks treatment. Estrone-sulphate levels increased by 20.1 pg/ml to 241pg/ml. These ranges are within those in the published literature.

Therefore the levels of estradiol, estrone & estrone-sulphate after 12 weeks treatment with prasterone are comparable to treatment with 10 µg of vaginal estradiol Vagifem.

The claimed indication is considered large with regard to the population enrolled in the phase III pivotal trials; indeed, some categories of subjects were excluded from the clinical study without clear rational (e.g. subjects with previous diagnosis of cancer - except skin-, thromboembolic disease, uncontrolled diabetes mellitus). Thus, the lack of information regarding the exposure of these subjects has been addressed in the product information.

The four co-primary endpoints are: decrease in percentage of parabasal cells, increase in percentage of superficial cells, decrease in vaginal pH, improvement in dyspareunia self-identified by subjects as the most bothersome VVA symptom to her at screening and at baseline (Day 1).

Of note, change in percentage of superficial and parabasal cells was examined on vaginal smears by an experienced cytopathologist blinded to the treatment regimens. A 100-cell count was performed to classify cells as parabasal, intermediate and superficial squamous cell types. Given the lack of a second confirmatory assessment by another cytopathologist, the reproducibility of the results (cell count) is questioned.

Efficacy data and additional analyses (ERC–231)

This study was conducted in Canada and in USA; no European women were included. Given the cultural dimension related to menopause and sexual activities, comparability between Canadian/US women and European women is questioned as well as the validity of extrapolation of the results obtained with studies having included only North American subjects.

At 12 weeks, a dose–dependent effect on percentage of parabasal cells, superficial cells and level of vaginal pH was observed in both dose groups (3.25 mg and 6.5 mg). Both doses had highly significant effect versus placebo. No placebo effect was observed on these PD parameters in study ERC-231.

Regarding the 4th co-primary endpoint considered as the only clinical parameter (improvement in the severity score of dyspareunia considered by the subjects as the most bothersome symptom), this parameter was self-assessed at predefined time points via a questionnaire, leading to a severity score from 0 (none) to 3 (severe). Of note, validation of the questionnaire was not provided in the dossier. At week 12, there was a placebo effect observed: a decrease in the dyspareunia severity score from a mean baseline value of 2.58 to 1.71 (-0.87 point).

The decrease of severity score in the DHEA group of 3.25 mg was from 2.56 to 1.54 (-1.01) and with the DHEA 6.5 mg, from 2.63 to 1.36 (-1.27). In this study, the percentages of subjects with an improvement in their dyspareunia symptom at week 12 (improvement, substantial improvement, relief) were not statistically different between placebo and Intrarosa groups.

Also, there is no information on frequency of intercourse in the efficacy population set. Indeed, women with VVA could be enrolled if they declared having sexual activity at least once a month. However, frequency of intercourse is an important parameter with regard to the clinical endpoint (dyspareunia).

Design and conduct of clinical study (Pivotal study ERC-238)

This was a (larger) phase III double-blind placebo-controlled study aimed to confirm the efficacy and safety outcomes obtained in the ERC-231 and to have sufficient exposure to DHEA, in line with the requirement of ICH E1 (exposure of at least 1500 subjects given the non-rare, non-life threatening disease).

Study design, population characteristics and treatment duration were similar to the study ERC-231. However, only one DHEA dose (6.5 mg) was compared to the placebo. No active comparator group was included and this despite the scientific advice recommendation.

The study was also conducted in Canada and US and extrapolation of the findings to European population is also questioned given the cultural dimension of questions related to menopause and sexual activities.

Subjects enrolled were postmenopausal women from 40 to 80 years old having VVA and having identified moderate to severe dyspareunia as most bothersome symptom.

A total of 558 subjects were enrolled and randomized to this study in a 2:1 ratio. The analysis of the primary endpoints was performed on ITT population composed of 325 subjects in the DHEA group and 157 in the placebo group. The compliance of subjects with regard to the number of treatment doses provided are not clear. Anyway, these data do not jeopardize the overall study outcomes as supported by the ITT former analysis and the randomized analysis newly provided by the Applicant, which take into account these protocol deviations.

Efficacy data and additional analyses (ERC–238)

The study was conducted in USA and Canada and no European subjects were included. As for the pivotal study ERC–231, the extrapolation of findings to European population is questionable, given the cultural dimension of questions related to menopause and sexual activities.

At week 12, there was a slight placebo effect on decrease in percentage of parabasal cells (-11.98% vs baseline) and increase in percentage of superficial cells (+1.75% vs baseline) and decrease in vaginal pH was -0.27. Surprisingly, this placebo effect on the aforementioned PD parameters was more important than the effect expected, based on the study ERC-231. The Applicant has no supported explanation of this difference.

With the daily DHEA 6.5 mg, the effect on PD parameters (at 12 weeks) was as follows: decrease in % of parabasal cells of -41.51 ($p<0.0001$ versus placebo), increase in % of superficial cells of + 10.20 ($p<0.0001$ versus placebo) and decrease in vaginal pH of -0.94 point.

Regarding dyspareunia (4th co-primary endpoint), a placebo effect was observed at week 12 with a decrease from baseline of 1.06 in the severity score. With the 6.5 mg of DHEA, the decrease in dyspareunia severity score of 1.42 point was observed, thus, 0.35 point over placebo. The clinical relevance of this difference over placebo is unknown.

This placebo effect is likely to be related to the vehicle effect on the vaginal epithelium, leading to a relief in some clinical parameters like dyspareunia (lubricant-like effect).

Results obtained on vaginal dryness (secondary endpoint) were comparable to those obtained on dyspareunia. At 12 weeks, the decrease in vaginal dryness severity score versus baseline became higher with DHEA: 0.27 point over placebo. Here also, the clinical relevance of this difference over placebo is unknown.

Also, the frequency of intercourse in the efficacy population is unknown. The change in number of intercourses before treatment/after treatment is not available. This parameter is important given the clinical endpoint (dyspareunia).

As a conclusion, ERC-238 was a pivotal clinical study which included a larger population than ERC-231 and had a comparable design and similar treatment duration than ERC–231. Efficacy results obtained at week 12 are in line with those obtained with the ERC-231. The size effect observed with placebo was more important than expected in this study.

2.5.4. Conclusions on the clinical efficacy

To select the optimal DHEA daily dose for the claimed indication (treatment of VVA in post-menopausal women), a dose–response study was conducted comparing the efficacy and safety outcomes of 4 DHEA doses: 0 mg (placebo), 3.25 mg, 6.5 mg and 13 mg. At the standard 12-week time interval, there was a difference in responses to all co-primary endpoints between the 3 DHEA arms and the placebo arm, but no clear trend to higher response with higher dose when considering only the 3 DHEA doses. Also, analysis of the 4th co-primary endpoint (dyspareunia) showed a clear placebo effect likely to be related to the excipients. There was no major difference in the safety pattern between the dose treatment groups.

The DHEA efficacy profile is based on two placebo-controlled phase III studies. Although local oestrogens are the “standard” VVA treatment in this population (postmenopausal women), no active comparator group was included in the study design and this point was not sufficiently justified. From the main pivotal studies ERC-231 and ERC-238, a slight placebo effect was observed on the PD endpoints (parabasal and superficial cell, vaginal pH). However, this placebo effect was more important than expected in the study ERC-238 compared to ERC-231. Regarding the 4th co primary outcome which is the clinical parameter in both phase III studies (dyspareunia), there was a clear improvement of this parameter (decrease in severity score of dyspareunia) with the placebo at the end of treatment period compared to baseline in both studies. This placebo effect on dyspareunia is probably related to the excipients (lubricant-like). Although the change versus baseline in the DHEA group was more important than the change versus baseline in the placebo group, the clinical relevance of this effect over placebo is unknown. Also, the frequency of intercourse in the efficacy population is unknown.

The phase III pivotal studies ERC–231 and ERC-238 were conducted in Canada and in USA. There were no European women exposed to the drug. Given the cultural dimension related to menopause and sexual activities, comparability between Canadian/US women and European women can be questioned as a different perception of the benefit in European women cannot be excluded.

Overall, clinical efficacy as demonstrated in the clinical trials was modest.

