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# A randomized, single center pilot study comparing hyaluronic acid to vaginal estrogen for treatment of genitourinary syndrome of menopause

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| **IND/IDE Number:** | N/A |
| **Regulatory Sponsor:** | N/A |
| **Study Product:** | Hyaluronic acid vaginal insert, Revaree |
| **Study Product Provider:** | JDS Therapeutics |
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**Initial version:** 08/07/2020

## Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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# List of Abbreviations

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| AE | Adverse Event/Adverse Experience |
| SAE | Serious Adverse Event |
| GSM | Genitourinary syndrome of menopause |
| HLA | Hyaluronic acid |
| VSQ | Vulvovaginal symptom questionnaire |
| VSI | Vaginal Symptom Index |
| FSFI | Female Sexual Function Index |
| VMI | Vaginal maturation index |
| MCG | Micrograms |
| ASCCP | American Society of Colposcopy and Cervical Pathology |
| VAS | Visual analog scale |
| PGI-I | Patient global impression of improvement |
| HIPAA | Health Insurance Portability and Accountability Act |
| IRB | Institutional Review Board |
| N | Number (typically refers to participants) |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| OHSR | Office of Human Subjects Research |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| US | United States |

# Protocol Summary

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| Title | **A randomized, single center study comparing hyaluronic acid to vaginal estrogen for treatment of genitourinary syndrome of menopause** |
| Short Title | HLA vs vaginal estrogen for treatment of GSM |
| Brief Summary | Non-hormonal alternatives for the treatment of genitourinary syndrome of menopause (GSM) are needed. In this proposed trial, patients who are diagnosed with GSM will be randomized to receive either a hyaluronic acid (HLA) vaginal insert or vaginal estrogen topical cream for 12 weeks. There will be a baseline visit and a 12 week follow up visit, at which points the patient will undergo a detailed history and physical examination including a pelvic exam, vaginal pH sampling, vaginal cell sample for microscopic analysis, and will fill out questionnaires (vulvovaginal symptom questionnaire (VSQ), vaginal symptom index (VSI), and female sexual function index (FSFI)). These study arms will be analyzed to assess the efficacy of HLA as compared to the gold standard of vaginal estrogen to treat GSM symptoms. |
| Phase | Pilot |
| Objectives | The primary objective is to assess the feasibility and acceptability of the proposed intervention of HLA insert as measured by the vulvovaginal system questionnaire (VSQ). Secondary objectives include the assessment of preliminary effectiveness of the HLA insert to improve GSM symptoms and GSM physical exam measures, as compared to vaginal estrogen. |
| Methodology | This is an open label, randomized, active control, parallel group study. |
| Endpoint | The primary endpoint is the VSQ – 21 item questionnaire that measures patient quality of life via GSM symptoms, their emotional impact, sexual impact, and life impact.<br><br>Secondary endpoints include study treatment compliance and retention through 12 weeks, vaginal maturation index (VMI), vaginal pH, vaginal rugal folds, and subjective changes in the visual analog scale (VAS) scores for dyspareunia, vaginal itching, and dryness in participants receiving HLA insert as compared to those receiving vaginal estrogen. |
| Study Duration | 1 year |
| Participant Duration | 12 weeks |
| Duration of IP administration | 12 weeks |
| Population | Post-menopausal women in New York |

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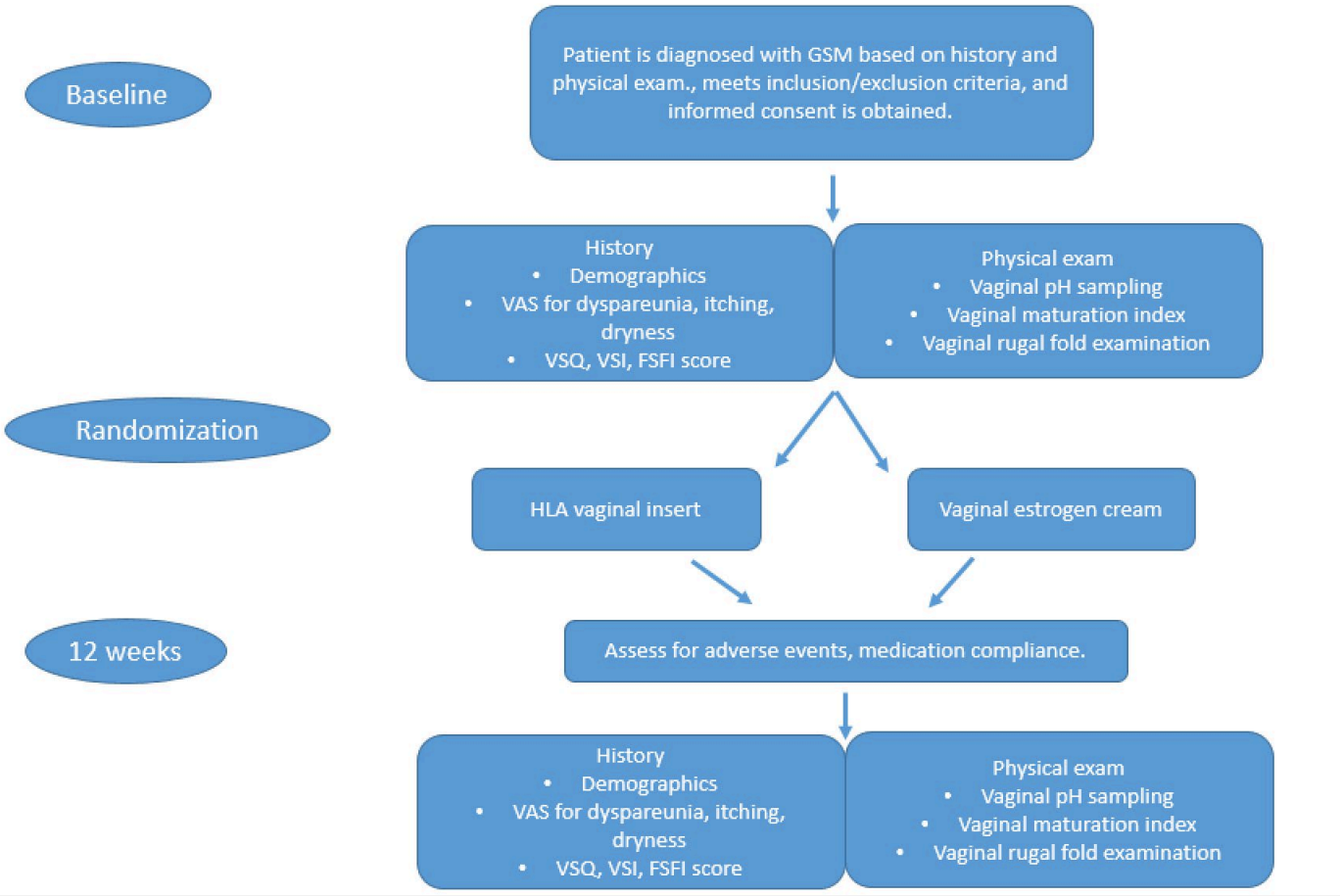
| Study Sites | 222 E 41st St, 11th floor, New York, NY 10017 |
| Number of participants | 40 |
| Description of Study Agent/Procedure | HLA Vaginal insert: 5mg of active medication in 2g vaginal insert |
| Reference Therapy | Vaginal estrogen cream, estradiol: 100mcg |
| Key Procedures | Sampling of vaginal tissue, sampling of vaginal pH |
| Statistical Analysis | Primary and secondary outcome measures will be summarized and described overall and by treatment group. Analysis will focus on the quality of life as well as objective measures of vaginal health improvement obtained in the HLA group, rather than hypothesis testing to compare outcomes to those receiving estrogen. Overall, and by treatment group, compliance and retention will be similarly described. |

# Schematic of Study Design



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# 2 Introduction, Background Information and Scientific Rationale

## *2.1 Background Information and Relevant Literature*

Genitourinary syndrome of menopause (also referred to as vulvovaginal atrophy, urogenital atrophy, and atrophic vaginitis) is a collection of vulvovaginal and urinary signs and symptoms that result from a decrease in estrogen (1). The most common symptoms include dryness, burning, dyspareunia, and urinary incontinence in menopausal women (2). The impact of these symptoms is widespread with 85% of women over the age of 40 who endorse vaginal dryness (3). Further, over half of the women with symptoms report that their quality of life is negatively impacted (4). Due to the deeply impactful effects of GSM, it is worthwhile to assess the mainstays of treatment and examine novel therapies in order to positively improve the quality of life of these women.

