

Study of Dilute Veregen ®, 5% sin catechins ointment, a botanical FDA approved drug derived from Green Tea Leaves Camellia sinensis, for the Treatment of Significant to Severe Vulvar Pain from Secondary Provoked Vestibulodynia in Sexually Active, Post-Menopausal Women with Vulvovaginal Atrophy

PROTOCOL:

1. STUDY SYNOPSIS:

Introduction: Secondary provoked vestibulodynia is defined as significant to severe pain of at least 3 months durations, in the vulvar vestibule during normal manipulation of the vulvar vestibule that is significant enough to cause the afflicted woman distress. Secondary vs primary provoked vestibulodynia is distinguished by whether the pain has been present since the patient's first episode of vaginal penetration (ie, lifelong or primary provoked vestibulodynia (PPVD) or after a period of pain-free activities (ie acquired or secondary provoked vestibulodynia (SPVD). This study is for women with secondary provoked vestibulodynia where a woman recalls a previous time when she did not experience vestibulodynia. Provoked indicates that a stimulus is needed to invoke the pain. For example, intercourse, masturbation, a tampon, digital manipulation or any other provocation. Pain at rest without manipulation is considered "unprovoked" and not subject of this study.

One cause of secondary provoked vestibulodynia may be the use of exogenous progesterone(s) leading to the aberrant proliferation of nociceptive (pain) sensory fibers in the vulvar vestibule. Topical estrogen creams are among the many different inconsistent or non-efficacious treatments for SPVD in post-menopausal women. Leclair CM<sup>1</sup>, Goetsch MF, Li H, Morgan TK. Histopathologic characteristics of menopausal vestibulodynia Obstet Gynecol. 2013 Oct;122(4):787-93. Not all menopausal women wish to take estrogen and is some women this type of treatment is medically contraindicated.

The study drug is Veregen® (sin catechins) Ointment, an FDA approved, 2006, marketed botanical drug product for topical use in the treatment of external genital warts. The drug Veregen® is 15% sin catechins, which is a partially purified fraction of the water-soluble extract of green tea leaves from Camellia sinensis, and is a mixture of catechins and other green tea components. Veregen ® is indicated to be topically applied as multiple 0.5 cm strands (i.e., to each and every visible genital wart) three times a day, continuously, for up to 16 weeks. In contrast, the study will be using Veregen ® ointment diluted, by the certified compounding pharmacy, with USP petrolatum w/w, to a drug concentration of 5% sin catechins. This diluted Veregen, 5% sin catechins ointment, will be topically applied to the external genitalia, (vulvar vestibule) as a single 0.5cm strand, once a day, for 6 weeks.

In a small group of 12 patients in Wendy Epstein, M.D., F.A.A.D.'s private clinical practice it was found that the topical daily application of 5% sin catechins, diluted Veregen ®, applied as a single, daily dose of 0.5cm strand to the vulvar vestibule relieved or eliminated secondary provoked vestibulodynia, (SPVD) in post-menopausal patients. This effect was seen without change in the vaginal maturation index. The vaginal maturation index (VMI) is an assessment done to establish the estrogen effect on the vagina. This is a ratio obtained by checking out on a smear the three main cell types found in the vagina: the parabasal cells, intermediate cells and superficial cells. This was a fortuitous clinical discovery because many post-menopausal women are unwilling or unable to use any form of exogenous estrogens. The current study is being independently conducted in order to demonstrate, compared to placebo, whether 5% sin catechins ointment, applied locally to the vulvar vestibule, can reduce or eliminate SPVD in post- menopausal women without

effecting the vaginal maturation index, thus not having an estrogenic effect on the vaginal epithelium. The National Vulvodynia Association's website is <https://www.nva.org/> and is an excellent resource for detailed information about vestibulodynia. An overview of vulvodynia including secondary provoked vestibulodynia (SPVD) maybe found in an excellent review of vulvodynia (Vulvodynia: Definition, Prevalence, Impact, and Pathophysiological Factors (Caroline F. Pukall, PhD, Andrew T. Goldstein, MD, Sophie Bergeron, PhD, David Foster, MD, Amy Stein, DPT, Susan Kellogg-Spadt, PhD, and Gloria Bachmann, MD J Sex Med 2016;13:291-304).