2.6. Clinical safety

Subject exposure

The safety population consisted of **1,542 women** exposed to the 0.25%, 0.50% or 1.0% intravaginal DHEA doses in studies ERC-210, ERC-213, ERC-230, ERC-231, ERC-234 and ERC-238 and 474 women who have received placebo. There were 1,196 women exposed to the 0.5% dose including 435 women exposed up to 52 weeks. Of note, more than **300 biopsies were available** after week 52 to assess endometrial safety. Overall, regarding the number of subjects exposed, the applicant respected the requirement from ICH–E1 population exposure in clinical trials.

Overall, the average age of the women enrolled in the safety population was 58.6 years with a median age of 58 years and a range of 40 to 80 years. Similar age distributions were observed in all the treatment groups. On average, the women measured 160.6 cm and weighed 68.2 kg with a BMI of 26.4. Similar BMI were observed between groups.

The women assigned to the different treatment groups had similar reproductive histories except for surgical history. In the 6.5 mg DHEA group, less women were hysterectomized or ovariectomized compared to placebo. This difference may be explained by the inclusion criteria of the Study ERC-230 (6.5 mg DHEA) that include only non-hysterectomized postmenopausal women. An average of 11.9 years (13.2 [Placebo] and 11.4 [0.50% DHEA]) have elapsed since their last menses. Menstrual cycles ceased naturally in more than half the population (61.4% [Placebo] and 78.3% [0.50% DHEA]). The average age at which the women in all treatment groups had their last menstrual period was 46.7 [49.1 years in women who had a natural menopause and 39.7 years in women who had a surgical menopause]. The mean age at menopause is lower than the expected average even in the group with natural menopause.

As **Prasterone's metabolites** are mainly **androgens** (see laboratory findings) which could have an action on **cardiovascular system** and **oestrogens** (to a lesser degree) which could be involved in **thromboembolic events** and **development of hormonal cancers**, women with history of thromboembolic accident, cancer (including hormonal cancer), cardiac failure or coronary heart disease and hypertension (>140/90 mmHg) were excluded from the studies. Thus, women with cardiovascular risk or cancer history or with gynaecological abnormalities have not been studied.

Similarly, subjects' concomitant medications excluded any form of hormonal replacement therapy (oral, implants, vaginal cream, pessary, transdermal, rings, gels, tablets, pellet, injectable, intrauterine) including contraceptives, as well as androgens and anabolic steroids products. Approximately 50 % of subjects across all groups had been treated with previous hormonal therapy.

Adverse events

The applicant submitted pooled data of all AEs reported during clinical trials. Only treatment-emergent adverse events (TEAEs) reported up to week 16 were analysed in the summary of safety. A TEAEs is defined as AEs that started or worsened after the first dose administration through 30 days after the last dose of study treatment. Applicant provided a summary table with the most frequent TEAEs (>1%) by treatment group up to 52 weeks. The presentation of TEAEs by age and by treatment group does not reveal differences in TEAEs incidence between age-class.

Half of the subjects in the safety population experienced at least one TEAE of any nature with frequencies ranging from 47.7% (placebo) to 64.1% (1.0% DHEA) of subjects. According to the Investigator's assessment, the majority of TEAEs were mild or moderate in intensity.

The assessment focused mainly on women treated with the dose of 6.5 mg of DHEA.

Up to week 52, the most frequent TEAEs belong to the following MedDRA SOC (incidence in treatment arm 6.5 mg > placebo):

- **Infection and infestation (27.7 vs 16.9%)**: mainly urinary tract infection
- **Reproductive and breast disorders (18.0 vs 12.4%)**: mainly cervical dysplasia and vaginal discharge
- **General disorders and administration site conditions (11.9 vs 6.5%)**: mainly application site discharge
- **Investigations (9.3 vs 4.0%)**: mainly weight increase or decrease
- **Skin and subcutaneous tissue disorders (6.9 vs 3.2%)**: mainly acne, erythema, hypertrichosis

- **Nervous system disorders (6.4 vs 3.8%)**: mainly Headache
- **Vascular disorders (1.8 vs 0.8%)**: mainly Hypertension

Application site/Vaginal discharge and urinary tract infection (UTI) were frequently reported, with respective incidence of 11% and 7.4%. The Applicant clarified the cause of UTI which were from fecal flora origin rather than skin or insertion technique. According to the Applicant, the cause of the application site/vaginal discharge is due to an increase in physiological discharge due to the improved pH & estrogenic status of the vaginal cells in women treated, in addition to the effect of liquid hard fat excipient. It was not due to infection.

The incidence of TEAEs by period of 3 months is only available for ERC-230 study. The following TEAEs were more frequent during the 16 first weeks: “application site discharge” and “hot flush”. On the contrary, “cervical dysplasia” (MedDRA term) occurred more frequently at the end of treatment (44-46 weeks).

Regarding long-term data, TEAEs observed up to week 52 are globally the same than those observed at week 16. However, several serious AEs occurred during ERC-230 (52 weeks study) were not previously reported at week 16: hypertension, breast cancer, breast hyperplasia, ovarian cancer, cervical/uterine polyps.

DHEA is mainly a precursor of androgens and secondary of estrogens. Since DHEA and its metabolites are significantly increased in serum of treated subjects, AEs related to exposure to sexual steroids are expected. **Estrogenic effects** include vaginal bleedings and hormonal tumours development (endometrial, breast, or ovarian cancers, cervix modifications). **Androgenic effects** include AEs such as acne, hypertrichosis, hirsutism, alopecia, metabolic changes (lipids increase, weight increase), cardiovascular disorders and psychiatric disorders are also expected.

The causal relationship between an AE and the investigational product was assessed by the Investigator based on his judgment. However, many frequent local AEs considered as not related or possibly related to prasterone seem likely related to prasterone pharmaceutical form, contrary to the applicant’s assessment. For example, only one case of vaginal discharge among the 27 reported has been related to prasterone and only 4 cases of vulvovaginal burning sensation on the 16 recorded. In this respect, an imbalance in the number of AEs regarding local tolerance is observed between treated women and placebo.

Similarly, several TEAEs classified as non-related or possibly related by investigators could be related to prasterone with regards its mechanism of action. Although the Applicant provided additional information, the role of prasterone could not be excluded in the occurrence of the following AEs:

- **Androgen effects**: hypertension

- **Estrogen effects**: Abnormal Pap smear (MedDRA term: cervical dysplasia), hormonal tumours development (breast, ovarian), uterine and cervical polyps, weight fluctuations, breast mass and breast tenderness.

Overall, the most frequent drug–related AEs were local effects (application site/vaginal discharge) which are considered by the applicant related to prasterone effect on vaginal secretions/pH and to the melting of the hard fat excipient. However, since the incidence is higher in the treated group than in the placebo (15% for 6.5 mg DHEA vs 8.4% in placebo) a causal relationship to prasterone seems to have been minimised for local AEs. Similarly, several AEs for which the pharmacology of prasterone could suggest direct imputability have also been assessed as not-related. These effects are either androgenic (hypertension) or estrogenic (Abnormal Pap smear (MedDRA term: cervical dysplasia), hormonal tumours development (breast, ovarian), uterine/cervical polyps, weight fluctuations, breast mass, breast tenderness).

Serious adverse events and deaths

No death was reported during clinical trials.

In women exposed to 6.5 mg DHEA, 26 (2.2%) experienced serious TEAE (including 16 cases up to week 16 of treatment) vs 5 in the placebo group (1%). The most frequently affected primary SOCs were “Injury, poisoning and procedural complications” (0.3%) and “Surgical and medical procedures” (0.3%), followed by “Gastrointestinal disorders” (0.2%) and “Musculoskeletal and connective tissue disorders” (0.2%) and are not related to prasterone.

However, among the serious TEAS, the responsibility of prasterone cannot be excluded in 3 cases: pulmonary embolism, ovarian cancer and breast cancer. Indeed a role of DHEA’s oestrogens derivatives cannot be excluded in the apparition (or worsening) of both hormonal tumours (breast or ovarian cancers) and thromboembolic events. Indeed, androgens and estrone concentration were significantly increased in the 6.5 mg treated group compared to placebo. A peripheral transformation of androgens into estrogens (aromatase) or Estrone transformation into estradiol are two possible pathways which can explain estrogenic AEs despite moderate elevation of estrogens in the serum of subjects.

Adverse events of special interest

As previously mentioned, the assessment of the causality was not considered relevant. Indeed, local tolerance AEs such as application site discharge or vulvovaginal disorders have not been assessed as related despite the high reporting rate and difference with the placebo arm (15% vs 8.4%).