For many years, topical estrogen therapy has been the standard of care for GSM, after over-the-counter vaginal moisturizers and lubricants have failed (5). In many ways, estrogen is a logical treatment choice due to the fact that it replaces what is lost in post-menopausal women. The topical estrogen functions to maintain the collagen content in the epithelium, optimize genital blood flow, and maintain levels of acid mucopolysaccharides and hyaluronic acid (HLA) within the epithelium.

However, some patients may be uncomfortable with hormonal therapies or in certain circumstances hormonal therapies may be contraindicated, even in topical form. Therefore, it is important to explore non-hormonal alternatives for the treatment of this common condition.

One such novel therapy is topical HLA. HLA is a large non-sulfated glycosaminoglycan that forms in the plasma membrane of cells and serves three major functions (6). First, it helps maintain the extracellular matrix. Second, it contributes to cell proliferation and turn over. Third,

it modulates moisture in the epithelium. Currently, HLA is FDA approved for use in osteoarthritis (albeit with limited efficacy), and is used in the treatment of dry skin, dry eye, and youth-promoting cosmetic products. Recently, the potential role for HLA in the treatment of GSM has been uncovered.

In a study of rats randomly assigned to oophorectomy plus placebo, oophorectomy plus vaginal HLA gel, or sham oophorectomy, it was found that HLA resulted in a reversal of vaginal atrophy with no associated increase in uterine weight (7). This study is particularly promising because it not only shows the reversal of atrophy, but also it suggests that HLA has no effect on uterine weight (a proxy for endometrial lining) which is a feared complication of unopposed systemic estrogen therapy.

One of the earliest human studies examining the potential application of HLA for GSM symptoms as a non-hormonal alternative comes from Italy in 2006 (8). A pilot study of just 10 patients was initially performed to assess the safety profile of use of HLA gel on the vulva for GSM symptoms for 30 days. No side effects or adverse events were noted between the start and end of the usage period. No lab abnormalities were found aside from a 'slight increase' in monocyte percentage (9 to 13%) between the start and end, which the investigators deemed to be unrelated to the HLA treatment. Subsequently, a larger trial of 100 post-menopausal women was conducted by the same group of investigators. In this cohort, HLA was applied vaginally and studied over a period of 12 weeks. Using the visual analog scale (VAS) for GSM symptoms—specifically vaginal dryness, itching, burning, and dyspareunia—clinically significant improvement was noted from baseline to the end of the study period. Again, no adverse events or side-effects were noted for the gel usage.

In a similar study from Italy, an open trial of 150 post-menopausal women were given a vaginal insert that contained HLA, vitamin E, and vitamin A to use for four weeks (9). Subjective and objective vaginal markers were compared over the four weeks and significant improvement was observed in the primary endpoint of vaginal dryness as compared to baseline with no side-effects to the HLA insert reported.

An open RCT conducted in China in 2013 comparing vaginal HLA gel to vaginal estriol cream confirmed HLA's overall efficacy and safety profile (10). Only mild adverse events were noted relating to HLA gel use. On laboratory testing, two patients were found to have vulvovaginal candidiasis and one patient was found to have bacterial vaginosis. These three patients had no symptoms, required no intervention, and the infections self-resolved. Only one patient was found to have symptomatic vulvovaginal candidiasis and was treated with no subsequent complications.

A small, recent study in Iran also noted the non-inferiority of vaginal HLA as compared to vaginal estrogen cream for symptomatic GSM (11). The study found that both treatment groups improved compared to baseline in dryness, itch, maturation index, pH, and a composite score of vaginal symptoms. However, only the HLA group showed improvement in symptoms of urinary incontinence. Further, improvement in the HLA group was significantly greater than the estrogen group for dryness, maturation index, and composite score. Meanwhile, a Turkish study found the opposite—vaginal estradiol tablets were more effective on improving vaginal symptoms as

compared to vaginal HLA tablets, but both treatments still significantly improved all vaginal symptoms studied (12).

Most studies above examined the individual parameters that make up the composite 'vaginal health index score' (13). The vaginal health index score is a tool that evaluates five parameters to establish the degree of vaginal atrophy: vaginal elasticity, vaginal secretions, pH, epithelial mucous membrane, and vaginal hydration. In congruence with the above studies, vaginal HLA use led to significant vaginal health index score improvements over time. In sum, the results of these international studies are promising in that they suggest a potential role for HLA use in the treatment of GSM as a non-hormonal alternative.

This study proposes comparing a HLA vaginal insert available in the US, Revaree, to the commonly used vaginal estrogen cream, estradiol, for the treatment of GSM. Not only would this be one of the first randomized controlled trials conducted in the US examining this non-hormonal alternative to the standard of care for GSM, but also the vulvovaginal system questionnaire (VSQ), would be the first to be used in a study on this issue.

The studies cited earlier primarily use some combination of the following measurement tools: VAS for vaginal symptoms (dryness, itching, burning, and dyspareunia), physical exam findings, and vaginal maturation index (VMI). Vaginal maturation index is a qualitative measure of hormonal influences on the vaginal epithelium. It measures the percentage of parabasal, intermediate, and squamous cells appearing on a smear and is a valuable tool when comparing the changes in two samples of the same patient (14).

While this study proposes using these aforementioned evaluation tools for GSM, we propose to use the VSQ as the primary outcome to globally assess quality of life as reported by the patient. The VSQ is a 21-question survey developed in 2012 that specifically asks about GSM symptoms, their emotional impact, sexual impact, and life impact. Among 120 post-menopausal women, this questionnaire was found to have reliability and internal consistency (15). Most importantly, in the absence of a gold standard instrument to assess the quality of life impact of GSM, this questionnaire is a critical new tool. It is more nuanced and disease-specific than VAS scoring, and thus far, an underutilized tool to understand the significant psychological impact of this disease. Because GSM is a symptom-driven disease and patients will likely adhere to a treatment plan if they perceive symptomatic improvement, this study's primary endpoint of treatment success will be measured by improvement in VSQ scoring.

In summary, the goal of this study is to compare and assess the acceptance and effectiveness of the non-hormonal alternative, HLA, to the standard of care, vaginal estrogen, for the treatment of GSM using a randomized, controlled, parallel trial. The primary objective will be assessed by the disease-specific, quality-of-life VSQ score that no study on this investigational product has used thus far. Further, this pilot randomized trial will be the basis for the protocol for assessment of effectiveness in a larger randomized trial.

## *2.2 Name and Description of the Investigational Agent*

### 2.2.1 Preclinical Data

The investigational treatment in this study, HLA vaginal insert, Revaree (brand name), is a FDA-approved class II medical device. It is a 2g vaginal insert that contains 5mg of HLA sodium salt and a base of semi-synthetic glycerides. It is an insert that does not require an applicator and should be placed in the vagina while laying down twice weekly. HLA in different formulations is currently used in disciplines such as ophthalmology and orthopedic surgery. As explained below, it is an extremely well tolerated medication with little to no side effects.

In a study of rats randomly assigned to oophorectomy plus placebo, oophorectomy plus vaginal HLA gel, or sham oophorectomy, it was found that HLA resulted in a reversal of vaginal atrophy with no associated increase in uterine weight (7). This study is particularly promising because it not only shows the reversal of atrophy but also it suggests that HLA has no effect on uterine weight (a proxy for endometrial lining) which is a feared complication of unopposed systemic estrogen therapy.

