Study Title: Comparison of Vaginal Dehydroepiandrosterone (DHEA) to Control for Treatment of Vaginal Symptoms in Postmenopausal Breast Cancer Survivors on Aromatase Inhibitors: A Phase II Randomized Trial

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Abbreviations

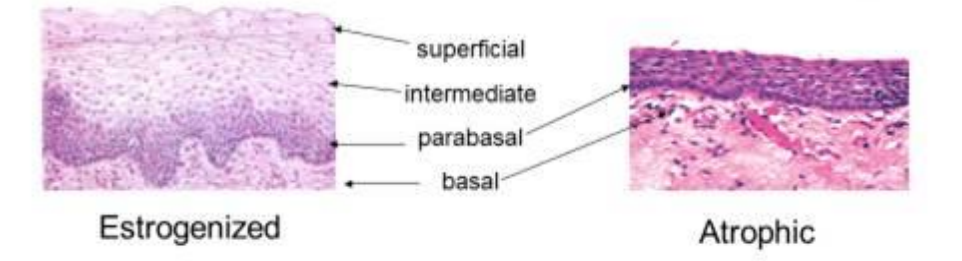
AE	Adverse Event
AI	Aromatase Inhibitors
AIS	Adenocarcinoma *in situ*
APR	Annual Progress Report
AR-AERS	AR-Adverse Events Reporting System
BSSC-W	Brief Sexual Symptom Checklist for Women
CFR	Code of Federal Regulations
CI	Confidence Interval
CIN	Cervical Intra-Epithelial Neoplasia
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DHEA	Dehydroepiandrosterone
F	Fahrenheit
FDA	Food and Drug Administration
FSFI	Female Sexual Function Index
FSH	Follicle-stimulating hormone
g	gram
HER2	Human Epidermal Growth Factor Receptor 2
HSIL	High Grade Squamous Intraepithelial Lesion
I	Intermediate
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IRB	Institutional Review Board
IU/L	International Units per Liter
mg	milligram
mL	milliliter
mm	millimeter
MAR	Missing at Random
MCAR	Missing Completely at Random
MNAR	Missing Not at Random
NCI	National Cancer Institute
ORRA	Office of Research Regulatory Affairs
P	Parabasal
QOL-CSV	Quality of Life-Cancer Survivor Version
RPRS	Research Participant Registry System
S	Superficial
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	Standard Error of the Mean
UAMS	University of Arkansas for Medical Sciences
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
VMI	Vaginal Maturation Index

Background and Rationale

Aromatase inhibitors (AI) are the preferred adjuvant treatment for postmenopausal females with hormone receptor-positive breast cancer for a duration of five to ten years to reduce the risk of recurrence and death, but rates of poor adherence and early discontinuation of AI therapy are high due to side effects [1]. Genitourinary symptoms, which arise from estrogen deprivation, are especially prevalent. In one study of females on AI, 74% reported insufficient lubrication and 56% reported dyspareunia [2]. Treatment with estrogen is the most efficacious treatment in the general population, but systemic estrogen therapy is contraindicated in patients with hormone receptor-positive breast cancer. Additionally, patients with breast cancer and their clinicians are reluctant to use vaginal estrogen [3], despite data that low dose vaginal estradiol can significantly improve symptoms and does not raise serum estradiol levels above the menopausal range [4]. Treatment of vaginal symptoms has been limited to vaginal moisturizers and lifestyle modification, providing only marginal improvements. More recently, vaginal dehydroepiandrosterone (DHEA, prasterone, Intrarosa®) was FDA approved to treat moderate to severe dyspareunia, which is a symptom of vulvar and vaginal atrophy due to menopause. Vaginal DHEA allows intracellular production of estrogen and testosterone in genital tissues with relatively little systemic effect [5]. Serum concentrations of metabolites of both estrogens and androgens remain within the normal postmenopausal range following daily intravaginal administration of 6.5mg prasterone at 12, 26 and 52 weeks of use. [6] Barton et al. demonstrated no effect on serum estrogen concentrations when it was used in females with breast cancer on AI [7]. Prior studies have demonstrated clinically and statistically significant improvement of patient-reported vulvovaginal atrophy symptoms and dyspareunia, which correlated with findings of decreased vaginal pH and improvement in the vaginal maturation index (VMI) after treatment with vaginal DHEA [8].

The VMI and vaginal pH have been well studied as indicators of the degree of vaginal atrophy, which is the end result of treatment with AI that leads to vaginal dryness and dyspareunia. VMI is the proportional relationship of parabasal (P) cells to intermediate (I) and superficial (S) cells in the vaginal epithelium (see Figure 1 below). A normal premenopausal vaginal mucosa is dominated by S cells, which makes it thicker. The VMI is a clinical measure of vaginal estrogenization derived from the maturation index. VMI = 1.0 x %S + 0.5 x %I + 0.0 x %P cells, which is the same as VMI = %S + (0.5 x %I) when simplified, with a potential range of 0-100. A VMI of 65-100 suggests a normal premenopausal environment, 50-64 indicates a moderate estrogenic effect, and < 50 indicates atrophy [9]. As the vaginal epithelium becomes thinner and more atrophic, the mucosa has less glycogen content and less lactobacilli to convert the glycogen into lactic acid, which results in an increase in the vaginal pH. A normal healthy vaginal pH is 4.5 [9].

Figure 1: Estrogenized Vaginal Epithelium vs Atrophic Vaginal Epithelium



The VMI will be used as an objective physiologic marker to determine the improvement in vaginal atrophy, which is the end result of treatment with AI that leads to vaginal dryness and dyspareunia. The more estrogen that the vaginal epithelium receives, the thicker it becomes, resulting in increased presence of I and S cells. Since VMI is a weighted sum of the percentage of I and S cells, a higher VMI suggests a healthier vaginal epithelium.

Significantly atrophied vaginal tissue has a higher percentage of P cells, a reduced percentage of I+S cells on the VMI, and an increase in pH compared to normal pre-menopausal vaginal tissue. The VMI is determined from the percentages of P, I, and S cells in vaginal scrapings and provides an approximate idea about status of vaginal walls. The approximate percentages of the P, I, and S cells in premenopausal and postmenopausal females are provided in Table 1 below.