Similarly, a higher incidence was observed for the following AEs suggesting DHEA systemic exposure:

1/ estrogenic effects

Due to the transformation of DHEA into estrogens (including estradiol and estrone), the main concern is the potential risk of hormonal tumours development. During the clinical trials, the following AEs were pointed out because they were more frequently reported in the active treatment arm (6.5 mg DHEA) than in placebo:

- Cervical dysplasia (MedDRA term) from vaginal and Pap smears (40 cases (3.3%) in 6.5 mg DHEA vs 6 cases (1.3%) in placebo): According to the Applicant, Pap smear was performed at screening only in ERC-231/234/238 studies whereas Pap smear was performed both at screening and at the end of the long-term study ERC-230 (52 weeks). Additionally, in all studies, additional vaginal smears were performed at week 2, 6 and/or 12 to assess vaginal cell maturation index (efficacy parameter). Vaginal smears were collected at the second third of the lateral wall of the vagina. Of note, a vaginal smear does not allow to detect “cervical dysplasia” (MedDRA term) contrary to a Pap smear. In the 6.5 mg treated subjects group, 40 (3.3%) cases of “cervical dysplasia” (MedDRA term) have been reported. The cases of “cervical dysplasia” (MedDRA term) were mainly detected on vaginal smears (29 cases on 40) and not from Pap smears which is the gold standard method to screen cervix abnormalities (11 cases on 40). Overall, 7 subjects were detected with ASCUS on Pap smears at week 52 with a negative HPV status and the outcome of these subjects is unknown.
- Breast safety and endometrial safety were monitored during the long-term study (ERC-230) up to 12 months in 435 women.
    - Regarding breast safety, one case of high grade ductal carcinoma and one intraductal epithelial hyperplasia were reported. All subjects had normal findings at screening, therefore, the lesions appeared during prasterone treatment. Preclinical data showed an

effect of prasterone on ductal growth in female rats. Prasterone role cannot be excluded in the occurrence of breast cancer and breast hyperplasia.

  - Regarding endometrial safety, the 389 exploitable biopsies at week 52 did not reveal abnormalities. Women not eligible to the endometrial biopsy or unwilling to undergo biopsies, underwent a transvaginal ultrasonography (TVUS). Five women had a thickness measurement above 4 mm. The endometrial histology was normal in two cases; in 2 cases, subjects had taken HRT (known to induce endometrial thickness) before the TVUS and in one case, no information was available. Data on endometrial safety are lacking in 37 women who had neither an end-of-study biopsy nor a TVUS. The reasons were mainly the discontinuation of the study and loss of follow-up. No further information are available on these 37 women. However, Applicant fulfilled the EMEA requirements (Scientific advice 2009) with a total of 389 exploitable biopsies at week 52, and the results of these biopsies did not reveal abnormalities.

- One ovarian cancer occurred in a woman treated with 6.5 mg DHEA. This cancer was diagnosed after the 52 weeks of treatment. The subject had a BRCA1 mutation which is a risk factor in the occurrence of ovarian cancer. However, the role of prasterone and its metabolites cannot be categorically excluded.
- Cervical and uterine polyps, ovarian cysts, breast mass and breast tenderness were more frequent in the treated women than in placebo (overall incidence 1.4% vs 0.2%). In all cases the polyps/masses were non-malignant; this is reassuring. The incidence of these gynaecological findings is in line with the expected incidence in this age group. However it is still greater than the incidence in the placebo control group and their occurrence may be hormone dependent.
- Vaginal bleedings occurred during clinical trials with similar incidence between the 6.5 mg DHEA treated-women and the placebo group (1.6% vs 1.3%). The histology of the endometrium was benign in all cases. No safety issue was thus identified.

One pulmonary embolism has been reported in the 6.5 mg DHEA treated group (one case also reported in placebo arm).

Finally, regarding AEs possibly related to estrogenic effects, the main issue pointed out is the cervical safety for which uncertainties remain about the outcome of 14 subjects. Cervical or uterine polyps/mass were not malignant but the greater incidence observed in the treated subjects vs placebo is of concern and could be related to local estrogenic impregnation. Moreover, three cases of possible hormonal tumours development were reported (two in breast and one in ovary) and should be considered in the frame of the consequences of a long-term systemic and local exposure to DHEA and its metabolites.

2/ Androgenic effects

Due to the transformation of DHEA into androgens including testosterone, the occurrence of cardiovascular disorders or skin problems (such as acne, hypertrichosis) has to be monitored. Regarding the following TEAEs, the incidence was higher in treated subjects with 6.5 mg DHEA than in placebo:

- Hypertension was more frequently reported in treated subjects (17 cases, 1.42% vs 0.8%). Of note, 8/17 subjects had pre-existing hypertension and 10 subjects received anti-hypertensive drugs as corrective treatments. A role of prasterone and its metabolites cannot be excluded in the occurrence or worsening of hypertension. Androgens are known to induce increase in blood pressure. The level of androgens in treated subjects (6.5 mg DHEA) was significantly increased compared to placebo. Safety data are limited in women with hypertension > 140/90 mmHg since

it was an exclusion criteria. Therefore, it is not possible to exclude the role of prasterone in the occurrence of hypertension especially in women with a history of hypertension.

- Skin effects (acne, hypertrichosis) were more frequent in treated subject but the overall incidence remains low (acne: 1.25% vs 0.42% / hypertrichosis: 0.59% vs 0.42%) and no causal relationship can be drawn.
- Lipids profile was modified in treated women who experienced more hypercholesterolemia and blood cholesterol increase than in placebo. The lipids modifications observed and their incidence seem rather related to the women`s condition (age, comorbidities and medical history) than to prasterone administration.

Weight modifications (increase or decrease) were reported more frequently in treated subjects than in placebo with incidence of 2.5% vs 1.3% for weight increase and 2.6% vs 1.3% for weight decrease.

The safety profile, after a daily vaginal administration of prasterone, shows that there are AEs which could be the clinical manifestation of the significant increase (as compared to baseline levels) of DHEA and metabolites in serum of treated subjects.

Laboratory findings

DHEA and related steroids

One of the most important safety parameter in the development of this product is the evaluation of the systemic crossing of DHEA and its metabolites.

The applicant performed measurements of DHEA and its metabolites in serum (DHEA, Androst-5-ene-3β,17β-diol; Androstenedione; Testosterone; Dihydrotestosterone; Estrone; Estradiol; DHEA-sulfate; Estrone Sulfate; Androsterone Glucuronide; Androstan-3α, 17β-diol 17-glucuronide) in all studies at baseline and at the end-of study. The data presented included data from studies up to 16 weeks.

First, a comparison between post-baseline and baseline serum concentration mean was performed (using a t-test). Then a comparison between the serum values in the treated group (either 0.25% or 0.5% or 1.0% group) and the placebo group was done using an ANCOVA test.

Vaginal administration of DHEA increases serum androgens concentrations compared to baseline and to placebo as shown by the increase of the following metabolites [Androst-5-ene-3β, 17β-diol (5-diol), Androstenedione (4-dione), Testosterone (Testo), Dihydrotetosterone (DHT), DHEA Sulfate (DHEA-S), Androsterone Glucuronide (ADT-G) and Androstane-3α, 17β-diol 17-Glucuronide (17G)].

Estrogenic metabolites are also increased compared to baseline and placebo (to a lesser degree than androgenic metabolites) as shown by the increase of Estrone (E1) and Estrone-Sulfate (E1-S). Moreover, the more the DHEA concentration administered is high, the more the androgen metabolites serum concentrations increase as shown by pharmacokinetics. Therefore, contrary to the Applicant's claim, the CHMP is of the opinion that DHEA crosses the vagina and is retrieved in blood.

An increase in DHEA AUC_{0-24} (2.26 fold on Day 7 in ERC-213 study) was observed after vaginal administration of prasterone which reflects a systemic exposure. The applicant considers the variation of the serum concentrations of DHEA and metabolites as not clinically significant based on a comparison to usual concentration references.

At this stage, a significant increase of DHEA and metabolites has been observed. The clinical meaning of this increase could be manifested by the occurrence of AEs such as abnormal Pap smear (MedDRA term: cervical dysplasia), uterine/cervical polyps, or hypertension.

Other laboratory parameters (urinalysis, haematology and chemistry):

There was a statistically significant change from baseline in haematocrit in the group treated with 0.5% prasterone.