**Study Design:** The study design is a prospective, randomized, placebo controlled, double blinded, clinical trial on the efficacy of 5% sinecatechins, green tea ointment in alleviating significant to severe vulvar pain in post-menopausal women with secondary provoked vestibulodynia.

**Study Related Procedures:** Drs. Dena Harris and Lila Nachtigall and their medical assistants will perform a standard of care routine gynecologic examination of the external genitalia and vagina. In order to establish an objective baseline of vestibular appearance, a visual inspection will be documented, including presence or absence of erythema. In order, to further establish the post-menopausal, non -estrogenized state of the vagina, testing of the vaginal pH as well as superficial smears of the lateral vaginal wall will be taken to determine vaginal maturation index, as is the standard of care. To document localization of areas of significant/severe pain in the vulvar vestibule, a standard of care, Q-tip test will be performed. The Q-tip test involves palpating the vulvar vestibule with a soft, cotton wool-tipped stick and noting both location and intensity of any pain. These procedures are standard of care. None of these procedures are experimental.

Industry standard questionnaires will be administered to subjects at the initial screening and each of the three subsequent study clinic visits. These include the following industry standard, well established in the literature, questionnaires: Female Sexual Function Index (FSFI) Wiegel M et al J. Sex Marital Ther. 2005; 31: 1-20, Vulvovaginal Symptoms Questionnaire (VVSQ) Erekson et al, Menopause 2013 September: 20(9): 973-979, Sexual Distress Scale-Revised (SDS-R) DeRogatis L, et al J. Sex Med. 2008: 5: 37-364., In addition, the subjects will be asked to keep a weekly diary documenting their pain on a 0- 10 point Numerical Rating Scale (NRS) of pain intensity where (0) is no pain; (1-3) is mild pain; (4-6) is moderate pain (7-9) is significant pain and ( 10) is severe pain, and to fill out the industry well established in the literature questionnaire: Sexual Activities Log (SAL) DeRogatis, L R, et al. J. Sex Med 2009;6:175-183 in order to document that they are sexually active and the impact that the study medication has or has not had on their sexual activity.

By definition, vestibulodynia, a manifestation of Genito-pelvic Pain/Penetration Disorder, a Female Sexual Disorder must be of significant to severe pain that causes a women distress with a duration of at least 3 months. The Numerical Rating Scale, pain scale, establishes that they meet the criteria of significant to severe pain to be included in the study. The Vulvovaginal Symptoms Questionnaire characterizes qualities of the pain. The Sexual Distress Scale-Revised demonstrates whether that the pain is significant enough to cause a women distress. The Female Sexual Function Index corroborates the existence of the pain and its effect on a woman's sexual function in 6 areas: sexual interest, sexual arousal, lubrication, orgasm, satisfaction, and pain. These questionnaires are standard of care. None of these questionnaires are experimental.

No costs will be incurred by the subjects. The Sponsor is funding the costs of the procedures.

**Background:** There is no known effective treatment for secondary provoked vestibulodynia and therefore a review of the literature is relevant only to illustrate what has not been effective in alleviating this common human malady. The National Vulvodynia Society and its website contains extensive documentation of the condition and accompanying literature relevant to the epidemiology, characterization and ineffective or marginally effective treatments.

### 3. OBJECTIVES:

The main objective in this study is to demonstrate whether topical 5% sinecatechins ointment is significantly more efficacious than placebo in alleviating or curing significant to severe vulvar pain due to secondary provoked vestibulodynia, as the most bothersome symptom, in post-menopausal women with evidence of estrogen deficiency (vulvovaginal atrophy) without estrogenic effects on their vaginal epithelium.