Table 1. *Percentages of P, I, and S cells in Premenopausal and Postmenopausal Females*

Components of VMI	Premenopausal (%)	Postmenopausal (%)
Parabasal (P) cells	5-10	70-75
Intermediate (I) cells	40	25
Superficial (S) cells	50-55	< 5

Breast cancer survivors are living longer and quality of life, including sexual health, is important. Females with estrogen deficiencies may suffer from vaginal dryness and atrophy that negatively impact sexual health. Chemoprevention treatment with AIs blocks estrogen production and compounds the problem. Vaginal DHEA, a non-estrogen product, is known to improve vaginal atrophy and sexual health. This study will evaluate the use of vaginal DHEA in breast cancer survivors on AIs.

Objectives and Rationale

The primary objective is to determine change in vaginal atrophy as assessed by the VMI after 12 weeks (±1 week) of treatment with vaginal DHEA 6.5 mg inserted nightly (Intrarosa®) when compared to a prefilled applicator of a polycarbophil vaginal moisturizing gel (6.7 g) (Replens™), into the vagina two times per week at night.

The secondary objectives are to 1) determine change in vaginal pH 2) determine improvement of vaginal symptoms and sexual function as assessed by the Brief Sexual Symptom Checklist for Women (BSSC-W) and the Female Sexual Function Index (FSFI) [10-11] and 3) determine improvement in quality of life using the Quality of Life - Cancer Survivor Version (QOL-CSV) [12] after 12 weeks (±1 week) of treatment with vaginal DHEA (Intrarosa®) when compared to polycarbophil vaginal moisturizer (Replens™) in breast cancer survivors on AI, and to compare side effects in each group that may impact patient acceptability.

It is hypothesized that the Intrarosa® arm will exhibit greater improvement in the VMI and decrease in vaginal pH when compared to Replens™ after 12 weeks (±1 week) of treatment. It is also hypothesized that the Intrarosa® arm will have improvement in vaginal and sexual symptoms as indicated by the validated symptom inventories to be administered both pre and post study period.

Of note, the BSSC-W, the FSFI, and the QOL-CSV have all been validated for use in a study population such as this one [10-12].

Study Population

Subjects will be postmenopausal breast cancer survivors, stage I-III, hormone receptor positive breast cancer (ER+, PR+) regardless of human epidermal growth factor receptor 2 (HER2) status, ages 18 to 70 years old, on AIs identified at UAMS Cancer Institute and Women's Health clinics and at CARTI Cancer Center. Up to 120 subjects will be screened for a total of 60 subjects enrolled, 30 in each arm of the study. See Appendix B.

Eligibility Criteria

Inclusion Criteria

- Females, ages 18-70
- Postmenopausal patients with a history of breast cancer who have completed primary treatment with curative intent and currently are on an AI and have been for at least 6 months
- Ductal carcinoma in situ (DCIS) or Stage I-III, hormone receptor-positive breast cancer regardless of HER2 status
- Postmenopause defined as ≥ 12 months spontaneous amenorrhea, ≥ 6 months spontaneous amenorrhea with serum FSH levels > 40 mIU/mL, or ≥ 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy. FSH level will be documented on all subjects.
- Reported dissatisfaction with sexual function on Question 1 of the BSSC-W No planned changes in AI during the study period
- Mammogram within the 12 months prior to study entry (if appropriate, as determined by the treating physician)
- Normal Pap within the 12 months prior to study entry (i.e., negative Pap results consistent with American Cancer Society (ACS) guidelines). Females whose cervix has been removed by surgery for reasons not related to cervical cancer or serious cervical pre-cancer [e.g., CIN 2 or 3 (HSIL, moderate or severe dysplasia) or AIS] may be excluded from this requirement.

Exclusion Criteria

- Use of any estrogen or progesterone depot-preparation drug or progestin implant in the last 6 months before study entry.
- Use of any androgen or anabolic steroids in the last 6 months before study entry.
- Use of any oral or transdermal hormonal products (estrogen, progestin, or DHEA) within the last 8 weeks prior to study entry; however, a subject can elect to wait for an 8-week washout period before study entry.
- Use of any vaginal or intrauterine hormonal products in the last 8 weeks; however, a subject can elect to wait for an 8-week washout before study entry.
- Use of any natural over-the-counter estrogenic products in the last 6 months; however, a subject can elect to wait for a 6-month washout before study entry.
- Concomitant vulvar and vaginal surgical or laser treatments
- Vaginal infection or confounding vulvar or active vaginal disease process
- Active malignant breast or gynecologic disease
- History of prior radiation to the pelvis or prior gynecologic cancer or pre-cancer
- Inability to tolerate a vaginal/speculum exam
- Undiagnosed, persistent or recurring genital bleeding or other indication of active pelvic disease process that has not been evaluated to determine the cause [6]
- Clinically significant uncontrolled depression or severe psychiatric symptoms
- If subject has an established routine of inert vaginal lubricant use for routine or occasional relief of vulvar or vaginal symptoms prior to the study period, it may be continued during the

study period along with the study drug.

Study Design and Procedures

This will be a two-armed, randomized, open-label Phase II trial. All study subjects will be asked to fill out the simple 5-question BSSC-W. If any concern about sexual functioning is noted with the BSSC-W question 1 as a no answer to “are you satisfied with sexual function”, the subject will also be asked to fill out the more extensive FSFI tool, to help determine which domain of sexual functioning is the most bothersome. Questions 7-10 on FSFI specifically assess degree of vaginal dryness while questions 17-19 assess pain with sex, which are both commonly associated with vaginal atrophy. Subjects who indicate that they are satisfied with their sexual function on BSSC-W in question 1 will be deemed ineligible for the study and will not complete the FSFI. All questionnaires will be administered in paper format.

Potential research subjects will be identified in the UAMS Cancer Institute and UAMS Women’s Health clinics (e.g. Women’s Cancer and Cancer Survivorship clinics, and Gynecology/Fertility clinics, etc.) and from the CARTI Cancer Center, during routine clinic appointments by the provider or research staff. For potential subjects being seen in the UAMS clinics, the study team will review daily clinic schedules to assess for possibly eligible subjects. If an individual is found, a request to the clinical team will be made to allow access to the patient to discuss the study. Potential research subjects may also contact the UAMS Cancer Institute’s Clinical Trials Office regarding participation based on the information found within the IRB-approved DHEA flyer that is to be distributed amongst UAMS and the CARTI medical clinics. No individual at CARTI will be involved with the recruitment, consenting, or treatment process; however, clinicians at CARTI whose patients may qualify for the research may inform the potential subjects of the study and refer them to the UAMS study team for more information. Interested research subjects who are referred to UAMS will subsequently interact with the UAMS study team for study treatment and consent. Postmenopausal patients on AIs, ages 18 to 70, who have had stage I-III, hormone receptor-positive breast cancer (ER+, PR+) regardless of HER2 status will be invited to enroll in the study after they have completed all adjuvant chemotherapy, radiation therapy and HER2-targeted therapy. All potential subjects will be referred to the UAMS Cancer Institute for consent and study treatment. Patients should have been on at least six months of an AI after the completion of all their adjuvant therapies before enrollment. Prior to any research activities, the research subject will provide informed consent.