Regarding chemistry, haematology and urinalysis parameters no specific issue was identified.

Safety in special populations

No specific analysis was performed in specific populations. The monitoring of the male partners did not reveal safety issues. Of note, in clinical trials age ranges from 40 to 80 years. The analysis of the TEAEs according to the age did not reveal difference in Aes incidence.

Safety related to drug-drug interactions and other interactions

The potential of dehydroepiandrosterone to act as a direct inhibitor of human cytochrome P450 isoforms (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) was evaluated in vitro using pooled human liver microsomes. In addition, 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 co-incubation.

Co-incubation of DHEA did not affect the activities of 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), CYP2E1 (chlorzoxazone 6-hydroxylation), and CYP3A4 (midazolam 1'-hydroxylation, testosterone 6β-hydroxylation) up to the highest tested concentration (IC50 >10 μM).

Furthermore, preincubation (30 min.) of DHEA with NADPH-supplemented human liver microsomes did not affect testosterone 6β-hydroxylation activity (82% after preincubation vs. 80% after coincubation in the presence of 10 μM DHEA) and midazolam 1′-hydroxylation activity (93% after preincubation vs. 89% after co-incubation in the presence of 10 μM DHEA), giving no evidence for time dependent inhibition of CYP3A4.

In conclusion, drug-drug interactions through inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 by dehydroepiandrosterone (DHEA) are unlikely. It is agreed from the results that the possibility that prasterone could inhibit human cytochrome P450 isoforms (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) is unlikely. Therefore no particular interactions are expected.

No Aes related to drug-drug interactions were reported from the clinical studies. The Applicant considers that such Aes are not expected given the local action of DHEA. However, since the following medications were excluded in subjects during clinical trials (oral and local hormone replacement therapy, hormonal therapy, vaginal lubricant, cream and shower) the clinical consequences of their concomitant use with prasterone is not known. This is reflected in the *PI and RMP safety concerns.*

Discontinuation due to adverse events

Of the total of 220 subjects who discontinued the studies, 62 discontinued due to TEAEs representing 28% of all cases. Of these 62 subjects who discontinued from the studies due to TEAEs, 10 (16%) were in the placebo group, 11 (18%) were in the 0.25% DHEA group, 40 (65%) were in the 0.50% DHEA group and 1 (1.6%) was in the 1.0% DHEA group. A total of 14 subjects discontinued due to Serious TEAEs.

The frequencies of the preferred MedDRA terms for the most frequently recorded TEAEs showed no relevant differences between the treatment groups. The most commonly reported preferred terms for the TEAEs that led subjects to discontinuations were application site discharge (0.5% of subjects) and Human papilloma virus test positive (0.2% of subjects). Vulvovaginal disorders (such as burning sensation, discomfort, pruritus, and erythema) were also reasons for treatment discontinuation. No specific TEAE which led to discontinuation arose after 16 weeks of treatment compared to the first 16 weeks of treatment.

These Aes were not serious but were troublesome enough to lead to discontinuations.

Post marketing experience

In Japan, prasterone pessaries have been marketed for 18 years in labor induction indication. A formulation of prasterone, known as KB 60, was developed by Kanebo in Japan for labour induction. It is a vaginal suppository formulation of sodium prasterone sulphate (600 mg) and was launched in Japan as Mylis®. During the marketing period, adverse effects were reported (shock, respiratory depression). The withdrawal from the market was due to doubtful efficacy and serious adverse effects observed in the foetus (bradycardia or foetal distress and cases of death have been reported). The effects observed concerned foetal AEs in a specific indication (cervical ripening). Of note, this medicinal product contained a much higher prasterone strength than Intrarosa.

Vaginal prasterone was licensed for Europe to Innothera where it was in phase IIb trials in France, Italy, Germany and Spain. However, Innothera discontinued development of this drug.

2.6.1. Discussion on clinical safety

Clinical safety has been assessed on the results of the 6 clinical studies. Every clinical trial had recorded Aes. However, among the 6 studies, four are clinically interesting, because of the time of exposure, the dose and the number of subjects. ERC-231, ERC-234 and ERC-238 encompasses 609 women exposed up to week 12. The strength of these studies is the design of the study: double-blind, placebo-controlled and randomized allowing a relevant comparison of prasterone safety profile to a placebo group. These studies were initially performed to assess efficacy and the safety are only secondary endpoints. Long term use of prasterone pessary has been studied in ERC-230 study where 435 non hysterectomized women were exposed up to week 52. Despite the long duration of this study (52 weeks), it is open-label and does not allow a comparison to placebo after a long-term exposure. It cannot be regarded as a pivotal study. Globally, these clinical studies allow a safety evaluation but an important limitation is the absence of an active comparator in the design to compare the safety profile of prasterone pessary with local oestrogens.

Prasterone and its metabolites have androgenic and estrogenic effects. The exclusion criteria applied during clinical trials reduce the risk of occurrence of adverse events such as Thromboembolic disorders, history of cancers, cardiac failure and hypertension above 140/90 mmHg. Moreover, the target population as proposed by the applicant generally is expected to have risk factors excluded in the CT. Therefore the CHMP considered that the limited safety data in these specific populations, due to exclusion criteria, should be reflected in the product information (contraindications; precautions and warnings).

During Intrarosa clinical trials, 1542 women have been exposed to various doses of DHEA (from 3.25 to 13 mg) and 474 to the placebo. On the 1542 women, 1196 were exposed to the 6.5 mg. Therefore, more than 1500 subjects were exposed fulfilling the EMA guidance on population exposure requirements (CPMP/ICH/375/95). Regarding the long-term safety, 435 subjects completed the 52

weeks study. More than 300 biopsies were available and thus satisfying to CHMP guideline on clinical investigation of HRT products (EMEA/CHMP/021/97).

Regarding subject characteristics, women's mean age was 58.6 years with an average age of menopause of 46.7 years. Similar BMI were retrieved between groups but it was slightly high (26.4 kg/m²). Globally, demographic features are similar between placebo and the 6.5 mg treatment arm except for hysterectomized and ovariectomized women which is lower in 6.5 mg treatment group than in placebo (23.4% vs 41.6%). This discrepancy does not constitute a problem since pathological findings are more expected in non-hysterectomized women. However, the type of hysterectomy (partial with cervix preservation or total) was not mentioned.

A few TEAEs were assessed as drug-related by the investigator and concerned mainly local tolerance Aes. A higher incidence of such AEs has been observed in the 6.5 mg DHEA treatment group than in placebo (15% *vs* 8.4%). The most frequent AE assessed as drug-related was application site discharge which seems related (in the applicant opinion) to improved pH & estrogenic status of the vaginal cells in women treated in addition to the effect of liquid hard fat excipient. This explanation seems reasonable.

Similarly, the higher incidence of urinary tract infections is more related to contamination by fecal flora than to the use of applicator.

The TEAEs profile by age-class reveals that the safety profile is similar regardless of the age.

The intracrinology concept, as claimed by the Applicant, has not been demonstrated. During clinical trials, serum steroid concentrations were significantly increased (AUC and means C_{max}) meaning that prasterone and its metabolites cross the vagina and are retrieved in blood. Despite a statistically significant increase of androgen metabolites and estrone in serum (after a treatment of 6.5 mg of DHEA), this increase is considered to be in the range of expected concentrations for the population of post-menopausal women.

Among TEAEs which could be related to **estrogenic exposure**, the following were reported in clinical trials: Abnormal Pap and vaginal smears (MedDRA term: cervical dysplasia) (40), hormonal cancers such as ovarian (1) or breast (1) cancer, breast hyperplasia (1), cervical or uterine polyps (4) and pulmonary embolism (1).

The abnormal smears (MedDRA term: cervical dysplasia) were mainly detected on vaginal smears (performed for maturation index evaluation) and not from Pap smears which is the gold standard method to screen cervix abnormalities. In placebo-controlled studies, the incidence of abnormal vaginal smears (MedDRA term: cervical dysplasia), is higher in treated subjects (6.5 mg DHEA) than in placebo. In ERC-230 study (no placebo arm), follow-up information on 7 subjects with abnormal Pap smears at week 52 with a HPV negative status is lacking. There is thus still limited data about the consequences of a long-term use of Prasterone on cervical safety.