### 2.2.2 Clinical Data to Date

One of the earliest human studies examining the potential application of HLA for GSM symptoms as a non-hormonal alternative comes from Italy in 2006 (8). A pilot study of just 10 patients was initially performed to assess the safety profile of use of HLA gel on the vulva for GSM symptoms for 30 days. No side effects or adverse events were noted between the start and end of the usage period. No lab abnormalities were found aside from a 'slight increase' in monocyte percentage (9 to 13%) between the start and end, which the investigators deemed to be unrelated to the HLA treatment. Subsequently, a larger trial of 100 post-menopausal women was conducted by the same group of investigators. In this cohort, HLA was applied vaginally and studied over a period of 12 weeks. Using the visual analog scale (VAS) for GSM symptoms—specifically vaginal dryness, itching, burning, and dyspareunia—clinically significant improvement was noted from baseline to the end of the study period. Again, no adverse events or even side-effects were noted for the gel usage.

In a similar study from Italy, an open trial of 150 post-menopausal women were given a vaginal insert that contained HLA, vitamin E, and vitamin A to use for four weeks (9). Subjective and objective vaginal markers were compared over the four weeks and significant improvement was observed in the primary endpoint of vaginal dryness as compared to baseline with no side-effects to the HLA insert reported. It is important to note that while the HLA insert used in the cited study is different than the one proposed for this study, it used the same dose of HLA, 5mg, as found in this study's HLA formulation.

An open RCT conducted in China in 2013 comparing vaginal HLA gel to vaginal estriol cream confirmed HLA's overall efficacy and safety profile (10). Four mild adverse events were noted relating to HLA gel use. On laboratory testing, two patients were found to have vulvovaginal candidiasis and one patient was found to have bacterial vaginosis. These three patients had no symptoms, required no intervention, and the infections self-resolved. Only one patient was found to have symptomatic vulvovaginal candidiasis and was treated with no complications.

A small, recent study in Iran also noted the non-inferiority of vaginal HLA as compared to vaginal estrogen cream for symptomatic GSM (11). The study found that both treatment groups improved compared to baseline in dryness, itch, maturation index, pH, and a composite score of vaginal symptoms. However, only the HLA group showed improvement in symptoms of urinary incontinence. Further, improvement in the HLA group was significantly greater than the estrogen group for dryness, maturation index, and composite score. Meanwhile, a Turkish study found the opposite—vaginal estradiol tablets were more effective on improving vaginal symptoms as compared to vaginal HLA tablets, but both treatments still significantly improved all vaginal symptoms studied (12).

In summary, the clinical data to date on this topic comes from international studies comparing different vaginal HLA formulations to different vaginal estrogen formulations. However, all studies showed a safe usage profile of vaginal HLA, with only one clinically symptomatic fungal infection that required treatment.

### 2.2.3 Dose Rationale (if applicable)

In the US, the only dosage available for a vaginal insert preparation of HLA is 5mg, to the author's best knowledge. As noted above, some international studies have used this dosage with good safety profiles.

## *2.3 Rationale*

GSM is a condition whose current standard of care is primarily hormone-based treatment. With patients being weary of using hormonal-based therapies and some patients being unable to receive such therapies even if willing, non-hormonal, safe alternatives must be explored. As noted earlier, there are a few preliminary international studies that have shown that HLA may be a promising new therapy for GSM. HLA alone has been shown in multiple studies to improve GSM symptoms.

This study proposes comparing HLA to vaginal estrogen cream because if the goal is to offer non-hormonal alternatives to all GSM patients, new therapies must be weighed against the standard of care. Additionally, no studies to date have used the VSQ proposed in this study as a tool to assess symptomatic and quality-of-life improvement. The hypothesis of this study is that HLA will be equal to estrogen in improving symptoms, quality of life, and physical attributes of GSM as compared to vaginal estrogen cream.

Both vaginal HLA and vaginal estrogen cream will be dosed and administered as recommended by the manufacturer to allow for reliable and realistic comparison of both therapies.

As mentioned above, HLA is associated with infrequent and usually mild side effects. The control in this study, vaginal estrogen cream, while also considered safe and FDA-approved for GSM, may be associated with certain side effects that would warrant further medical treatment. For example, if a patient starts to experience vaginal bleeding while on vaginal estrogen, the normal work-up for post-menopausal bleeding will be initiated.

Last, the intervention period of 12 weeks was chosen to allow for adequate time for therapeutic effect. Vaginal estrogen therapy can offer symptomatic improvement after just three weeks of

use, but can take four to six weeks in some patients (16). Thus, 12 weeks will maximize vaginal estrogen's therapeutic effect, allowing for a proper comparison of a novel therapy.

## *2.4 Potential Risks & Benefits*

### 2.4.1 Known Potential Risks

Regarding vaginal HLA usage, the only observed risk thus far has been a fungal or bacterial infection in four patients, three of which were asymptomatic and did not require intervention and the remaining one was treated with no complication (10). Otherwise no other adverse events have been noted in studies.

Regarding the vaginal estrogen cream in this study, on the package insert for Estrace (see attached hyperlink), the risks of local vaginal estrogen are not separated from oral hormone replacement therapy (HRT). The package insert states that the risks include thromboembolism, retinal thrombosis, heart attack, stroke, breast cancer, ovarian cancer, endometrial cancer, endometrial hyperplasia, hypercalcemia, gallbladder disease, and probable dementia. It also includes possible exacerbation of the following conditions: hereditary angioedema, hypothyroidism, asthma, endometriosis, diabetes mellitus, epilepsy, migraine, hypertriglyclideremia leading to pancreatitis, hypoparathyroidism, porphyria, systemic lupus erythematosus, and hepatic hemangiomas (19).

However, when examining vaginal dosing of estrogen formulations, first, the dose is significantly less than oral HRT. Second, the risks associated with oral HRT, as mentioned above, have not been found in studies examining different—comparable to Estrace—vaginal estrogens. The reported cases of endometrial hyperplasia, breast or endometrial cancer were no different than those prior to initiation of therapy (20-24). Third, circulating levels of estradiol have been shown to be minimal with low-dose vaginal estrogen creams, tablets and the estrogen ring (25). Thus, systemic effects from these low-dose topical therapies are felt to be extremely rare. The other concern with any unopposed estrogen is endometrial safety. There have been several large studies that have established endometrial safety of various low-dose formulations of vaginal estrogen (Vagifem™, Estring™ and conjugated estrogen cream at a dose of 0.3mg) (20-22). Therefore, with low systemic absorption and no significant increase in endometrial pathology with low-dose vaginal estrogen, it is generally thought that the use of progestins is not necessary to protect the endometrium (23).

Reactions reported in randomized controlled trials of vaginal estrogen include application site reaction, vaginal bleeding/spotting, breast changes/pain, abdominal bloating/cramps, nausea/vomiting, cervical secretion changes, headache/migraine, fluid retention, elevated blood pressure, mood changes, candidiasis, glucose intolerance, weight changes, libido changes, contact lens intolerance, vision changes, rash, melasma/choasma, hair loss and hirsutism. Despite this risk profile, vaginal estrogen is well tolerated in most patients and is the recommended treatment if first-line over-the-counter vaginal moisturizers and lubricants do not work.

Regarding the office visit, the only potential risk of vaginal tissue sampling may be minimal bleeding, for which local pressure will be applied. If a patient is on oral HRT within 6 weeks of the study, she will not be able to participate in this study.

### 2.4.2 Known Potential Benefits

The potential physical benefits of vaginal HLA insert discussed in detail above come from multiple international studies. They include improvement in symptoms (dyspareunia, itching, dryness, vaginal bleeding), vaginal maturation index, vaginal pH, and urinary symptoms secondary to GSM (8-13). Regarding the vaginal estrogen cream to be used in this study, estrace, is FDA approved for the treatment of vulvovaginal atrophy secondary to menopause. Additionally, studies examining similar formulations of vaginal estrogen have showed improvement in GSM symptoms (20-22).

Regarding potential psychological benefits, no study to date has examined vaginal HLA's impact on quality of life; it is included in the primary objective of this study. A study that compared a vaginal moisturizer to vaginal estrogen tablets—very similar to the control being used in this study—found there was significant improvement in the overall sexual function domain and overall Menopause Quality of Life scores in the vaginal estrogen group (17).