Potential research subjects have the ability to review the informed consent and DHEA flyer through MyChart prior to any clinic visit. The flyer provides a description of the program and its processes in layman’s terms. These items are intended to augment the consenting process and provide a useful tool for the consenter and consentee to communicate. The potential subject will also have the option within MyChart to indicate whether they are interested in consenting to the study prior to their visit. The Arkansas Clinical Data Repository (AR-CDR) will be utilized to find and recruit subjects who may meet eligibility criteria. Information requested from AR-CDR will be a list of female patients between the ages of 18 and 70 years old with a history of breast cancer who are currently on an aromatase inhibitor and have been for at least 6 months. Patients who fit these criteria will be contacted via email, phone, or patient portal and asked if they are interested in learning more about the study. If they are, a study staff member may contact the patient via email, phone or patient portal to discuss further. If a patient prefers to not be contacted, they can opt out of further communications by responding via email, phone or patient portal to notify the research team.

Females of childbearing age and potential must have negative pregnancy test at screening. Subjects who are post-menopausal (as defined in the inclusion criteria) will not require a

pregnancy test.

At baseline, subjects will undergo a physical exam including clinical breast and gynecological exam. During gynecologic exams, the vaginal pH will be determined and a swab of vaginal epithelium will be sent to pathology to calculate the VMI. These will be used as objective physiologic markers to determine the improvement in vaginal atrophy. The cytologists reading the specimens will be blinded. If the VMI results are "unsatisfactory", the swab of vaginal epithelium will need to be recollected within 4 weeks of Day 1, Week 1 to calculate a new VMI.

Additionally, at baseline, all study subjects will be asked to fill out the BSSC-W, QOL-CSV, and DHEA Trial Supplemental Clinical Survey. FSFI will also be completed at baseline by all subjects who indicate sexual complaints on Question 1 of the BSSC-W at baseline; any consented individuals who do not indicate sexual complaints on Question 1 of the BSSC-W at baseline will be considered a screen fail and will not complete the FSFI or continue in the study. Questionnaires will be administered in paper format. Subjects will be instructed not to use vaginal products other than water-based lubricants during intercourse throughout the duration of the study period. Subjects will be given a paper diary to record the dates and approximate times the treatment was used. Subjects will be advised to complete this at home. These diaries will be used to track compliance with study treatment. All adverse events (AEs) will be analyzed, tabulated and organized by organ-system and included in the primary analysis.

At 1 week (±3 days) from Day 1, Week 1, subjects will be followed up with via phone call to ensure study drug was received, emphasize study compliance with study treatment, remind subjects to correctly complete diary entries, and assess any changes in the subject's health.

At 6 weeks (±1 week) from Day 1, Week 1, subjects will be followed up with via phone call to emphasize study compliance with study treatment, remind subjects to correctly complete diary entries, and assess any changes in the subject's health.

Both follow-ups (1 week and 6 week) will be recorded/documented in eMR.

At 12 weeks (±1 week), from Day 1, Week 1, subjects will undergo a physical exam including clinical breast and gynecological exam. During gynecologic exams, the vaginal pH will be determined and a swab of vaginal epithelium sent to pathology to calculate the VMI. These will be used as objective physiologic markers to determine the improvement in vaginal atrophy. The cytologist's reading the specimens will be blinded.

Additionally, at 12 weeks (±1 week) from Day 1, Week 1, all study subjects will be asked to fill out the BSSC-W, QOL-CSV, and FSFI. Questionnaires will be administered in paper format. Diaries will be collected at the completion of study treatment, 12 weeks (±1 week) from Day 1, Week 1, or if treatment is not completed per protocol, when treatment is stopped.

All AEs will be analyzed, tabulated and organized by organ-system based on NCI CTCAE v5 and included in the primary analysis.

Diary progress should be submitted after Week 4 (±1 week), Week 8 (±1 week), and Week 12 (±1 week) of treatment. Diaries can be submitted in person, via self-addressed envelope to the cancer clinical trials office, text photos to the research nurse cellphone, email photos to the research nurse email, sent photos through MyChart, or faxed to the cancer clinical trials office. There will be no deviation for subjects who do not submit diary progress at Week 4 or Week 8. There will be a deviation for subjects who do not submit diary progress at Week 12 (or by the end of study

participation, if they end treatment early).

Compensation is available to subjects upon submission of diaries and completion of study-related activities. The first payment of $25 will be made to the subject upon submission of diary at Week 4 and completion of the Week 6 phone call. The second payment of $50 will be made to the subject upon completion of the Week 12 visit, which includes clinic attendance for physical exam, estradiol level, and return of questionnaires/survey, diaries, drug boxes, unused products/packaging. Subjects will be issued a Greenphire Clincard, which will be used to receive payment and funds will be available for use within 1 business day once approved to be released to the card.
See Appendix A: Study Calendar for summary of study protocol and procedures.

Randomization

Subjects who complete the screening will be randomly assigned to either the Intrarosa® or Replens™ arm in a 1:1 ratio. Subjects randomized to the Intrarosa® arm will use 6.5 mg daily for 12 weeks (±1 week). Subjects randomized to the Replens™ arm will use a vaginal applicator two times per week for 12 weeks (±1 week).

The study coordinator will use the Research Participant Registry System (RPRS) to randomize subjects to either the Intrarosa® arm or the Replens™ arm. Once a subject is registered in RPRS, the computer system will generate a randomly assigned arm. The UAMS Research Pharmacy will dispense study drugs after the subject has been randomized.

Investigational Product

Intrarosa® (Vaginal DHEA) Description

Intrarosa® (prasterone) is vaginally administered steroid indicated for the treatment of moderate to severe dyspareunia, a frequent symptom of vulvovaginal atrophy due to menopause or genitourinary syndrome of menopause. The mechanism of action of Intrarosa® in postmenopausal females with vulvar and vaginal atrophy is not fully established [13]. Intrarosa® presumably acts like endogenous DHEA, which is an inactive steroid secreted by the human adrenal glands that is converted into small quantities of active androgens and/or estrogens. However, prior studies of normal postmenopausal females and those on AIs have shown that serum estrogen and testosterone concentrations were maintained in the normal postmenopausal ranges after use of Intrarosa® with no detectible change in metabolism with up to 52 weeks of treatment [6-7].