Regarding endometrial safety, no abnormal findings were detected after 52 weeks in the 389 exploitable biopsies available. Sixty-three (63) women, who completed the study or not, did not have results of end-of–study biopsy due to bad samples or ineligibility to biopsy or subject's reluctance. For these women, a TVUS to measure endometrial thickness was performed. On the 43 women who underwent TVUS, five had thickness > 4 mm and the endometrial histology was normal for 4 cases (unknown in 1 case). However, data are lacking for 37 women who did not have endometrial biopsy nor TVUS due to consent withdrawal or loss of follow-up. However, despite the absence of information in these 37 women, the EU requirement to provide more than 300 exploitable biopsies after 12 months is fulfilled.

A causal role of prasterone in one case of breast cancer, one case of ovarian cancer, and one case of breast hyperplasia cannot be excluded. At screening none of these subjects had abnormal or malignant findings except microcalcifications in both cases of breast cancer and breast hyperplasia. Events occurred one year after prasterone beginning thus time to onset is compatible. Moreover, pre-clinical data showed abnormal proliferation of mammary ductal cells in female rats after 12 months of skin exposure to high dose (30 mg) of prasterone. In the case of ovarian cancer, although the subject had a BRCA1 mutation which is a risk factor in the development of ovarian cancer, a role of prasterone cannot be excluded.

The histology performed in women with gynaecological findings (such as cervical or uterine polyps) were non-malignant. The incidence of these gynaecological findings is in line with the expected incidence in this age group. However it is still greater than the incidence in the placebo control group and their occurrence may be hormone dependent.

Regarding **androgen impregnation**, some AEs were slightly increased in 6.5 mg treated women compared to placebo: Acne (1.25% vs 0.42%) and hypertrichosis (0.59% vs 0.42%). Considering the low incidence and the weak difference between the incidences in treated subject and the placebo, no conclusions can be drawn.

Cardiovascular AEs analysis showed that hypertension was more frequently reported in treated subjects than in placebo (1.4% vs 0.8%). However, when taking into account the number of treatment-days, the incidence is similar between both groups (7.9 vs 6.6 / 100,000 subjects-days). Of note, the incidence provided by the Applicant is expressed by subjects/days and not subjects/years, the incidence is 3,000/100,000 subjects-years in the placebo group and 2,400/100,000 subjects-years in the 6.5 mg DHEA group. Of note, subjects with history of cardiac diseases or hypertension (140/90 mmHg) were excluded in both pivotal studies and ERC-230. Half of women who had hypertension during prasterone treatment had previous hypertension. More than half of the women received anti-hypertensive medicine as a corrective measure, which can explain the high recovery level in hypertensive women. In 6 cases, blood pressure above 140/90 mmHg was reported fulfilling the criteria of hypertension. The calculated incidence in the treated group is thus (6/1196 i.e., 0.5%). It is thus not possible to rule out prasterone in the occurrence of hypertension.

The lipid modifications reported during clinical trials concerned mainly obese and overweighed women and thus prasterone role can hardly be drawn. Analysis of psychiatric disorders did not reveal safety issues. Weight modifications occurred (increase or decrease in weight) without a specific trend. The incidence of weight fluctuations was more frequent in treated subjects.

Twenty-six serious cases were reported in the 6.5 mg prasterone group (2.2%) compared to 5 in the placebo group (1.1%). Most cases were related to surgical or procedures but not to prasterone use. Prasterone role cannot be excluded in 3 serious cases: one pulmonary embolism, one ovarian cancer and one breast carcinoma. No death was reported in clinical studies.

Similar incidence of discontinuation due to TEAEs was found for the 6.5 mg DHEA treatment arm and placebo (28% vs 23%). Application site discharge and vulvovaginal disorders (burning sensation, discomfort, etc.) were the most frequent reason for discontinuation.

TEAEs observed up to week 52 are globally the same than those observed at week 16. However, several serious AEs occurred during ERC-230 (52 weeks study) were not previously reported at week 16: hypertension, breast cancer, breast hyperplasia, ovarian cancer, cervical/uterine polyps.

Pharmacokinetics data provided by the applicant showed a systemic passage of prasterone, androgens and estrone (see PK section). A peripheral transformation of androgens into estrogens is possible (via aromatase in the adipose tissue, in breast *etc.*). The comparison to daily administration of Vagifem (estradiol vaginal tablets) showed similar estrogen levels in serum (indirect comparison with literature

data). However, the increase observed remains within the normal ranges observed for this population (post-menopausal women) according to several literature sources independent from the Applicant.

The clinical relevance of this systemic exposure could be manifested by the occurrence of androgenic-related AEs (hypertension) and of estrogenic-related problems (uterine and cervical polyps, abnormal Pap smear (MedDRA term: cervical dysplasia).

Remaining uncertainties persist regarding the occurrence of hormonal-dependant cancers.

These uncertainties regarding the long-term safety of vaginal prasterone administration have been reflected in the product information and the Risk management plan, especially regarding the population to be contraindicated and the warning and precautions which have to be taken (see PI).

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of prasterone is still uncertain.

Although the most frequent TEAEs were non serious and concerned local AEs such as vaginal discharge, a higher incidence of local AEs is observed in the treated group compared to placebo (15% *vs* 8.4%) suggesting a role of prasterone and not only a role of the pharmaceutical form (pessary).

Pharmacokinetics data confirmed the systemic exposure to DHEA and its androgenic and estrogenic metabolites. However, the concentrations observed after an administration of a daily dose of 6.5 mg prasterone (vaginally) remain within the normal ranges observed for the post-menopausal women. The hypothesis that prasterone has a local effect *via* intracrinology mechanism of action (as claimed by the applicant) is not supported. Contrary to what the applicant said (i.e. that the statistical difference in serum concentration has no clinical relevance since it is in the normal post-menopausal range), the systemic exposure observed could have a clinical relevance. Indeed, AEs suggesting an estrogenic exposure were observed in the DHEA group, mainly driven by frequent AEs such as abnormal Pap smears (MedDRA term: cervical dysplasia) and uterine/cervical polyps. Other serious AEs suggesting an estrogenic-like effect were reported, such as breast and ovarian cancers. AEs suggesting androgenic effect such as hypertension were observed in the DHEA group.

The broad exclusion criteria applied during clinical trials excluded women with cardiovascular disorders, previous history of cancers or gynaecological abnormal findings. Therefore, limited data on long-term safety of intravaginal administration of prasterone are available in the target-population. A Drug Utilisation study is planned to assess compliance with the mandatory contra-indications in the product information, i.e. to evaluate whether EU prescribers abide by the contraindications as stated in the EU SmPC.

An oral explanation was held at the CHMP meeting on 13 September 2017, where the applicant was given the opportunity to discuss the outstanding issues in view of addressing uncertainties in the long-term safety profile of Intrarosa, in summary:

- To reflect in the Intrarosa SmPC the information contained in the annex I to the Core SmPC for ‘oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains within the normal postmenopausal range’, along with the exclusion criteria applied during the clinical development.
- Regarding the RMP:
    - Inclusion of abnormal Pap smear (ASCUS) (MedDRA term: cervical dysplasia) as an important identified risk, and inclusion of development of oestrogen-dependent cancers such as ovarian cancer or breast cancer as an important potential risk. Revisions to the

proposed DUS synopsis (primary objectives, databases to be used, sample size and statistics description).

Further to the oral explanation, the applicant committed to comply with the CHMP requests and the uncertainties are thus managed by the product and the DUS which is planned.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Abnormal Pap smear (ASCUS)
Important potential risk	• Oestrogen-dependent cancers such as ovarian or breast cancer
Missing information	• Long-term use (after 12 months) • Use in women with active or past oestrogen-dependent malignant tumours (breast and endometrial cancer) • Use in women with gynecological findings (including uterine fibroids, abnormal Pap smear (ASCUS), untreated endometrial hyperplasia or undiagnosed genital bleeding) • Use in women with cardiovascular disease or uncontrolled hypertension (blood pressure above 140/90 mmHg) • Use in women with current or previous thromboembolic disease (either arterial or venous) • Women with a current hormonal treatment: hormone replacement therapy (e.g. oestrogen alone or combined with progestogens or androgen treatment).