# 3 Objectives and Purpose

## *3.1 Primary Objective*

The primary objective is to measure symptoms and quality of life for GSM in those randomized to vaginal HLA versus vaginal estrogen cream in a contemporary cohort.

## *3.2 Secondary Objectives (if applicable)*

The secondary objective is to measure objective and physical attributes of GSM, as well as treatment compliance and retention in those receiving vaginal HLA or vaginal estrogen cream.

# 4 Study Design and Endpoints

## *4.1 Description of Study Design*

This will be an open, randomized, active control, parallel design study. This is a pilot randomized trial to gain understanding of symptom and quality of life, physical measurements, and overall protocol administration. There are two study arms, HLA vaginal insert (investigational) and vaginal estrogen cream (standard of care). Participants will be recruited and treated at a single-center study. Both interventions will last for 12 weeks. There will be no protocol changes to either medication in this study. Randomization will not be stratified.

## *4.2 Study Endpoints*

### 4.2.1 Primary Study Endpoints

The primary endpoint will be the change in the VSQ score, between the baseline visit and 12 week follow-up.

The VSQ is a 21-question survey developed in 2012 that specifically asks about GSM symptoms, their emotional impact, sexual impact, and life impact. Among 120 post-menopausal women, this questionnaire was found to have reliability and internal consistency (15). Most importantly, in the absence of a gold standard instrument to assess the quality of life impact of

GSM, this questionnaire is critical. It is more nuanced and disease-specific than VAS scoring, and thus far, an underutilized tool to understand the significant psychological impact of this disease. Because GSM is a symptom-driven disease and patients will likely adhere to a treatment plan if they perceive symptomatic improvement, this study's primary endpoint of treatment success will be measured by improvement in VSQ scoring.

### 4.2.2 Secondary Study Endpoints

The secondary study endpoints will include: the change in the FSFI and VSI score from baseline to the 12 week visit, the change in the percentage of superficial squamous cells in the vaginal maturation index, the change in vaginal pH, the qualitative change in rugal fold appearance, and the change in VAS scoring for vaginal dyspareunia, itching, and dryness. These are well-studied measurement tools for GSM research and have been used in some combination in all of the studies cited earlier.

Vaginal pH in a postmenopausal woman is generally between 6.0 and 8.0, while an estrogenized vagina will have a pH of 3.5 to 4.5 (18). Thus, the change in pH can be a surrogate marker for the hormonal influence on vaginal epithelium.

VMI is a qualitative measure of hormonal influences on the vaginal epithelium. It measures the percentage of parabasal, intermediate, and superficial squamous cells appearing on a smear and is a valuable tool when comparing the changes in two samples of the same patient (14).

Patient global impression of improvement (PGI-I), a one question assessment, will also be asked at the follow up visit for overall patient satisfaction assessment.

### 4.2.3 Exploratory Endpoints

N/A

# 5 Study Enrollment and Withdrawal

## *5.1 Inclusion Criteria*

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Postmenopausal status as defined by amenorrhea for ≥12 months or history of bilateral salpingo-oophrectomy or if the patient has had a hysterectomy and menopausal symptoms for >1 year or FSH > 40
2. Symptoms of GSM
3. Pap smear screening as per ASCCP (American Society of Colposcopy and Cervical Pathology) guidelines. If Pap smear was indicated in last three to five years, it must be negative.
4. Capable of giving informed consent
5. Ambulatory
6. Capable and willing to follow all study-relation procedures

## *5.2 Exclusion Criteria*

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Use of any HRT (systemic or local) or raloxifene within six weeks of proposed start date
2. History of estrogen-sensitive tumor
3. Undiagnosed vaginal bleeding in the past 12 months
4. History of thromboembolic event
5. Currently have or have had liver problem
6. Bleeding disorder
7. Impaired mental status
8. Prior pelvic irradiation
9. Active vaginal infection
10. Any medical reason the investigator deems incompatible with treatment with vaginal estrogen

## *5.3 Vulnerable Subjects*

No vulnerable subject populations based on federal regulations are included in this trial. Children and fetuses are not affected by this disease, pregnant women by definition are not post-menopausal, and prisoners are not treated as outpatients at any of the study sites. The elderly are potential vulnerable subjects; however they need to be included in our study population to make the results useful in clinical practice as the average age of menopause is 51.2 years old. However, those who are no longer able to provide consent for themselves will be excluded.

## *5.4 Strategies for Recruitment and Retention*

All patients seen at Dr. Brucker's office will be offered participation in this randomized controlled trial.

Informed consent will take place at Dr. Brucker's office. Patients will be asked personal demographic information. Only staff (attendings, fellows, residents, medical students,) involved in the study will have access to this information.

### 5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will not utilize EPIC or Data Core to identify subjects.

## *5.5 Duration of Study Participation*

There is no pre-screening to visit one. After visit one, the patient will have a follow-up visit approximately 12 weeks later. There is no follow up required after the 12 week visit. Thus, the duration of study participation is 12 weeks.

## *5.6 Total Number of Participants and Sites*

Recruitment will end when approximately 60 participants are enrolled at this single site at NYUMC. It is expected that approximately 60 participants will need to be enrolled in order to retain 40 evaluable participants at 12 weeks of follow up (an overall 33% drop out rate).

### *5.7 Participant Withdrawal or Termination*

#### 5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

#### 5.7.2 Handling of Participant Withdrawals or Termination

Patients who withdraw or terminate participation in this study will be called and a follow-up office visit will be set up at 12 weeks regardless of their participation. If the patient refuses to come in, a phone call will be made to discuss adverse events or unanticipated problems over the phone. If a patient is lost to follow-up, two phone calls to the patient and subsequently two phone calls to next-of-kin will be made in an attempt to reach the patient. There is low concern for long-term and short-term safety with either study agent, particularly for the duration of eight weeks only.

### *5.8 Premature Termination or Suspension of Study*

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. Nachtigall JDS Therapeutics, NYU medical center, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

## 6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

### *6.1 Study Agent(s) and Control Description*

The study agent is the HLA vaginal insert, Revaree (brand name). It is a FDA-approved class II medical device. It is a 2g insert that contains 5mg of HLA sodium salt and a base of semi-synthetic glycerides. The off-label use of this device for GSM is considered non-significant risk (NSR) as it does not meet the criteria for significant risk device set forth in 21 CFR 812.3(m). This device is approved as a personal lubricant for vaginal application. This device does not pose significant risk because as mentioned earlier, multiple international trials have shown no side

effects and the only adverse event noted that required treatment was one episode of vulvovaginal candidiasis (10).

The control agent is vaginal estradiol cream, Estrace (brand name). It is a cream composed of 100mcg estradiol in a non-liquefying 1g base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and di-glycerides, hypromellose 2208 (4000 cps), sodium lauryl sulfate, methylparaben, edetate di-sodium and tertiary-butylhydroquinone. It is FDA approved for GSM treatment.

### 6.1.1 Acquisition

Both study agents will be acquired and shipped to Dr. Brucker's Manhattan office by JDS Therapeutics.

### 6.1.2 Formulation, Appearance, Packaging, and Labeling

The study agent, Revaree, is manufactured by JDS Therapeutics. It is a semi-solid, off-white suppository for the vagina. The suppository must be removed from its packaging by pulling two pre-cut flyers of the plastic strip. This is a commercially marketed medical 'device,' available for human use in the form, route, and dose planned in this trial.

The control agent, Estrace, is manufactured by Allergan. It is a white cream that must be squeezed onto a calibrated applicator to dose it. This is a commercially marketed medication, available for human use in the form, route, and dose planned in this trial.

### 6.1.3 Product Storage and Stability

Revaree should be stored at 39°F to 77°F, avoiding void heat over 86°F. Estrace should be stored at 68°F to 77°F with excursions permitted to 59°F to 86°F.

### 6.1.4 Preparation

No preparation of the study agents is needed.

### 6.1.5 Dosing and Administration

The study agent, Revaree, has only one dose. As per the manufacturer, the suppository should be placed in the vagina at bed time. It should be removed from the packaging before insertion, inserted into the vagina while laying down with knees bent, and then pushed further into the vagina gently, as far as tolerated. It should be placed twice weekly.