Prasterone is identified chemically as 3β-hydroxyandrost-5-en-17-one. It has the empirical formula $C_{19}H_{28}O_2$ with a molecular weight of 288.424 g/mol. Prasterone is a white to off-white crystalline powder insoluble in water and soluble in sodium lauryl sulfate (SLS). Each Intrarosa® (prasterone) vaginal insert contains 6.5 mg of prasterone in 1.3 mL of off-white hard fat (Witepsol), which is formed into a smooth, white to off-white solid bullet-shaped suppository measuring 28 mm in length, 9 mm in width at its wider end, and weighing 1.2 g.

Intrarosa® is manufactured for Endoceutics, Inc. (Quebec City, Canada) and distributed by Millicent Pharma (East Hanover, NJ, USA). It will be provided to the UAMS Research Pharmacy in sterile packaging. It will be supplied, from the commercial line, in boxes containing 28 applicators and small boxes of 4 blister packs containing 7 vaginal inserts (28 vaginal inserts per box). It may be stored either at room temperature or in refrigeration (5°C-30°C).

One Intrarosa® vaginal insert will be self-administered with the provided applicator once daily at bedtime for 12 weeks (±1 week).

Replens™ Description

Replens™ is cleared (K101098) for over-the-counter use as a personal lubricant for vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity and supplement the body's natural lubrication. Replens™ is non-sterile, water-based, white to off-white, non-irritating, non-greasy, non-staining vaginal gel delivered as a long-lasting moisturizer for vaginal dryness Replens Vaginal Moisturizer contains ingredients commonly used in other products for vaginal use sold as medical devices and cosmetics (purified water, glycerin, mineral oil, polycarbophil, carbomer homopolymer type B, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide). All ingredients are either NF, USP, or are considered "generally recognized as safe" for their intended use.

Replens™ is manufactured for Dwight and Church Co. Inc., (Ewing, NJ USA). Replens™ will be obtained from commercial supply in packages of 8 prefilled applicators by the UAMS Research Pharmacy. It should be stored at room temperature (15°C-30°C).

Replens™ personal lubricant will be self-administered with the prefilled applicator two times per week on non-consecutive days as prescribed at bedtime for 12 weeks (±1 week).

Investigational Product Accountability

Intrarosa® and Replens™ will be stored in the UAMS Research Pharmacy under the supervision of the research pharmacist who will be responsible for receiving the investigational product, storing the supply according to the manufacturers' specifications, dispensing the investigational product for administration and maintaining all accountability logs. Standard UAMS accountability logs will be used. Investigational product accountability records will be maintained per Pharmacy, Institutional, FDA, and other applicable policies.

Intrarosa® and Replens™ Dosing Delays

If there are any delays or missed doses in the subjects' usage of Intrarosa® or Replens™, subjects are to notify the clinical research nurse immediately. Subjects are to also notify the clinical research nurse when they begin usage of Intrarosa® or Replens™ again.

Subject will be terminated from the study due to non-compliance (see "Subject Termination" section below) for either of the following dosing delays:

- Missing >1 week of consecutive treatment (seven consecutive doses of Intrarosa® or two consecutive doses of Replens™).

  OR

- If at any point it is discovered that the subject has missed ≥25% of the total prescribed treatment doses (21 doses of Intrarosa® or 6 doses of Replens™).

Risks and Benefits

Although prior trials have not reported serious physical side effects with DHEA, there is a risk of possible side effects from DHEA. The most significant side effect reported in prior studies was an increase in vaginal discharge, reported in 6% of users [14-15]. In an extended 52-week trial, changes in Pap smear were reported in 2.1% (11 of 521) subjects. None of the reported abnormal Pap results were high-grade lesions [14-15]. During the final gynecologic exam, a Pap smear may be done at the treating physician's discretion if abnormal cervical changes are suspected.

Intrarosa® package insert lists the following adverse reactions from clinical trials experience [6]:

- Vaginal discharge (incidence of ≥ 2%, and greater than reported in the placebo group)
- Abnormal Pap smear (incidence of 2.1%)

Under a "warnings and precautions" section, the package insert lists "current or past history of breast cancer," noting that exogenously-administered estrogen is contraindicated in females with history of breast cancer, and that estrogen is a metabolite of prasterone. Additionally, it states, "Intrarosa® has not been studied in women with breast cancer." [6] However, since publication of the package insert in 2016, high-quality studies have concluded that serum estrogen and testosterone concentrations were maintained in the normal postmenopausal ranges in breast cancer survivors on AI's after extended use of Intrarosa® [7,13,16] mitigating concern for this subgroup, who are the focus of the study proposed here.

There is a risk of minor discomfort with the pelvic exams proposed in this study. Subjects will undergo a physical exam outside of the scheduled visits if a subject experiences distress from side effects she perceives to be resulting from the study treatment.

There is a risk of psychological distress due to subjects filling out questionnaires about sexual health and quality of life. These questionnaires will be assessed and subject's feelings about sexual health and quality of life will be monitored for the duration of the study.
Another risk to study subjects is the potential for loss of confidentiality. Measures to protect the confidentiality of study subjects will be implemented as described in the Data Handling and Recordkeeping section below. No social or economic harms are anticipated.

Data Handling and Recordkeeping

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying number. The key to the code will be kept in a locked file in the principal investigator's office. Only Investigators and study staff shall have access to the code and information that identifies the subject in this study. At the conclusion of the study, the data will be permanently de-identified. Per UAMS Admin Guide, the data will be retained for seven years after final reporting. The data will be destroyed after it has been retained for the appropriate time.

Though not expected, any AEs experienced will be captured in the medical record. In addition to AEs, the following will also be collected from the subject or subject's medical record:

- Age
- Race
- History of disease (including stage and treatments)
- Menopause - natural
- Menopause - surgical (i.e. removal of ovaries)
- Weight
- Height
- Which AI (anastrozole/letrozole vs exemestane)
- # of months on current AI
- Previous (not current) endocrine therapy (tamoxifen, anastrozole/letrozole, exemestane) and duration of each in months
- Previous adjuvant chemotherapy (yes/no)
- Most bothersome vaginal symptom (dyspareunia vs vaginal dryness/discomfort)
- Duration of dyspareunia (# of months)
- Duration of vaginal dryness/discomfort (# of months)

- Cigarette smoking (current, past or never)
- Medical conditions (e.g. diabetes, hypertension, cardiac disease, stroke, etc.)