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Drug utilization of Intrarosa (6.5 mg prasterone pessaries) in European Countries. Planned. Category 1 (Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation)	Among female subjects initiating Intrarosa: 1-Describe their baseline and historical characteristics such as age, indication (by ICD-10 code), history or current : oestrogen-dependent cancers such as ovarian or breast cancer, endometrial cancer, endometrial hyperplasia, abnormal Pap smear, deep venous thrombosis, pulmonary embolism, thrombophilic disorders, angina, myocardial infarction, acute liver disease, porphyria and indication for use. 2-Estimate the proportion of subjects that may have been prescribed Intrarosa outside of the specifications of the product label ('off-label use').	Important identified and potential risks as well as the missing information.	Protocol submission	Q1 2018

Risk minimisation measures

Safety concern	Risk minimisation measures	Additional risk minimisation measures
Abnormal Pap smear (ASCUS)	Routine risk communication: *SmPC section 4.4.* *PL section 2*	None proposed
Oestrogen-dependent cancers such as ovarian or breast cancer	Routine risk communication: *SmPC section 4.3 and 4.4.* *PL section 2*	None proposed
Long-term use (after 12 months)	Routine risk communication: *SmPC section 4.4.* *PL section 2*	None proposed
Use in women with active or past oestrogen-dependent malignant tumours (breast and endometrial cancer)	Routine risk minimisation measures: *SmPC section 4.3 and 4.4* *PL section 2*	None proposed
Use in women with gynecological findings (including uterine fibroids, abnormal Pap smear (ASCUS), untreated endometrial hyperplasia or undiagnosed genital bleeding)	Routine risk minimisation measures: *SmPC section 4.3 and 4.4* *PL section 2*	None proposed
Use in women with cardiovascular disease or uncontrolled hypertension (blood pressure above 140/90 mmHg)	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2*	None proposed
Use in women with	Routine risk minimisation measures:	None proposed

Safety concern	Risk minimisation measures	Additional risk minimisation measures
current or previous thromboembolic disease (either arterial or venous)	*SmPC section 4.4* *PL section 2*	
Women with a current hormonal treatment (e.g. oestrogen alone or combined with progestogens or androgen treatment)	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2*	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.6 is acceptable.

In addition, with regard to the Drug Utilisation Study (category 1 study in the RMP), the CHMP and PRAC considered that further clarifications about the **sample size** (proposal for a minimum number of subjects that would be needed to provide reliable estimate of on label/off label use) and the **data analysis plan** (submission of a separate data analysis plan including statistical methods and tables and clarification to which analyses are precluded to be performed in which countries, based on limitations in database availability or validity) should be discussed in the framework of the study protocol assessment after the granting of the Marketing Authorisation.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the lengthy frequency of the PSUR submission for the already existing entry for prasterone in the EURD list, the CHMP is of the opinion that a separate entry in the EURD list for Intrarosa is needed, as it cannot follow the already existing entry for prasterone. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 16.11.2016. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of prasterone with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers that prasterone is not a new active substance. Prasterone, is a constituent of three medicinal products previously authorised within the European Union (Biosteron, Stymen and DHEA Eljot). In addition, prastone enanthate, an ester of prasterone, is used as active substance in Gynodian Depot, which is registered in Europe.

As the proposed active substance is exactly the same as in other authorised medicinal products in the EU, it can be concluded that prasterone is not a NAS.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Intrarosa (prasterone) is included in the additional monitoring list as it has an imposed category 1 PASS at the time of authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Vulvar and vaginal atrophy (VVA) is a relatively common condition symptomatically affecting approximately 50% of postmenopausal women. It is the consequence of reduced estrogenization of urogenital and pelvic tissue that results in a loss of vaginal elasticity, dryness, decreased lubrication with associated irritation, dyspareunia and urinary symptoms.

Vulvovaginal atrophy can occur at any time in a woman's life cycle, although it is more common in the postmenopausal phase, a time of hypoestrogenism. Other causes of a hypoestrogenic state include lactation, various breast cancer treatments, and use of certain medications. In situations other than menopause, VVA may resolve spontaneously when estrogen levels are restored.

Numerous retrospective studies have evaluated the prevalence of symptoms of VVA. Although these studies differ in type of symptoms elicited, study design, and study population, they provide a range of estimates of VVA prevalence. They all used self-reported symptoms of vaginal dryness to determine the prevalence of VVA. In general, the prevalence ranged from about 4% in the early premenopausal groups to 47% in the late postmenopausal group.

The initial symptom is often lack of lubrication during intercourse. Eventually, persistent vaginal dryness may occur. Thinning of the epithelial lining may also cause pruritus, soreness, and a stinging pain in the vaginal and vulvar area, which, in turn, may further contribute to dyspareunia. Vaginal spotting, due to small tears in the vaginal epithelium, may also occur. Women with VVA may report a thin yellow or grey watery discharge secondary to the rise in pH that accompanies VVA.

3.1.2. Available therapies and unmet medical need

Non-hormonal treatment:

Current OTC treatments include non-hormonal vaginal moisturizers for VVA symptoms and lubricants for dyspareunia.

- Vaginal moisturizers are water based, available as liquids, gels, or pessaries inserted every few days. Vaginal moisturizers can be safely used long term, but they need to be used regularly for optimal effect.
- Vaginal lubricants are shorter acting than moisturizers and are applied at the time of sexual activity to reduce dyspareunia. They can be either water or silicone based, with the water-based products being the most widely available. They are applied to the vaginal opening and/or to the penis and often require repeated application during sexual activity. Silicone-based lubricants require application of only a very small amount and last longer. The choice of lubricant may depend on individual preferences and product availability.

Hormonal treatments:

Because the lack of circulating natural estrogens is the primary cause of atrophic vaginitis, the use of estrogen orally, transdermally or vaginally has been shown to be effective in improving symptoms and signs of VVA. Estrogen replacement restores normal pH levels and thickens and re vascularizes the epithelium. Adequate estrogen replacement therapy increases the number of superficial cells, may alleviate existing symptoms or even prevent development of urogenital symptoms if initiated at the time of menopause.

Although vaginal estrogens applied as a cream, vaginal tablets, or a low-dose vaginal ring are to some extent systemically absorbed, the rise in serum estrogen levels appears to remain well below premenopausal levels. Nonetheless, this may be of concern to women with a history of breast or other hormonally sensitive cancers

In addition, Senshio is a daily oral SERM (selective estrogen receptor modulator) recently approved in Europe in the treatment of moderate to severe symptomatic VVA in postmenopausal women who are not candidate to local estrogen therapy. Senshio is available on the market in some countries of the EU.

3.1.3. Main clinical studies

The clinical development of prasterone contains mainly two pivotal phase III studies ERC-231 and ERC-238, randomised, double-blind, placebo-controlled, conducted to assess efficacy of 6.5 mg of vaginal prasterone in postmenopausal women with VVA, who have dyspareunia as most bothersome symptom. In study ERC-231, 81/87/87 subjects were randomized respectively to placebo, prasterone 3.25 mg and prasterone 6.5 mg. In study ERC-238, 157/325 subjects were randomized respectively to placebo and prasterone 6.5 mg. Based on the exclusion criteria, several categories of populations were not exposed to prasterone during the development.

Prasterone was administered vaginally once a day for 12 weeks. The design of both studies was comparable, as well as population characteristics and treatment duration. There were 4 co-primary endpoints including change in vaginal maturation index (increase in % of superficial cells, decrease in % of parabasal cells), change in vaginal pH and improvement in dyspareunia. The selected efficacy endpoints are relevant as they combine PD parameters and clinical criterion. The clinical criterion (dyspareunia) was self-assessed using a severity score. Other criteria as vaginal dryness and improvement in quality of life were part of the secondary endpoints. No active comparator group was included in the clinical programme of prasterone. The design of the studies was adequate, though a weakness was the lack of an active comparator arm.

In addition, an open label safety study (ERC-230) was conducted during 52 weeks to assess the safety outcome of long term administration. Overall, 530 subjects were enrolled in this study.

An additional phase III efficacy and safety study (ERC-234) was conducted where two doses of prasterone were compared to placebo. However, the administration regimen was different from the claimed one and from the regimen used in the studies ERC-231 and ERC-238.

3.2. Favourable effects

The clinical efficacy of intravaginal DHEA (dehydroepiandrosterone, or prasterone) on the symptoms and signs of vulvovaginal atrophy (VVA) has been mainly evaluated in 2 pivotal clinical studies conducted in Canada and USA. Efficacy was assessed using co-primary endpoints consisting of three PD parameters (change on characteristics of cells in vaginal epithelium) and one clinical parameter (severity of pain at sexual intercourse, or vaginal dryness). The selection of these efficacy endpoints is in line with the US Guidance for Industry on assessment of products in vulvar and vaginal atrophy. No specific European guideline with regard to this indication is available.