The control agent, Estrace, is dosed by the amount of cream applied to the vagina. The patient will need to attach the applicator to the tube and squeeze the cream into the calibrated applicator accordingly before application at bed time. The dosing will be 100mcg of estradiol (1g of cream) inserted into the vagina twice a week. This dosing is consistent with the manufacturer recommended maintenance dosing for Estrace and it mimics the usage pattern of the other study agent, HLA. Additionally, a study of a similar vaginal cream, Premarin, showed that twice weekly dosing was as efficacious and safe as using the cream daily for 21 days and 7 days off for GSM symptoms (22).

#### 6.1.6 Route of Administration

Vaginal for both study agents.

#### 6.1.7 Starting Dose and Dose Escalation Schedule

The starting doses are mentioned above. There will be no escalation.

#### 6.1.8 Dose Adjustments/Modifications/Delays

There will be no dose adjustments for the study agent, Revaree. It is not physically possible with this formulation of the drug.

Dose modification for the vaginal estrogen cream, Estrace, may occur if a patient exhibits side effects. If a patient starts to exhibit the most common side effects of breast pain, vaginal spotting, or headache, the dose may be decreased or the treatment may be discontinued depending on the clinical context. If there is any concern for an AE, the treatment may be discontinued. If the patient is responding positively to treatment, the dosing will not be increased.

#### 6.1.9 Duration of Therapy

The duration of therapy will be 12 weeks. This is based on evidence that vaginal estrogen therapy can can take up to six weeks to offer symptomatic relief in some patients (16). Additionally, with four weeks of usage, vaginal administration of HLA has shown to have significant impact on GSM symptoms.

#### 6.1.10 Tracking of Dose

Subject diary will be used to track date/time of dosing of vaginal estrogen or HLA insert.

#### 6.1.11 Device Specific Considerations

N/A

### *6.2 Study Agent Accountability Procedures*

NYU Investigational pharmacy will be used to ensure the drug and device are stored and dispensed in a regulated manner through the faculty group practice study site. Unused product will be returned to JDS Therapeutics (1 Manhattanville Road, Suite 104, Purchase, NY 10577). Both medications will be stored at the office in a locked cabinet. There will be no additional interventions.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

## 7 Study Procedures and Schedule

### *7.1 Study Procedures/Evaluations*

#### 7.1.1 Study Specific Procedures

- Medical history: will be obtained by interview
    - Included: genitourinary symptoms
- Medication history:

    - All history of HRT use currently or in the past
        - Any usage of HRT in the last six weeks would prohibit participation until six weeks off HRT
- Physical Exam:
    - Pelvic:
        - Vaginal pH sample
        - Vaginal tissue sample via scraping for VMI
- VSQ, FSFI, VSI
- Counseling on usage of medication depending on the study arm randomization
- Patient report of medication compliance at twelve week follow-up

### 7.1.2 Standard of Care Study Procedures

- Demographic information
- Medical history: will be obtained by interview
    - Included: obstetrical, gynecologic, medical, and surgical history
- Medication history:
    - All current medications (prescription and over the counter) usage and dosages
- Physical Exam:
    - Vitals: blood pressure, heart rate, respiratory rate, temperature, height, weight
    - Cardiovascular exam: lung and heart auscultation
    - Abdominal exam: skin, surgical scars, distention, tenderness
    - Pelvic:
        - Speculum: external genitalia and urethral opening, vulva, vaginal, cervix
- Bimanual: cervical os, uterine size (if present), adnexal fullness, adnexal tenderness

## *7.2 Laboratory Procedures/Evaluations*

N/A

### 7.2.1 Clinical Laboratory Evaluations

- After enrollment
    - Vaginal pH test: will be checked at office at visit one and two
    - Vaginal scraping for microscopy analysis for VMI: will be checked at the office at visit one and two
    - Urine analysis: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.

### 7.2.2 Screening

There will be no screening visit separate from the enrollment visit.

### 7.2.3 Enrollment/Baseline

**Screening/Enrollment/Baseline Visit (Visit 1, Day 0)**

- Obtain informed consent of potential participant verified by signature on study informed consent form
- Obtain demographic information, history of present illness, medical history, surgical history, obstetrical history, gynecologic history, medication history, HRT usage history
- Perform physical exam: vitals, cardiovascular, abdominal, pelvic
- Diagnose GSM
- If GSM diagnosis, explain study and verify inclusion and exclusion criteria
- Obtain urine pregnancy test: result must be negative and available prior to administration of study agents

- Obtain urine analysis: result must be negative and available prior to administration of study agents
- Record VAS scores for dyspareunia, itching, and dryness
- Record rugal fold analysis
- Collect pelvic samples for vaginal pH and vaginal tissue scraping for VMI
- Have patient fill out VSQ, FSFI, VSI
- Perform randomization and determine patient study arm
- Give patient appropriate prescription (HLA vs vaginal estrogen)
- Counsel on medication dosage, usage, and application
- Counsel on communication routes to inform research team about side effects and/or AE

### 7.2.4 Final Study Visit

**Final Study Visit (Visit 2, Week 12 +/- 3 to 5 days )**

- Record AE as reported by participant or observed by investigator
- Record participant's adherence to treatment regimen
- Record VAS scores for dyspareunia, itching, and dryness
- Record vital signs, results of physical exam including pelvic
- Collect pelvic samples for vaginal pH and vaginal tissue scraping for VMI
- Have patient fill out VSQ, FSFI, VSI, PGI-I
- Discuss the preliminary changes in their symptoms, if any exist
- Provide contact information for Dr. Shavy Nagpal to communicate any AE or side-effect experienced after the end of the study if patient believes it is related to the study

### 7.2.5 Withdrawal/Early Termination Visit

If 12 weeks of study agent usage:

- Record AE as reported by participant or observed by investigator
- Record participant's adherence to treatment regimen
- Obtain GSM symptom history, and record VAS scores for dyspareunia, itching, and dryness
- Record vital signs, results of physical exam including pelvic
- Collect pelvic samples for vaginal pH and vaginal tissue scraping for vaginal maturation index
- Have patient fill out VSQ
- Discuss the obvious, preliminary changes in their symptoms, if any exist
- Provide contact information for Dr. Shavy Nagpal to communicate any AE or side-effect experienced after the end of the study if patient believes it is related to the study

If <12 weeks of study agent usage:

- Record AE as reported by participant or observed by investigator
- Record participant's adherence to treatment regimen
- Record vital signs, results of physical exam including pelvic
- Provide contact information for Dr. Shavy Nagpal to communicate any AE or side-effect experienced after the end of the study if patient believes it is related to the study

### 7.2.6 Unscheduled Visit

- Obtain patient's reason for visit
- Perform relevant physical exam
- Based on the clinical context, determine whether study agent should be continued or discontinued or modified
- Discuss plan with patient
- Based on the clinical context, document whether patient will continue in study or be removed

### *Concomitant Medications, Treatments, and Procedures*

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

### *Prohibited Medications, Treatments, and Procedures*

Treatment with systemic HRT will not be permitted during or within 6 weeks of starting this study.

### *Participant Access to Study Agent at Study Closure*

HLA is an over the counter medication so patients will have access to the study agent after closure. However, the cost will not be covered after study closure and will be the subject's responsibility, so purchasing the study agent may be cost prohibitive.

# 8 Assessment of Safety

## *8.1 Specification of Safety Parameters*

### 8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- 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

### 8.1.2 Definition of Serious Adverse Events (SAE)

**Serious Adverse Event**

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a

seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

### 8.1.3 Definition of Unanticipated Problems (UP)

**Unanticipated Problems Involving Risk to Subjects or Others**

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

## *8.2 Classification of an Adverse Event*

### 8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

### 8.2.2 Relationship to Study Agent

*For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.*

- ***Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.*

- ***Probably Related*** *– There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
- ***Possibly Related*** *– There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
- ***Unlikely to be related*** *– A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*
- ***Not Related*** *– The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

### 8.2.3 Expectedness

Dr. Nachtigall will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

## *8.3 Time Period and Frequency for Event Assessment and Follow-Up*

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. 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 to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

## *8.4 Reporting Procedures – Notifying the IRB*

### 8.4.1 Adverse Event Reporting

The patient will be given Dr. Shavy Nagpal, Dr. Christina Escobar, and Dr. Lila Nachtigall's contact to report any AE. AE's deemed to be related to the study will be reported to the IRB within 7 days of the investigator becoming aware of the event. Dr.Nachtigall, the principal investigator, will be responsible for completing and signing off on AE reports.