Adverse Events (AEs)

Following consent, safety will be measured by assessment of AEs throughout the duration of the study, which is approximately 12 weeks (±1 week) from Day 1, Week 1 of treatment. AEs will be documented at every visit by the study staff or clinic nurses. Subjects may report AEs at any point during the study (clinic visits, on diaries, by phone or email, etc.) The PI and/or delegated designee will evaluate and assess all AEs based on NCI CTCAE v5.

Definitions

Adverse Event (AE)

An AE is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study, whether or not it has a causal relationship to the study treatment. Concurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event (SAE)

An event is “serious” if it involves considerable detriment or harm to one or more persons (who may or may not be subjects), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. SAEs include:

- Death
- Life-threatening experience - Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the end point of the clinical trial analysis is survival
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in subject’s offspring
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

To avoid confusion, as the terms “serious” and “severe” are not synonymous, the following clarification is given: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on subject/event outcome or action usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. [ICH-E2A(II)(B)]

Related

An event is “related” if more likely than not it was caused by the research activity.

Unexpected
An event is "unexpected" when its specificity, nature, severity, or incidence is not accurately reflected in the consent form, protocol, or investigator's brochure previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected.

Study Period
Following consent (i.e. study entry), baselines/pre-existing conditions will be assessed until initiation of study treatment. All AEs will then be recorded through the end of the designated follow-up period (i.e. week 12, ±1 week). All AEs will be recorded within the research database AR-Adverse Events Reporting System (AR-AERS).

Abnormal Laboratory Values Defined as AEs
An abnormal laboratory value is considered an AE if the laboratory abnormality is characterized by any of the following, for test done as part of the research protocol:

- Results in discontinuation from the study
- Requires treatment, modification of study treatment dose, or other therapeutic intervention
- Is judged by the Investigator to be of significant clinical impact/importance
- Grade 3 or Grade 4 lab abnormalities regardless of significance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE. If the laboratory abnormality was not a part of a diagnosis or syndrome, then the abnormality should be recorded as the AE.

Estradiol levels will be measured at baseline and 12 weeks (±1 week) from Day 1, Week 1 of treatment. A report will be sent to FDA for any subject with an estradiol level out of the normal postmenopausal range at 12 weeks (±1 week) from Day 1, Week 1 of treatment.

Monitoring, Recording and Reporting of AEs
All relevant historical medical conditions, laboratory abnormalities, or physical findings with an onset date prior to the subject signing consent (present at Baseline) are considered to be pre-existing in nature and will be recorded as part of the subject's medical history (not as AEs). All AEs, which completely resolve and then recur, should be recorded as a new AE, regardless of whether it is related or not. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the first administration of the study drug is considered an AE. If the study subject's condition deteriorates or exacerbates at any time during the study, it will be recorded as an AE.

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs that are still ongoing at the end of the study period must be followed for up to 30 days to determine the final outcome. Any SAE that occurs after the study period and is considered to be definitely/probably/possibly related to the study treatment or study participation should be recorded and reported immediately to the Sponsor.

All AEs and SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed until adequate resolution or to study termination.

All subjects will be monitored for AEs during the study. Assessments may include monitoring the subject's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures.

AE data collection and reporting, which are required as part of every study, are done to ensure the safety of subjects enrolled in the studies and those who will enroll in future protocols. AEs are to be reported in a routine fashion at scheduled times during the trial, such as with the annual continuing review to the IRB. Certain AEs must be reported in an expedited fashion to allow for timely monitoring of subject safety and care.

The reporting of these events depends on the characteristics of the event:
1. Seriousness (grading of event)
2. Relatedness to study therapy
3. Expectedness

Steps to Determine if the Event Requires Expedited Reporting:
1. Identify the type of event using NCI CTCAE version 5.0
2. Grade the event using NCI CTCAE version 5.0
3. Determine whether the AE is related to the investigational drug. Attribution categories are as follows:
    - Unrelated
    - Unlikely
    - Possible
    - Probable
    - Definite
4. Determine expectedness of event. Expected events are those previously identified resulting from administration of the agent. An AE is considered unexpected when the type or severity of the event is not listed in the:
    - Package inserts
    - Protocol

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event occurring more than 30 days after the last dose that is possible, probably, or definitely attributable to the investigational drug must be reported according to the instructions above.

Expedited Reporting of AEs

Institutional Review Board Reporting

Only AEs meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) will need to be reported to the UAMS IRB within the required 10-day allotment of being notified of the event. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s). All other AEs should be recorded and reported to the UAMS IRB at continuing review.

Sponsor Reporting

The Sponsor will be promptly notified of all SAEs that are definitely/probably/possibly related to the study intervention. These SAEs will be reported to the Sponsor using the FDA MedWatch 3500A. SAEs that are definitely/probably/possibly related and unanticipated/unexpected will be reported to FDA in an IND safety report (i.e. 7- or 15-day expedited report). The Sponsor will

report all events to FDA in accordance with 21 CFR 312.

All other SAEs will be reported to the Sponsor and FDA in the Annual Progress Report.

Deaths that are related to research will be reported to the Sponsor immediately upon Investigator notification. A death due to a terminal condition of the research subject would be considered anticipated and not related to the research.

THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21 CFR 312.

Monitoring

The PI will have the overall responsibility for assuring safety and gathering the data for the study with assistance from the sub-investigators, and research staff, under the guidance of the Institutional Review Board (IRB) and the study Sponsor. Clinical site monitoring will be conducted on behalf of the Sponsor, UAMS, by the Office of Research Regulatory Affairs (ORRA), to ensure that the rights and well-being of human subjects are protected; the trial data are accurate, complete and verifiable from source documents; and the trial is conducted in compliance with currently approved protocol/amendment(s), ICH GCP, and applicable regulatory requirements.

Monitoring specialists from ORRA will conduct periodic on-site, comprehensive monitoring as determined by a protocol-specific monitoring plan, as provided by the ORRA Monitoring Unit.

Study Discontinuation

The Medical Monitor will review **ALL** Grade 3 or higher AEs, using the NCI CTCAE v5.0. Grade 3 AEs are severe or medically significant events (but not immediately life-threatening), hospitalization, or prolongation of hospitalization. The Medical Monitor may choose to halt the study temporarily if serious concerns arise regarding subject safety.