From the clinical development, the extent of exposure to vaginal prasterone was in line with the ICH E1 guideline as “the total number of individuals treated with the investigational drug, including short-term exposure, was about 1500.”

Phase III efficacy studies ERC-231 and ERC-238 showed a statistically significant difference in response to all co-primary endpoints between the DHEA arms and the placebo arm. This difference was clear with regard to the three PD parameters (effect on % of parabasal and superficial cells of a vaginal smear, effect on vaginal pH) at the 12 week time-interval. Please refer to the effects table in section 3.6 for details on effect size for each parameter.

3.3. Uncertainties and limitations about favourable effects

- **Mechanism of action**: the hypothesis of “intracrinology” is proposed by the Applicant to explain the mechanism of action on VVA. This hypothesis suggests a conversion of DHEA to active metabolites inside the vagina cells and a local action on the different epithelium layers, followed

by negligible systemic absorption. However, data of serum levels shows an increase in DHEA and metabolites in subjects treated with prasterone. The length of this increase is unknown. In case of long-term use, clinical consequences of this exposure cannot be excluded.

- **The lack of active comparator**: No active comparator group (local oestrogens) was included in the clinical development. Prasterone was only compared to placebo. Absence of comparison to the gold standard is an additional efficacy uncertainty in the overall dossier.
- **Regarding the clinical endpoint (dyspareunia)**: the clinical relevance of the improvement on dyspareunia over the vehicle is modest. Decrease (versus baseline) in severity score of dyspareunia at week 12 for prasterone 6.5 mg and placebo respectively was -1.42 and -1.06 in study ERC-238, and -1.27 and -0.87 in study ERC-231. The effect observed following a local administration of a drug includes also the influence of the vehicle (liquefied hard fat excipient in the case of intravaginal DHEA) which can add to the effect of the drug itself. Data submitted by the Applicant (Responder analysis) show also an improvement in symptoms in the placebo group probably due to the fat component of the pessary. In other words, results of the pivotal studies ERC-231 and ERC-238 showed an improvement versus baseline in the clinical criterion (dyspareunia) in both the placebo and Prasterone groups. Although the length of improvement in the prasterone group was larger compared to the length of improvement with placebo, the clinical benefit of Intrarosa on dyspareunia is modest.
- **Absence of European population exposed to the product:** The clinical development of prasterone was performed in USA and Canada and European populations were not exposed to the drug. Although a recent international survey (Nappi and Kokot-Lierepa 2010) has shown that subjects from various European countries are not essentially different from those in the USA or Canada with regard to issues related to vaginal atrophy, given the cultural dimension of the questions related to menopause and to sexual activities, a different perception of the benefit in European women cannot be excluded.

3.4. Unfavourable effects

Safety data were collected during the 6 clinical trials performed. Regarding the duration of exposure, four studies had a 12 weeks design and one study concerned a long-term treatment of 52 weeks.

Application site discharge was the most frequently ADR reported (8.7% DHEA and 3.4 % placebo). It was also the main reason for treatment discontinuation in 6.5 mg DHEA group. This ADRs could be the consequence of increased physiological discharge due to the improved pH following Prasterone administration.

Uterine or cervical polyps (benign) have been reported more frequently in treated subjects but with a low frequency. **Breast mass (benign) / breast tenderness** were also reported (0.7% vs 0.2%). Considering the higher frequency and the increased serum concentration of DHEA and its metabolites (including estrone) the causal relationship is at least a reasonable possibility.

Abnormal smears (MedDRA term: Cervical dysplasia) detected by vaginal smears were more frequently reported in subjects exposed to DHEA 6.5 mg than in placebo. Considering only the cases diagnosed by Pap smears (gold standard method to screen cervix abnormalities) in the open-label ERC-230 study with no placebo arm, 7 cases are of special interest. The frequency reaches 1.6% (7/435 women exposed up to 52 weeks). In these subjects, the HPV status is negative. The abnormalities are all classified as ASCUS (Atypia of squamous cells of undetermined significance) and were detected at W52. No follow-up were available for these subjects (no additional Pap smears nor colposcopy). The outcome of these subjects is unknown. Cervical abnormalities were exclusion criteria

during clinical trials and all subjects had normal Pap smear at screening before the start of the studies. Therefore the abnormalities occurred during Intrarosa treatment. The causal relationship is at least a reasonable possibility.

Hypertension was more frequently reported in treated subjects (17 cases, 1.42% vs 0.8%). However, when the incidence is calculated on the number of treatment-days basis, the incidence is similar between both groups. Six subjects fulfil the definition of hypertension (i.e., >140/90 mmHg) in the treated group. 8/17 subjects had pre-existing hypertension and 10 subjects received anti-hypertensive drugs as corrective treatments. Prasterone and its metabolites role cannot be excluded in the occurrence or worsening of hypertension. Androgens are known to induce increase in blood pressure. The level of androgens in treated subjects (6.5 mg DHEA) was significantly increased compared to placebo. Safety data are limited in women with hypertension > 140/90 mmHg since it was an exclusion criteria. Therefore, it is not possible to exclude the role of prasterone in the occurrence of hypertension especially in women with a history of hypertension.

Weight increase or decrease were reported more frequently in the subjects treated with DHEA 6.5 mg than in placebo (respectively 2.5% vs 1.3% and respectively 2.6% vs 1.3%). Weight may be modified by hormonal fluctuations and given the increase of DHEA and its metabolites in serum of treated subjects, the causal relationship is at least a reasonable possibility.

No death was reported from the phase III studies.

3.5. Uncertainties and limitations about unfavourable effects

Several uncertainties remain with regard to the safety profile of prasterone:

- **Serious AEs suggesting estrogenic effects** were observed in the 6.5 mg prasterone group and none in placebo: breast cancer (1), breast hyperplasia (1), ovarian cancer (1). These AEs were detected at week 52 in the long-term safety study (ERC-230; no placebo arm). Of note, PK data showed significant increase in androgens and estrone serum concentrations after vaginal administration of prasterone 6.5 mg. This increase remains within the normal ranges observed for this population (post-menopausal women). It cannot be excluded that the systemic exposure after treatment with prasterone may induce a malignant cell proliferation or a worsening of a pre-existing hormonal tumour. Moreover, for breast cancer, a preclinical study on female rates showed abnormal mammary ductal growth which is close from the clinical findings (intraductal epithelial hyperplasia and high grade ductal carcinoma).

- **The outcome of cervical safety** remains unknown; overall, in placebo-controlled studies, frequency of abnormal vaginal smears (MedDRA term: cervical dysplasia) was more elevated in women exposed to DHEA (6.5 mg) than in placebo and a role of Prasterone in the occurrence of these AEs is considered possible. However, the long-term consequences of such findings is still unknown. In the open-label ERC-230 study (no placebo arm), the outcome of 7 subjects with results of ASCUS or LGSIL (on Pap smears) is not available because no follow-ups were performed after the end of the study. This concern is important given the possible long-term use and the risk of cervical cancer.

- **The exclusion criteria** applied in the clinical development were large as subjects with risk factors such as cardiac disorders, gynaecological findings (polyps, cervical abnormalities, and genital bleedings) or hormonal cancers were excluded. In the “real life”, postmenopausal women to be treated for VVA are likely to have such co morbidities.

- **No active comparator group was included in the clinical development (local estrogens)**. Only indirect comparison (of limited reliability) with local estrogens is provided with no clinical safety data. Considering the safety results from the clinical development (see above) and the PK data

showing a systemic exposure, there are no reasons to expect a better safety pattern with prasterone than local estrogens, in particular with long-term use.

3.6. Effects Table

Table 18: Effects Table for Prasterone in the treatment of vaginal atrophy.