### 8.4.2 Serious Adverse Event Reporting

The patient will be given Dr. Shavy Nagpal, Dr. Christina Escobar, Dr. Lila Nachtigall's contact to report any SAE. SAE deemed to be related to the study will be reported to the IRB within 3 days of the investigator becoming aware of the event. Dr. Nachtigall, the principal investigator, will be responsible for completing and signing off on SAE reports.

### 8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 3 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IR's receipt of the report of the problem from the investigator.

### 8.4.4 Reporting of Pregnancy

This study is being conducted in post-menopausal women. But in the rare circumstance that a patient becomes pregnant while in this study, the treatment (either arm) will be discontinued, follow-up visit will be scheduled to assess for safety, and a request will be made to follow the patient through her pregnancy to the pregnancy outcome.

## *8.5 Reporting Procedures – Notifying the Study Sponsor*

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

## *8.6 Study Halting Rules*

Administration of study agent will be halted when three grade 3 AEs determined to be “probably related” are reported to the PI. There are no predicted grade 3 AE’s for either study agent. The PI will inform the FDA of the temporary halt and the disposition of the study.

### *8.7 Safety Oversight*

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. The monitoring plan includes two official review time points of all AE's noted by patients within the time frame of the study. Since the planned time frame of the study is one year, there will be one review at the 6 month mark and one at the end, 12 month mark. The outcomes of the data safety monitoring and AE's will be summarized and submitted as a progress report to the IRB with the Continuing Review Submission.

## 9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Dr. Shavy Nagpal will monitor the data for accuracy and completeness and the safety review will be performed by Dr. Nachtigall. The monitoring reports will be distributed to all study investigators.
- Independent audits will not be conducted.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

## 10 Statistical Considerations

### *10.1 Statistical and Analytical Plans (SAP)*

As the study is a pilot randomized trial, the results are expected to inform the overall protocol design for a larger effectiveness evaluation, including the statistical analysis plan. Our overall strategy will be to estimate the primary and secondary outcomes for those randomized to HLA, along with the contemporary cohort randomized to vaginal estrogen. Formal comparisons between randomized groups are not of focus, but we will estimate treatment effects along with measures of variability in these measures (95% CI).

### *10.2 Statistical Hypotheses*

We expect no clinically meaningful differences in baseline characteristics or baseline assessment of outcomes between those randomized to HLA or to vaginal estrogen, however this is possible given the limited pilot trial sample size. These differences will be assessed and considered in the evaluation of outcomes for primary and secondary endpoints.

We expect a clinically meaningful improvement in the change measured at 12 weeks (comparison of VSQ at 12 weeks, adjusted for baseline) in VSQ in the HLA group, and expect this to be greater as compared to those randomized to vaginal estrogen. Similarly, we expect to observe clinically meaningful improvements in the HLA group at 12 weeks, beyond those observed in those randomized to the vaginal estrogen cohort. These include VSI, FSFI, VAS for dyspareunia, itching, and dryness, vaginal pH, and presence of rugal folds.

These estimates will provide estimates for establishing effectiveness in future trials.

## *10.3 Analysis Datasets*

The analysis dataset will include the intent to treat cohort, to include all those randomized to treatment, as well as a per protocol set to include who used either the control or investigational product for at least 12 weeks.

## *10.4 Description of Statistical Methods*

Baseline (pre-randomization) participant demographics and clinical characteristics will be summarized through descriptive statistics overall, and by randomized group. Clinical characteristics will include past HRT use, uterus present or not, and components of their medical and gynecologic history. Details of each outcome measure is provided below. Analysis of the primary and secondary measures will include summarizing each by the mean and standard deviation at baseline and all measured time points, including at the primary outcome time of 12 weeks. For continuous measures, a linear mixed effects regression model will estimate the mean outcome at 12 weeks, both unadjusted and adjusted for baseline measurement. No further adjustment for participant characteristics is expected given the limited trial size. The linear mixed effects regression model will allow all participants to be included in analysis, regardless of completion of study follow up at 12 weeks, under the assumption of this assessment being missing at random.

Missing outcome data will be summarized by participant characteristics to understand how to better retain individuals in treatment.

### 10.4.1 Analysis of the Primary Endpoint

- VSQ score (see attached below):
    - Definition: 21 question survey
    - Interval variable overall (binary responses; a ‘yes’ equates to one point, a ‘no’ equates to zero points for each question which is then added up to a sum)
    - Single endpoint measure with a score that can range from 0 to 21

### 10.4.2 Analysis of the Secondary Endpoint(s)

- FSFI score (see attached below):
    - Definition: 19 question survey
    - Graded responses from 0 to 5
    - Single endpoint measure with a score that can range from 0 to 95
- VSI score (see attached below):
    - Definition: 19 question survey
    - Graded responses from 0 to 3
    - Single endpoint measure with a score that can range from 0 to 15
- Vaginal pH
    - Definition: pH number
    - Interval variable ranging from 0 to 14
    - Single endpoint
- Vaginal maturation index (VMI)
    - Definition: microscopic analysis of vaginal tissue that assigns a percentage to the amount of parabasal, intermediate, and squamous cells visualized that add up to 100%

  - Ratio variable ranging from 0 to 100
  - Single endpoint (only the % of squamous cells will be reported since that is most closely correlated with hormonal influence on the vaginal tissue)
- Visual analog scale (VAS) score for dyspareunia, itching, dryness
  - Definition: visual scale attempting to capture the intensity of a symptom
  - Ratio variable ranging from 0 to 10
  - Single endpoint
- Vaginal rugal folds
  - Definition: visualization of the presence of vaginal rugal folds on pelvic exam
  - Continous variable
  - Single endpoint

### 10.4.3 Safety Analyses

- Safety endpoints will be analyzed as summary statistics during treatment
- Adverse events will be coded using the Medical Dictionary for Regulatory Activities
  - Each AE will be counted only once for a given participant
  - Each AE will be presented by System Organ Class
  - The duration, relationship, severity, and outcome of each AE will be reported
  - AE's will be ascertained from adherence and PI-reported
  - AE's leading to premature discontinuation from the study and serious treatment-emergent AE's will be presented in a table

### 10.4.4 Adherence and Retention Analyses

Due to the nature of this study, study agent usage will be assessed solely by patient self-report. Participation and study retention will be assessed by a ratio of those who participated divided by the total starting cohort for that study arm. Those that discontinue and provide a reason for discontinuation will be categorized and the information will be presented in a table.

### 10.4.5 Planned Interim Analysis

No interim analyses are planned.

#### 10.4.5.1 Safety Review

There are no anticipated side-effects to the investigational agent. The control agent is FDA approved for the condition being studied in this trial. Thus, study enrollment will only be stopped if unforeseeable, significant side effects or life-threatening adverse events occur in either study cohort. No statistical rules will be used to halt enrollment due to the short duration of the study and lack of interim analysis.

Patients will be counseled at the start of the study to call Dr. Shavy Nagpal or Dr. Lila Nachtigall for any side-effect or AE they believe is related to study medication usage. Otherwise, after the baseline visit, the next formal visit will be the final visit at week 12 when medication safety questions will be asked.

### 10.4.6 Additional Sub-Group Analyses

Due to the small cohort size of this pilot study, there will be no sub-group analysis.

### 10.4.7 Exploratory Analyses

N/A

### *10.5 Sample Size*

This study would be the first US-based randomized trial investigating HLA's usage for GSM treatment, to the authors' best knowledge. Thus, the sample size of 60 has been chosen to pilot the presented protocol, to assess feasibility and acceptability in quality of life for HLAs and to gather preliminary effectiveness for planning a larger effectiveness trial. The authors acknowledge the limitations of having enrolling 60 individuals, including generalizability. However in this initial stage of study implementation and design, expect this number to provide sufficient information.