Individual Subject Stopping Rules

Any subject who experiences a grade 3 or higher related AE will discontinue study treatment. The study will be suspended if any subject experiences grade IV or higher related AE. These activities can re-start only after notifying the applicable regulatory authorities and with a permission to resume from the Medical Monitor and Sponsor.

Study Stopping Rules

After accrual of the first six subjects who have been randomly assigned to the Intrarosa® arm, enrollment will be paused until the Medical Monitor has reviewed all Grade 3 or higher AEs in this cohort. The Medical Monitor may begin reviewing the AEs as soon as enrollment is paused; however, review of AEs will continue until each subject in the cohort has either completed study treatment or has otherwise stopped study treatment (see Subject Withdrawal and Subject Termination sections below). If two or fewer subjects (total, regardless of assigned treatment arm) experience a Grade 3 or higher related AE, the study will reopen to enrollment until six more subjects have been randomly assigned to the Intrarosa® arm. Enrollment will once again be paused until the Medical Monitor has reviewed all Grade 3 or higher AEs and approves additional enrollment. Enrollment will continue in cohorts in this manner until either all 60 subjects have been accrued or the study is terminated. If at any point in the study, three or more subjects (cumulative, including both arms) experience Grade 3 or higher related AEs, the study will be terminated.

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects, the IRB, and Sponsor and will provide the reason(s) for the termination or

suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule. If only suspended the study may resume once all concerns have been addressed, and satisfy the Sponsor, IRB, and/or the FDA.

Protocol Deviations and Violations

Deviations

Protocol Deviation: any unintentional change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be tracked and compiled in a Protocol Deviation Log. Deviations should be reported to the IRB at the time of Continuing Review and at the time of the Annual Progress Report (APR). Deviations that potentially cause concern for the subject health, safety, or rights will be reported to ORRA, the Sponsor, as soon as possible for guidance on reporting. Deviations will be made available for Monitors to check against source data at each monitoring visit.

Violations

Protocol violation: a change to, or non-compliance with the IRB-approved procedures without prior Sponsor and IRB approval. Violation may affect health, safety, or rights of a subject. Any violation will be reported immediately to the Sponsor for guidance on reporting. Violations will be made available for Monitors to check against source data at each monitoring visit.

If the protocol deviation/protocol violation does not represent a significant alteration in the approved protocol and/or affect the safety or welfare of the subject, it will be reported to the UAMS IRB at the time of Continuing Review. If the protocol deviation or protocol violation represents a significant alteration in the approved protocol and/or if it affects the safety or welfare of the subject, it must be reported to the UAMS IRB immediately.

Compliance

All drug boxes and unused product will be collected from subject at last visit by research staff and will be given to the research pharmacy to log for compliance. No serious harm is anticipated from non-adherence or cessation of use of the investigational products.

Subject Withdrawal

Subjects may withdraw from treatment or consent from the study at any time for any reason, without penalty.

Subjects who voluntarily withdraw from study treatment will stop taking the study drug but will still participate in the research-related assessments. These research-related assessments include physical exam (including clinical breast and gynecological exam for pH and VMI), estradiol level, completion of BSSC-W, QOL-CSV, and FSFI, and reporting of AEs until the end of the study duration [i.e., Week 12 (±1 week)].

Subjects who withdraw consent from the study will stop taking the study drug and all research-related assessments will be ceased. Any data previously collected will be used but no further data will be collected following the subject's withdrawal of consent. Subjects will be encouraged to report AEs thought to be possibly/probably related to the study drug for 30 days after discontinuation.

For evaluation and reporting purposes, reasons for early withdrawal may be discussed with willing subjects for purposes of identifying potential problems with the drug or study design. When possible, subjects will be notified that any improvement in symptoms they perceived to be the

result of the study intervention may recede and a return to the pre-study baseline can be expected.

Subject Termination

An investigator may terminate a subject's participation from the study drug treatment to protect the subject from excessive risk without demonstrated benefit (e.g., a side effect such an allergic response making symptoms worsen instead of improve).

Additionally, in the interest of protecting the integrity of the data, an investigator may terminate a subject's participation from the study all together if the subject is not following procedures or is deliberately falsifying information. In the event of termination, the investigator will explain the reasons to the subject and discuss other available treatment options. The subject will refrain from using the study drug and return unused product and packaging for drug accountability. The subject will be instructed to return the completed diary and refrain from using the study drug for 30 days after discontinuation. The subject will also be instructed to report any AEs that occur during the 30 days following drug discontinuation via phone or email to the clinical research nurse. Subjects will be contacted 30 days (+3 days) from the date of drug discontinuation by the clinical research nurse for final safety evaluation. The subject's study status will be listed as 'Withdrawn' and the date of withdrawal will be 30 days (+3 days) after discontinuation. Subjects may obtain drug (Intrarosa® or Replens™) and resume use at their own discretion after the 30-day time period has elapsed after discontinuation.

Specimen Handling and Storage

Vaginal smears will be obtained by scraping the second third of the sidewall of the vagina. A 100-cell count will be performed to classify cells as S, I, and P. Vaginal pH will be measured using a pH indicator strip directly applied to the lateral wall of the vagina. The swab of the vaginal mucosa will be collected during the gynecologic exam, labeled and placed in sterile solution, sent for determination of VMI, then discarded per the usual cytology lab protocol.

Data Analysis

Efficacy and Safety Populations

The efficacy population will include all subjects with a baseline assessment who have received at least two weeks of treatment with either Intrarosa® or Replens™. Subjects who discontinue participation in the study (stop the assigned treatment, withdraw consent, etc.) before 2 weeks of treatment will not be included in the efficacy population. Subjects who discontinue participation in the study after 2 weeks but prior to 12 weeks will be included in the efficacy analysis. These subjects will be invited to complete the end of study evaluation at the time of discontinuation; these evaluation values will be included in the efficacy analyses.

The safety population will include all subjects who received at least one administration of either Intrarosa® or Replens™.

Efficacy Endpoints

The primary efficacy endpoint is VMI Response, which is defined as the change in the subject's calculated VMI from baseline to the end of treatment at 12 (±1 week).

Secondary efficacy endpoints: Secondary efficacy endpoints for all study subjects will be determined both at baseline and at the end of treatment. They consist of the following:

- Vaginal pH,
- Dyspareunia and vaginal dryness scores on the BSSC-W and the FSFI,
- Quality of life using the QOL-CSV.