### 4. SUBJECT SELECTION:

64 women will be recruited from the practice of Drs. Dena Harris and Lila Nachtigall and their colleagues. Inclusion criteria will include being sexually active (either with partner or self), post- menopausal, (without spontaneous menses for at least two years, a non-estrogenized vaginal maturation index and a vaginal pH >4.6); experiencing at least 3 months duration with, at least, significant pain on the Numerical Rating Scale (NRS) 0-10-point scale (0-no pain, 1-3 mild, 4-6-moderate, 7-9-significant, 10-severe pain) from secondary provoked vestibulodynia (SPVD). The pain must be significant enough to cause them distress as measured by Female Sexual Distress Scale-Revised (FSDS-R). A score of  $\geq 11$  effectively discriminates between women with Female Sexual Distress and no FSD. The pain must be significant enough to affect their sexual function, Female Sexual Function Index (FSFI) with a score of 26 or less and effect their sexual activities noted weekly with the standard Sexual Activities Log (SAL).

The intake pelvic examination, including of the vagina, will be normal for a woman's age and years since menopause.

Subjects may or may not have points of erythema in the vulvar vestibule as is common in women suffering from provoked secondary vestibulodynia.

A subject to be included in the study, must have at least significant (7) or above on the Numeric Rating Scale (NRS) of pain intensity (NRS) during the Q-tip test performed at the initial screening visit. Whereas, the Q-tip test must elicit at least significant pain intensity, visible erythema is not necessary to be included in the study. The descriptive characteristics of the pain will be documented using the standard Vulvovaginal Symptoms Questionnaire (VVSQ).

Generally healthy women must meet the following eligibility criteria:

1. For surgically menopausal women, be 20-70 years of age and at least 12 months post menopause.
2. For naturally postmenopausal women, be 40-70 years of age and at least 1 year post menopause (defined as no spontaneous menses for 1 year).
3. In screening their vaginal pH will be 4.6 or greater and their vaginal maturation index will be consistent with vaginal atrophy. Vaginal atrophy is thinning, drying and of the vaginal walls due to having less estrogen in the body.
4. Be, sexually functional, both psychologically and physically, whereby a woman is to be psychologically interested in sexual activity and physically sexually active with regular vestibular including vaginal introital genital manipulation whether through masturbation or partner sex, whether using digits, oral sexual contact, sex toys, and/or penile penetration present at regular intervals each month during the 4-week pre-treatment and the 6- week treatment period of the study and the 8th- week follow-up period of the study.

5. Be able and willing to participate in the study as evidenced by providing written informed consent.
6. Answer affirmatively to ALL of the following questions:
  - a. Before your vulvar pain, would you say that in general, your sex life was good and satisfying?
  - b. Since you have been experiencing vulvar pain, do you feel you have experienced a meaningful loss in your desire for sex?
  - c. Since experiencing vulvar pain, do you feel you have experienced a significant decrease in your sexual activity?
  - d. Are you concerned or bothered by your current level of desire for or interest in sex?
  - e. Would you like to see an increase in your level of interest or desire for sex and sexual activity?

Exclusion Criteria:

Women will be screened for study participation according to the following exclusion criteria at Visit 1 (Week -4) or as specified. Eligible women must not:

1. Have taken estrogen-containing treatments, either by systemic or local route, for three months or more.
2. Have any physical limitations or sexual trauma that would interfere with normal sexual function.
3. Have used estrogen, including vaginal conjugated equine estrogen, or estrogen progestin therapy, vaginal oestrinol or low-dose vaginal oestradiol or any other exogenous estrogenic compound pharmaceutical including OTC plant based estrogenic substances in the last 12 weeks. Have used tablet or powder forms of phyto-estrogens for less than 12 weeks prior to Visit 1 (Week 0).
4. Have used within the last 12 weeks any of the following medications/preparations that may interfere with the study purpose: systemic corticosteroids (acute use for fewer than 7 days is accepted), SSRI's, tricyclic antidepressants, anti-androgens, spironolactone, PDE5 inhibitors (Viagra®), or SERMS, including tamoxifen, aromatase inhibitors.
5. Have occasionally used (averaging more than once a week) in the past 30 days the following preparations that may interfere with the study purpose: DHEA or other drugs or supplements that may, in the opinion of the Investigator, affect sexual function.
6. Be experiencing any chronic or acute life stress relating to any major life change, such as recent loss of income or the death of a close family member, that may, in the opinion of the Investigator, significantly interfere with sexual function.
7. Have significant psychiatric disorder, a significant alcohol or drug dependency and/or be receiving pharmacologic treatment for such illness or disorder.
8. Have evidence of clinically significant organic disorder on the history and/or physical examination that would, in the opinion of the Investigator, put the patient at risk, prevent the patient from completing the study, or otherwise affect the outcome of the study.
9. Have a history of genital herpes because of the episodic nature of genital herpes and of the known possibility of occurrence of herpetic pain without visible dermatologic manifestations of herpes. Genital herpes and its accompanying genital pain may obscure the source of the genital pain experienced and confound the ability to determine the efficacy of treatment/placebo on endpoint of alleviation of pain in women with SPVD.
10. Have any infection of the genitalia
11. Have lichen sclerosis, lichen planus, contact dermatitis, psoriasis or any inflammatory condition or abrasions of the vulva