No study to date has used the VSQ to assess the impact of treatment modalities for GSM, so there is no historical data to provide an assumed mean score. However, with 30 individuals randomized to each study treatment, we expect to have at least 80% probability of achieving a 95% confidence interval (CI) width of 1.7, assuming a standard deviation in the VLM of 2. With fewer individuals at any timepoint, the width of the CI will increase.

The assumed drop-out, withdrawal, cross-over and missing data rate is assumed to be 33%, which explains the enrollment goal of 60 to allow for 40 evaluable patients. This is a conservative estimate because the missing data rates in RCT's from four major journals has shown to be 20% or greater in about 18% of trials, which was also seen in quality-of-life studies (26, 27). We will monitor reasons for drop out and withdrawal of treatment to improve study adherence and follow up.

All participants will be included in the intent to treat analyses, and those participants who use the study intervention for at least 12 weeks will be included in the per-protocol analysis.

### *10.6 Measures to Minimize Bias*

#### 10.6.1 Enrollment/Randomization/Masking Procedures

While blinding would be desired in this study, it is not feasible due to the study drugs having different formulations. Therefore, once randomization is performed, investigators and patients will know which study arm patients are assigned to. The implication of lack of blinding is that there could be potential bias regarding patient report of symptomatic improvement and provider record of measurements, such as VAS scores. However, the goal of this study is to be a pilot study to allow for a larger RCT in the future that could potentially be blinded and allow for minimization of biases.

To reduce bias, randomization will be used with allocation 1:1 to each treatment group. Block randomization will be used due to the small sample size of each study arm using Trialmaster. Replacement of patients who discontinue will not be allowed since the enrollment goal of 60 is conservative to account for drop-outs, early discontinuation, and lost to follow up patients.

## 11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects'

diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

# 12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

# 13 Ethics/Protection of Human Subjects

## *13.1 Ethical Standard*

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## *13.2 Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

## *13.3 Informed Consent Process*

### 13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol: patient consent form, key study information.

### 13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

## *13.4 Posting of Clinical Trial Consent Form*

N/A

## *13.5 Participant and Data Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

### 13.5.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to study GSM. No genetic testing will be performed.

- Storage: Access to stored samples will be limited using locked cabinets. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using Trialmaster.

Data collected for this study will be analyzed and stored using TrialMaster. After the study is completed, the de-identified, archived data will be transmitted to and stored on the NYUMC computer network, under the supervision of Dr. Shavy Nagpal, for use by other researchers including those outside of the study without patient identifiers. Permission to transmit data to NYUMC computer network will be included in the informed consent.

There will be no biological samples stored.

When the study is completed, access to study data will be provided through the password protected NYUMC computer network.

# 14 Data Handling and Record Keeping

## *14.1 Data Collection and Management Responsibilities*

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

## *14.2 Study Records Retention*

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the

sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

### *14.3 Protocol Deviations*

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

### *14.4 Publication and Data Sharing Policy*

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and AE. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

# 15 Study Finances

## *15.1 Funding Source*

This study is financed by JDS therapeutics.

## *15.2 Costs to the Participant*

All office visits, tests and treatment drugs for the trial will be provided to the patient free of cost. However, the patient will not be compensated for participating in the study, nor will reimbursement be provided for travel costs to the office.

# 16 Study Administration

## *16.1 Study Leadership*

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study Chairman, the PI of the Coordinating Center, the PI of the clinical sites, chairperson of the Study Coordinators subcommittee, and the PI of the Central Biochemistry Laboratory. The Steering Committee will meet in person at least annually.

# 17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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# 19 Attachments

## 19a The Vulvovaginal Symptom Questionnaire

**The Vulvovaginal Symptom Questionnaire**

The following questions were developed to assess skin symptoms of women. The skin surrounding the vagina is called the vulva. Just like skin in other parts of the body, the vulva can sometimes become irritated. Many women experience discomfort in the region of the vulva. These symptoms may be mild, but can sometimes be severe. The following questions will ask you about your vulvar skin symptoms during the past week.

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**During the past week, have you been bothered by:**

| | | |
|---|---|---|
| **1.** | Your vulva itching? | 0□ No 1□ Yes |
| **2.** | Your vulva burning or stinging? | 0□ No 1□ Yes |
| **3.** | Your vulva hurting? | 0□ No 1□ Yes |
| **4.** | Your vulva being irritated? | 0□ No 1□ Yes |
| **5.** | Your vulva being dry? | 0□ No 1□ Yes |
| **6.** | Discharge from your vulva or vagina? | 0□ No 1□ Yes |
| **7.** | Odor from your vulva or vagina? | 0□ No 1□ Yes |
| **8.** | Worry about your vulvar symptoms? (for example, that it will spread, get worse, scar, etc.) | 0□ No 1□ Yes |
| **9.** | The appearance of your vulva? | 0□ No 1□ Yes |
| **10.** | Frustration about your vulvar symptoms? | 0□ No 1□ Yes |
| **11.** | Embarrassment about your vulvar symptoms? | 0□ No 1□ Yes |
| **12.** | The effects of your vulvar symptoms on your interactions with others? | 0□ No 1□ Yes |
| **13.** | The effects of your vulvar symptoms on your desire to be with people? | 0□ No 1□ Yes |
| **14.** | Your vulvar symptoms making it hard to show affection? | 0□ No 1□ Yes |
| **15.** | The effects of your vulvar symptoms on your daily activities? | 0□ No 1□ Yes |
| **16.** | Your vulvar symptoms affecting your desire to be intimate? | 0□ No 1□ Yes |
| **17.** | Are you currently sexually active with a partner? □ No→ Thank you. You are done with this questionnaire. □ Yes→ Please proceed with the next 4 questions | |
| **18.** | The effects of your vulvar symptoms on your sexual relationships? | 0□ No 1□ Yes |
| **19.** | Your vulvar symptoms causing pain during sexual activity? | 0□ No 1□ Yes |
| **20.** | Your vulvar symptoms causing dryness during sexual activity? | 0□ No 1□ Yes |
| **21.** | Your vulvar symptoms causing bleeding during sexual activity? | 0□ No 1□ Yes |

## 19b Revaree Package Insert

revaree™
(HYALURONIC ACID SODIUM SALT 0.25%)
Vaginal suppositories
For intravaginal use only

**PRODUCT DESCRIPTION**
REVAREE vaginal suppositories are semi-solid, off-white suppositories for intravaginal administration. Each 2 g vaginal suppository contains 5 mg of hyaluronic acid sodium salt in a base consisting of a mixture of semi-synthetic glycerides. REVAREE vaginal suppositories carry out its activity thanks to the presence of hyaluronic acid, a mucopolysaccharide which is abundantly distributed in many body tissues. Hyaluronic acid has the capacity of retaining water thereby forming a moist environment that is supportive of hydration and lubrication.

**INDICATIONS**
REVAREE is 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. This product is not compatible with natural rubber latex, polyurethane, and polyisoprene condoms.

**INSTRUCTIONS FOR USE**
Place the suppository into the vagina, preferably at bedtime.
The frequency with which the product should be used depends on the grade of the vaginal dryness. One vaginal suppository every two or three days for a period of thirty days is suggested, unless otherwise recommended by a health care provider. Avoid excessive handling of the vaginal suppository; it is designed to melt at body temperature.


*Figure 1*

1. Remove the vaginal suppository from its packaging by pulling on the two pre-cut flyers of the plastic strip (as shown in Figure 1).
2. Holding the suppository with your thumb and a finger, insert it into the vagina.
3. Using your finger, gently push the suppository into the vagina as far as it will comfortably go. This should be done while lying on your back with your knees bent.
4. Once inside the vagina, the suppository melts. Lie down as soon as possible. This will keep leakage to a minimum.

**INGREDIENTS**
Hyaluronic acid sodium salt 5 mg, semi-synthetic glycerides.

**CONTRAINDICATIONS**
The administration of the product is contraindicated in any patient with a known or suspected hypersensitivity to any of its ingredients.