Analysis Plan

Descriptive Analysis*:* Each efficacy endpoint will be summarized by treatment group and time point as the mean, standard deviation (SD), minimum, 1st quartile, median, 3rd quartile, and maximum. Within each subject, the endpoint's response to treatment will be defined (and calculated) as the endpoint's value at 12 weeks minus its value at baseline; the resulting endpoint responses will be summarized by treatment group as the mean, SD, minimum, 1st quartile, median, 3rd quartile, and maximum. Graphical displays will consist of box plots and scatter plots along with profile plots, a.k.a. "spaghetti plots", that show how the individual subjects respond over time to their assigned treatment. Adherence to distributional assumptions will be assessed, and data transformation to increase such adherence will be implemented, if warranted.

Primary Efficacy Analyses*:* To determine each treatment arm's VMI response to treatment, the Intrarosa® arm will be compared to the Replens™ arm for the difference in their VMI responses using Student's t-test if group variances are equal, Welch's t-test if group variances are unequal, or Wilcoxon's rank-sum test if data violate normality assumptions. In keeping with the research hypothesis that the Intrarosa® arm will exhibit greater improvement in the VMI when compared to the Replens™ arm after 12 weeks (±1 week) of treatment, this primary-efficacy comparison will be conducted using a one-sided test at an $\alpha = 0.05$ significance level to look specifically for increased VMI response in the Intrarosa® arm. The follow-up of this primary-efficacy comparison will be analyzed using an ANCOVA model that has 12-week VMI as the outcome variable, treatment arm as the factor of interest, and baseline VMI as the continuous covariate.

Secondary Efficacy Analyses*:* For each secondary endpoint, the treatment arms will be compared for a difference in the endpoint at baseline, a difference in the endpoint at 12 weeks (±1 week), and a difference in the endpoint's response to treatment. All comparisons will be conducted using 1-sided tests that employ a multiple-comparison-adjusted $\alpha = 0.01$ significance level to look specifically for improvements with Intrarosa® compared to Replens™. The tests will consist of Student's t-test, Welch's t-test, or Wilcoxon's rank-sum test depending on the endpoint's adherence to distributional assumptions. In follow-up analysis, each secondary endpoint will be analyzed using an ANCOVA model that has the endpoint's 12-week value as the outcome, treatment arm as the factor of interest, and endpoint's baseline value as the continuous covariate.

Sample Size and Power*:* The study is powered to detect an effect size of 0.8 SDs for the expected improvement in VMI response among subjects on the Intrarosa® arm compared to subjects on the Replens™ arm. Specifically, if the study meets its enrollment goal of 60 subjects (30 in each treatment arm), then 30 subjects per arm provide Student's t-test and Wilcoxon's rank-sum test (both 1-sided at $\alpha = 0.05$) with 92.2% power and 91.2% power, respectively, to detect an effect size of 0.8 SDs in VMI response. Moreover, even if the study were to suffer an attrition rate of 20%, then the remaining 24 subjects per arm (48 subjects that remain) still provide Student's t-test and Wilcoxon's rank-sum test (both 1-sided at $\alpha = 0.05$) with 86.1% power and 84.9% power, respectively, to detect an effect size of 0.8 SDs in VMI response.

To see that a 0.8-SD effect size is reasonable for VMI response, we call attention to the studies of Archer *et al*. [14] and Labrie *et al*. [8]. Although neither study utilized VMI itself as the outcome, both studies utilized the percentages of P and S cells as outcomes when reporting the 12-week differences they observed between their DHEA (6.5mg) arms and their placebo arms. Archer *et al.* [14] observed treatment-arm differences of 1.52 SDs in %P cells and 1.02 SDs in %S cells at 12 weeks, whereas Labrie *et al.* [8] observed treatment-arm differences of 1.11 SDs in %P cells and 0.99 SDs in %S cells at 12 weeks. These prior observations of ≥ 1-SD effect sizes for VMI-related endpoints show that it is reasonable to expect an effect size of 0.8 SDs for VMI response,

and thus that our study has sufficient power to achieve its research objectives.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

A Partial HIPAA Waiver for Recruitment will permit study staff to prescreen potential subjects prior to obtaining consent/HIPAA authorization to determine use of prohibited medical products requiring either an 8-week or 6-month washout in order to meet eligibility.

The formal consent of each subject will be obtained at UAMS before that subject is submitted to any study procedure using an IRB-approved consent form, which will describe this study and provide sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form will be signed by the subject or legally authorized representative, and the individual obtaining the consent. A copy of the signed consent will be given to the subject, and the informed consent process will be documented in each subject's research record.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a subject. The study will be listed on clinicaltrials.gov in accordance with FDA requirements.

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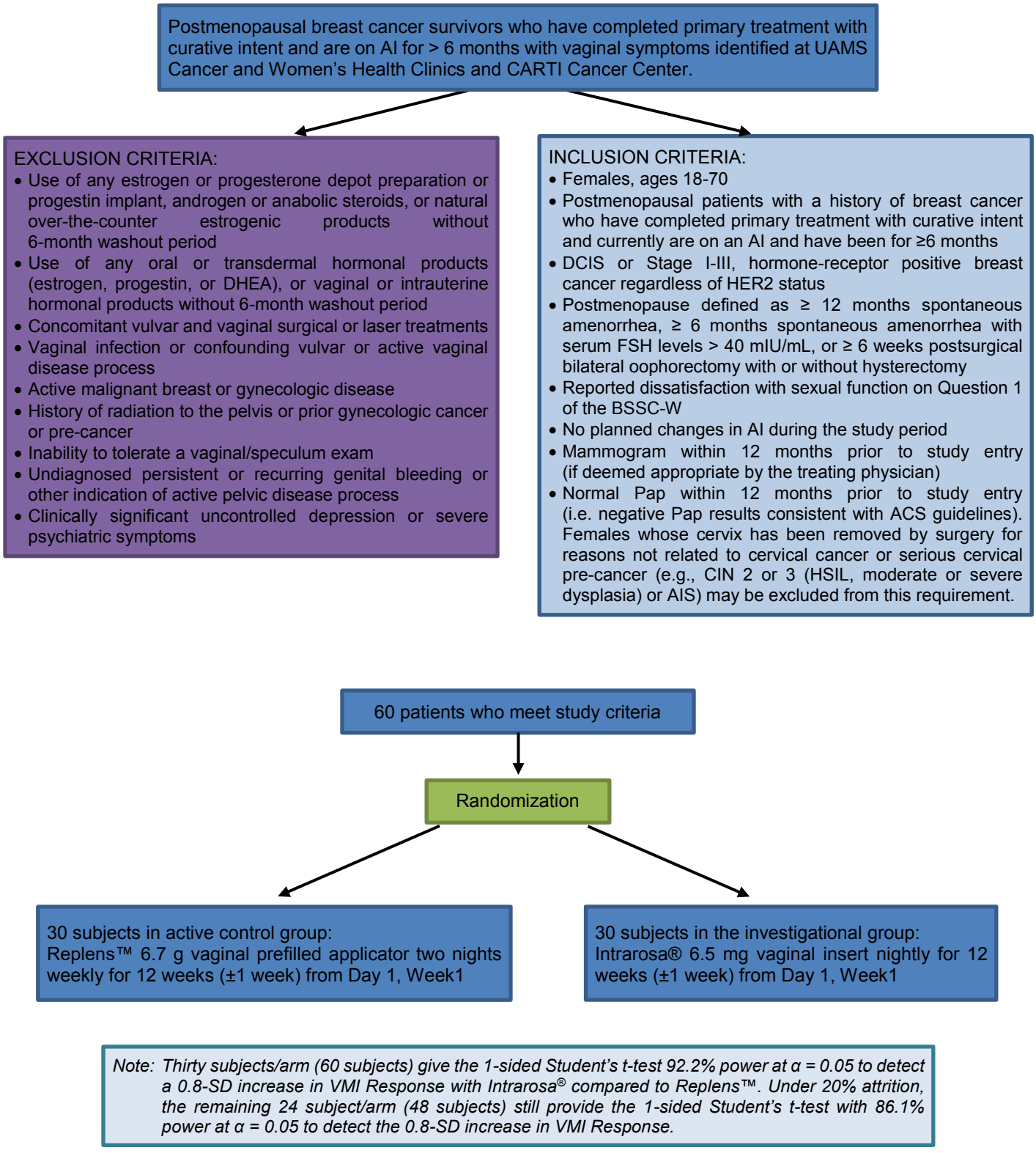
Appendices