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Decrease vs baseline in parabasal cells	Observation at 12 weeks on vaginal smear using a 100-cell count method	Change in %	3.25 mg: -37.29 6.5 mg: -47.40	Placebo: -1.62	Clear effect of DHEA doses on PD parameters	Study ERC-231
Increase vs baseline in superficial cells	Observation at 12 weeks on vaginal smear using a 100-cell count method	Change in %	3.25 mg: +4.75 6.5 mg: +5.62	Placebo: +0.91	Clear effect of DHEA on PD parameters	Study ERC-231
Decrease vs baseline in vaginal pH	Measured at 12 weeks at vaginal level	pH decrease	3.25 mg: -0.77 6.5 mg: -1.04	Placebo: -0.21	Clear effect of DHEA on PD parameters	Study ERC-231
Decrease vs baseline in severity score of dyspareunia (clinical symptom)	Self-assessed at 12 weeks using a questionnaire	Decrease in total score (out of 3 points)	3.25 mg: -1.01 6.5 mg: -1.27	Placebo: -0.87	There is a placebo effect on the clinical symptom likely related to the excipients (lubricant-like effect).	Study ERC-231
Decrease vs baseline in parabasal cells	Observation at 12 weeks on vaginal smear using a 100-cell count method	Change in %	6.5 mg: -41.51	Placebo: -11.98	Clear effect of DHEA on PD parameters	Study ERC-238
Increase vs baseline in superficial cells	Observation at 12 weeks on vaginal smear using a 100-cell count method	Change in %	6.5 mg: +10.20	Placebo: +1.75	Clear effect of DHEA on PD parameters	Study ERC-238
Decrease vs baseline in vaginal pH	Measured at 12 weeks at vaginal level	pH decrease	6.5 mg: -0.94	Placebo: -0.27	Clear effect of DHEA on PD parameters	Study ERC-238
Decrease vs baseline in severity score of dyspareunia (clinical symptom)	Self-assessed at 12 weeks using a questionnaire	Decrease in total score (out of 3 points	6.5 mg: -1.42	Placebo: -1.06	There is a placebo effect on the clinical symptom likely related to the excipients (lubricant-like effect). The difference with the DHEA effect is 0.35 point in the severity score. The clinical relevance of this effect over placebo is questioned.	Study ERC-238
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Application site discharge	AEs related to vaginal tolerance reported during clinical trials	%	10.9	1.3	A higher incidence of local AEs is observed in treated group than in placebo. Discharges probably due to the pH changes induced by the treatment.	ISS
Hormonal cancers	Ovarian cancer Breast cancer Breast hyperplasia	Number of case	1 ovarian cancer 1 breast carcinoma 1 breast hyperplasia	NA (No placebo arm in this study)	All subjects with normal findings at screening, thus the cancers developed during prasterone treatment and diagnosed at week 52. Ductal growth observed in preclinical data.	ERC-230 (long –term, open-label study)
Abnormal Pap smear (MedDRA term: cervical dysplasia)	ASCUS and LGSIL found during clinical trial	%	7 ASCUS detected by Pap smears at week 52 in subjects with negative HPV status	NA (No placebo arm in this study)	Abnormal Pap smears (MedDRA term: cervical dysplasia) detected by Pap smears. No follow-up available after the end of the study. Cervical safety data at long-term are limited.	ERC-230 (long-term, open-label study)
Gynecological findings	Cervical and uterine polyps Breast mass and breast tenderness	%	1.4%	0.2%	Since DHEA and estrone metabolite are increased in treated women such findings could be expected.	ISS
Hypertension	AE related to androgens impregnation	%	1.5% 6.6/100,000 Pers-Days	0.8% 7.9/ 100,000 Pers-day	Androgens metabolites are increased in treated subjects and androgens are known to induce cardiovascular disorders. Prasterone role cannot be excluded in the occurrence or worsening of hypertension.	ISS
Weight fluctuation	AEs related to hormonal exposure	%	Weight increase (2.5%) Weight decrease (2.6%)	Weight increase (1.3%) Weight decrease (1.3%)	Androgens metabolites are increased in treated subjects and androgens and estrogens are known to induce metabolism disorders. No details on these cases available.	ISS

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The claimed indication of prasterone is the “treatment of VVA in postmenopausal women”. VVA is a non-life threatening condition, relatively common symptomatically, affecting approximately 50% of postmenopausal women.

Alternative treatments include non-hormonal OTC products (vaginal moisturizers for VVA symptoms and lubricants for dyspareunia) and hormonal drugs, as HRT or local estrogens.

No European population was exposed to the treatment.

From prasterone clinical development, a placebo effect was observed on the clinical parameter. The proper clinical benefit of Intrarosa is therefore modest.

The safety pattern observed from the clinical development shows AEs suggesting androgenic (hypertension) and estrogenic effects (uterine and cervical polyps, abnormal Pap smear (MedDRA term: cervical dysplasia)). These adverse events observed are likely to be the clinical result of the increase in DHEA and metabolites serum levels - observed from PK data - after intravaginal administration.

In the placebo-controlled studies, the incidence of abnormal vaginal smears (MedDRA term: cervical dysplasia) is higher in the subjects exposed to Prasterone 6.5 mg than in placebo and the causal relationship is considered at least possible. However, the long-term consequences of the abnormalities detected on Pap smears (ASCUS or LGSIL) in the long-term study ERC-230 (no placebo arm) is unknown since no follow-ups are available.

Also, 1 case of breast cancer, 1 case of breast hyperplasia and 1 case of ovarian cancer were observed with prasterone. Although strict causal relationship cannot be confirmed, we cannot exclude the role of (increased) hormonal serum levels in the occurrence of such hormonal dependant cancers.

Of note, given the treated condition (VVA in postmenopausal women), a long-term use is expected. Also, exclusion criteria were large and women with risk factors with regard to androgenic effects (CV disorders) and estrogenic effects (hormone dependant disorders) were excluded. Moreover safety in women treated with Intrarosa and other hormonal treatments such as androgens, estrogens or progestins is not known since such concomitant treatments were excluded in clinical trials. Exposure of these populations in case of approval cannot be excluded.

Thus, long-term use of prasterone in the target population (post-menopausal women with VVA) has unknown consequences especially regarding the hormonal dependant cancers.

3.7.2. Balance of benefits and risks

For a long term treatment of non-life-threatening disease, a strong benefit/risk balance would have been expected, including an important effect on vaginal symptoms and a reassuring safety pattern.

Efficacy demonstrated for prasterone is modest. A statistically significant difference in response to all co-primary endpoints has been shown between the DHEA arms and the placebo arm in the main efficacy studies (ERC-231 and ERC-238). The difference at the 12 week time-interval was clear for the three pharmacodynamic parameters (effect on % of parabasal and superficial cells of a vaginal smear, effect on vaginal pH); it was more modest for the clinical parameter (improvement in dyspareunia), as in particular for dyspareunia a placebo-effect was observed.

Regarding safety, application site discharge was the most frequently observed adverse event with higher incidence with Intrarosa versus placebo. Other AEs related to estrogenic and androgenic exposure (abnormal Pap smears (MedDRA term: cervical dysplasia), uterine and cervical polyps, HT) were more reported with Intrarosa, although their frequencies were limited. The causality between these AEs and Intrarosa is considered at least possible. Therefore, abnormal Pap smears (ASCUS) (MedDRA term: cervical dysplasia) constitutes a safety concern which warrants inclusion in the safety specification of the RMP as an important identified risk.

Rare cases of breast and ovarian cancers were reported with Intrarosa during the clinical trial programme. None of these cases were reported with the placebo group, although there was no placebo arm in the long-term study ERC-230. No firm conclusion can be drawn given the limited number of

cases; however breast and ovarian cancers constitute a potential safety concern which warrants inclusion in the safety specification of the RMP as an important potential risk.

In order to address limitations around the benefit-risk, additional warnings and contraindications in the product information were implemented and a Drug Utilisation Study (DUS) was imposed as a category 1 study (condition to the MA). The main objective of this DUS is to assess compliance with the contra-indications in the product information, i.e. to evaluate whether EU prescribers abide by the contraindications as stated in the EU SmPC. The results of this DUS are considered relevant and key to the B/R balance of the product in its actual use (real-life situation).

In conclusion, the benefit-risk of Intrarosa is considered positive based on modest clinical efficacy and an acceptable safety profile.

3.8. Conclusions

The overall B/R of Intrarosa for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Intrarosa is favourable in the following indication:

Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
Non-interventional PASS - Drug Utilisation Study (DUS) to describe the baseline characteristics, utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC.	Final study report by Q4 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

The CHMP, based on the available data, considers that prasterone is not a new active substance. Prasterone, is a constituent of three medicinal products previously authorised within the European Union (Biosteron, Stymen and DHEA Eljot).

In addition, prastone enanthate, an ester of prasterone, is used as active substance in Gynodian Depot, which is registered in Europe.

As the proposed active substance is exactly the same as in other authorised medicinal products in the EU, it can be concluded that prasterone is not a NAS.