**PRECAUTIONS**
There are no studies of REVAREE vaginal suppositories in pregnant and breast feeding women. Therefore, in such circumstances, the safety of use of the product has not been established and it is necessary to consult a doctor.

**WARNINGS**
- Use of all products for topical use, especially if prolonged, may cause sensitisation. If this occurs, stop treatment and consult the doctor to start suitable therapy.
- If your condition worsens, consult a doctor immediately.
- Keep the product out of the reach of children.
- Avoid contact with eyes.
- Do not swallow.
- The expiry date (EXP) is stated both on the pack and on the plastic strip and it refers to the product in an unopened and correctly stored pack. Do not use after the date stated on the pack, or if the pack is opened or damaged.
- Do not use with condoms.
- This is not a spermicide and does not provide protection against pregnancy.

**INTERACTIONS**
Interactions with other products are not known, therefore it is advisable to consult a doctor before using REVAREE vaginal suppositories in association with other medical devices, drugs or other products for vaginal use.

**ADVERSE REACTIONS**
All suspected adverse reactions occurring during the treatment with REVAREE vaginal suppositories should be reported to a doctor.

**HOW SUPPLIED**
REVAREE is available as suppositories for vaginal use. Each pack contains 10 single-use vaginal suppositories of 2 g.

**STORAGE**
Store the product tightly closed, away from light and heat, preferably at a temperature between 4 °C (39 °F) and 25 °C (77 °F). Avoid heat over 30 °C (86 °F).

**NOT MADE WITH HORMONES NOT MADE WITH PARABENS**

**MANUFACTURED BY:** FARMA-DERMA s.r.l.
Via dell'Artigiano 6-8 — 40010 Sala Bolognese (BO) — ITALY

**DISTRIBUTED BY:** JDS Therapeutics, LLC
1 Manhattanville Road, Suite 104 Purchase, NY 10577

**DATE OF REVISION** 2018/02 DRA1367022018

USA 961: REV 01 • 02/2018

## 19c Estrace Package Insert
https://www.allergan.com/assets/pdf/estrace_pi

## 19d Data Tracking Sheet Sample

NYU HLA vs. Estrogen Study Tracking Document

| | | | | | | Baseline Measures ------> | | | | | | 8 Week Measures ------> | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject Number | Subect Name or Initials | Study Treatment | Age | Years Post-menopausal | HRT history | Baseline VSQ score | Baseline VMI | Baseline pH | Baseline Itching VAS score | Baseline Dryness VAS score | Baseline Dyspareunia VAS score | 8 week VSQ score | Week 8 VMI | Week 8 pH | Week 8 Itching VAS score | Week 8 Dryness VAS score | Week 8 Dyspareunia VAS score |
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## 19e Patient Consent Form
Attached separately

## 19f Patient Key Information
Attached separately

## 19g Female Sexual Function Index

**Appendix 1. Female Sexual Function Index Scoring**

| Question | Response Options |
|---|---|
| 1. Over the past 4 weeks, how **often** did you feel sexual desire or interest? | 5 = Almost always or always<br>4 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>2 = A few times (less than half the time)<br>1 = Almost never or never |
| 2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest? | 5 = Very high<br>4 = High<br>3 = Moderate<br>2 = Low<br>1 = Very low or none at all |
| 3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse? | 0 = No sexual activity<br>5 = Almost always or always<br>4 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>2 = A few times (less than half the time)<br>1 = Almost never or never |
| 4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse? | 0 = No sexual activity<br>5 = Very high<br>4 = High<br>3 = Moderate<br>2 = Low<br>1 = Very low or none at all |
| 5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse? | 0 = No sexual activity<br>5 = Very high confidence<br>4 = High confidence<br>3 = Moderate confidence<br>2 = Low confidence<br>1 = Very low or no confidence |
| 6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse? | 0 = No sexual activity<br>5 = Almost always or always<br>4 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>2 = A few times (less than half the time)<br>1 = Almost never or never |

| | |
|---|---|
| 7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse? | 0 = No sexual activity<br>5 = Almost always or always<br>4 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>2 = A few times (less than half the time)<br>1 = Almost never or never |
| 8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse? | 0 = No sexual activity<br>1 = Extremely difficult or impossible<br>2 = Very difficult<br>3 = Difficult<br>4 = Slightly difficult<br>5 = Not difficult |
| 9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse? | 0 = No sexual activity<br>5 = Almost always or always<br>4 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>2 = A few times (less than half the time)<br>1 = Almost never or never |
| 10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse? | 0 = No sexual activity<br>1 = Extremely difficult or impossible<br>2 = Very difficult<br>3 = Difficult<br>4 = Slightly difficult<br>5 = Not difficult |
| 11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)? | 0 = No sexual activity<br>5 = Almost always or always<br>4 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>2 = A few times (less than half the time)<br>1 = Almost never or never |
| 12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)? | 0 = No sexual activity<br>1 = Extremely difficult or impossible<br>2 = Very difficult<br>3 = Difficult<br>4 = Slightly difficult<br>5 = Not difficult |
| 13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse? | 0 = No sexual activity<br>5 = Very satisfied<br>4 = Moderately satisfied<br>3 = About equally satisfied and dissatisfied<br>2 = Moderately dissatisfied<br>1 = Very dissatisfied |
| 14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner? | 0 = No sexual activity<br>5 = Very satisfied<br>4 = Moderately satisfied<br>3 = About equally satisfied and dissatisfied<br>2 = Moderately dissatisfied<br>1 = Very dissatisfied |
| 15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner? | 5 = Very satisfied<br>4 = Moderately satisfied<br>3 = About equally satisfied and dissatisfied<br>2 = Moderately dissatisfied<br>1 = Very dissatisfied |
| 16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life? | 5 = Very satisfied<br>4 = Moderately satisfied<br>3 = About equally satisfied and dissatisfied<br>2 = Moderately dissatisfied<br>1 = Very dissatisfied |
| 17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration? | 0 = Did not attempt intercourse<br>1 = Almost always or always<br>2 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>4 = A few times (less than half the time)<br>5 = Almost never or never |
| 18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration? | 0 = Did not attempt intercourse<br>1 = Almost always or always<br>2 = Most times (more than half the time)<br>3 = Sometimes (about half the time)<br>4 = A few times (less than half the time)<br>5 = Almost never or never |
| 19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration? | 0 = Did not attempt intercourse<br>1 = Very high<br>2 = High<br>3 = Moderate<br>4 = Low<br>5 = Very low or none at all |

## 19h Vaginal Symptom Index

Vaginal Symptom Index Score

1. Vaginal dryness
0=none
1=mild
2=moderate
3=severe

2. Vaginal soreness
0=none
1=mild
2=moderate
3=severe

3. Vaginal irritation
0=none
1=mild
2=moderate
3=severe

4. Vaginal discharge
0=none
1=mild
2=moderate
3=severe

5. Dyspareunia
0=none
1=mild
2=moderate
3=severe

## 19i Patient Global Impression of Improvement

Check the number that best describes how your post-intervention condition is now, compared with how it was before the intervention:

Very much better = 1

Much better = 2

A little better = 3

No change = 4

A little worse = 5

Much worse = 6

Very much worse = 7

# 20 Schedule of Events

| Activity | Visit 1 (Day 0) | Visit 2 (12 weeks +/- 1 week) |
|---|---|---|
| **Study team procedures** | | |
| Routine history of present illness, medical, obstetrical, gynecological, surgical, medication, HRT usage history | x | |
| Vitals and routine physical exam including pelvic | x | x |
| GSM Diagnosis | x | |
| Consent | x | |
| VAS score for dyspareunia, itching, and dryness | x | x |
| Rugal fold presence | x | x |
| VSQ, FSFI, VSI | x | x |
| Randomization | x | |
| Study drug/device dispensation | x | |
| Participant study drug/device compliance check | | x |
| Check for side-effects and/or AE due to study agent | | x |
| ***Laboratory Assessments*** | | |
| Urine pregnancy test | x | |
| Urine analysis | x | |
| Vaginal pH | x | x |
| VMI | x | x |