Appendix A: Study Calendar

	Pre-Study/Baseline[a]	Day1, Week 1[b]	Week 2-12	End of Treatment[c]
Determine eligibility for study:	x			
Study consent discussed and signed	x			
Pregnancy test[d]	x			
Collect relevant disease-related data (mammogram, Pap smear)[e], FSH level[f], baseline conditions, height, weight, and medical history	x			
Complete BSSC-W	x[g]			x[g]
Complete FSFI[h]	x[g]			x[g]
Complete DHEA Trial Clinical Supplemental Survey	x[g]			
Physical exam (including gynecologic[i] and breast exams)	x			x[j]
Vaginal pH to be determined	x			x
Swab of vaginal epithelium collected and sent to pathology to calculate VMI[k]	x			x
Estradiol level[l]	x			x
Complete QOL-CSV	x[g]			x[g]
Randomize to treatment arm	x			
Assigned treatment and study diaries dispensed to subject		x		
Self-administration (starts same day as dispensed) • Intrarosa® 6.5 mg insert nightly ~OR~ • Replens™ 6.7 g prefilled applicator intravaginal two non-consecutive nights weekly		x	x	
Collect AEs[m]		x	x	x
Diary Submissions			x[n]	x[o]
Drug boxes and unused products collected from subject				x
Follow up call			x[p,q]	

a Pre-study/Baseline should be completed within 28 days prior to Day 1, Week 1.
b Day 1, Week 1 visit may be done the same day as Pre-Study/Baseline visit if all Pre-Study/Baseline activities are completed and eligibility has been confirmed prior to Day 1, Week 1 activities.
c End of Treatment should be completed at week 12 from Day 1, Week 1, i.e., Week 12 ±1 week).
d Subjects who are post-menopausal will not require a pregnancy test. SoC pregnancy test results may be used if completed within 7 days of Day 1, Week 1.
e Mammogram (if deemed appropriate by the treating physician) and normal Pap must be documented within 12 months prior to study entry. If these are not documented in the medical history, they will be obtained for the study. SoC Pap and mammogram (if appropriate) may be used if completed within 28 days of Day 1, Week 1. Pap is not required for females whose cervix has been removed by surgery for reasons not related to cervical cancer or serious cervical pre-cancer.
f If FSH level is not documented in the medical history, one will be obtained prior to study entry.
g Should be completed in-person but can be completed over the phone, if necessary.
h FSFI is to be completed only if participant answers no to question 1 on the coinciding BSSC-W.
i Gynecologic exam, including vaginal pH and VMI activities can take place on the same day as consent and Day 1, Week 1 as long they are completed after consent, all other eligibility criteria have been met, and prior to Day 1, Week 1 activities. SoC breast and pelvic exams may be used if completed within 28 days of Day 1, Week 1.
j During the gynecologic exam, a Pap smear may be performed at the treating physician's discretion if abnormal cervical changes are suspected.
k If the VMI results are "unsatisfactory", the swab of vaginal epithelium will need to be recollected within 4 weeks of Day 1, Week 1 to calculate a new VMI.
l A report will be sent to FDA for any subject with an estradiol level out of the normal postmenopausal range at week 12 (±1 week).
m All AEs reported during clinic visits, on diaries, by phone or email, etc. are to be documented, assessed by the PI or designee, and tabulated.
n Diary progress should be submitted after Week 4 (±1 week), Week 8 (±1 week) of treatment. Diaries can be submitted in person, via self-addressed envelope to CTO, text photos to the research nurse cellphone, email photos to the research nurse email, sent photos through MyChart, or faxed to CTO. There will be no deviation for subjects who do not submit diary progress at Week 4 or Week 8.
o Diary progress should be submitted after Week 12 (±1 week) of treatment, or end of treatment. Diaries can be submitted in person, via self-addressed envelope to CTO, text photos to the research nurse cellphone, email photos to the research nurse email, sent photos through MyChart, or faxed to CTO. There will be a deviation for subjects who do not submit diary progress at Week 12 or if they come off treatment early.
p Follow-up call should occur at 1 week ±3 days after Day 1, Week 1.
q Follow-up call should occur at 6 weeks ±1 week after Day 1, Week 1.

Appendix B. Eligibility Flow Diagram



Note: Thirty subjects/arm (60 subjects) give the 1-sided Student's t-test 92.2% power at α = 0.05 to detect a 0.8-SD increase in VMI Response with Intrarosa® compared to Replens™. Under 20% attrition, the remaining 24 subject/arm (48 subjects) still provide the 1-sided Student's t-test with 86.1% power at α = 0.05 to detect the 0.8-SD increase in VMI Response.