12. Have an episiotomy scar in the area where pain is perceived as it may confound the etiology of the perceived pain
13. Have diabetes.

## 5. STUDY PROCEDURES:

Duration of Study: Once subjects are screened and enrolled into the study, the duration of participation in the study will be 6 weeks from the beginning of the study to the last visit. Follow up questionnaires will be filled out at 8 weeks and electronically entered or mailed in to Drs. Dena Harris or Lila Nachtigall's study clinic office.

Subjects will be given a written description of the study and possible untoward effects of the protocol. They will sign the IRB-approved informed consent. The schedule and activities of visits will be given to the subject, along with instructions about notification in case of untoward events.

Accepted subjects will be randomized and only a non-participant in the clinical trial will hold the code. Except for subjects who decide to leave the trial because of any adverse reactions (i.e., irritation), prior to its completion, the code will not be broken prior to the completion of the last subject's protocol.

Study Procedures: Each and every procedure performed is a standard procedure. These procedures will be performed at a screening visit and each of the three subsequent study clinic visits. Initial screening; week 0, week 3; week 6. Please note, in addition to study related procedures that a standard of care medical history, including past and current medical history, medications, allergies, height, weight and blood pressure will be taken initially and reviewed for any changes on each study clinic visit.

Examination: The intake pelvic examination, including of the vulva and vagina, will be normal for a woman's age and years since menopause.

Documentation of Erythema: At each visit, erythema of the vestibule will be noted as "present" or "not present" and its location and that of the Q-tip induced pain entered as a drawing on the study chart, see below. There will be no photographic documentation of subjects.

The Q-tip test will be performed at the initial screening visit and all subsequent clinic visits (week 0, 3, 6). The Q-tip test is a standardized test and involves palpating the vulvar vestibule with a soft, cotton wool-tipped stick and noting the existence of any pain, its location and intensity. Documentation is then made of both the location and intensity of any pain. The intensity of the pain is rated using a standard Numeric Rating Scale (NRS) of pain intensity where. (0) is no pain; (1-3) is mild pain; (4-6) is moderate pain (7-9) is significant pain and (10) is severe pain. Upon initial screening the pain intensity must be at least 7 (significant). Documentation of sites of elicited or provoked pain will be noted on a clock face standardized clock face diagrammatic drawing with 6 o'clock being at the center of the posterior fourchette of the vulvar vestibule.

Assessment of vaginal atrophy: The Vaginal Maturation Index and Vaginal pH together will be used to establish the lack of estrogenic effect on the vaginal epithelium. Weber MA<sup>1</sup>, Limpens J, Roovers JP Assessment of vaginal atrophy: a review Int Urogynecol J. 2015 Jan;26(1):15-28. . Tucker KM, Godha, Mirkin Archer DF Vaginal pH: a simple assessment highly correlated with vaginal morphology and symptoms in postmenopausal women Menopause. 2018 Mar 5.

Vaginal Maturation Index: Vaginal smears will be taken from the upper one third of the lateral vaginal wall for the Vaginal Maturation Index. The Vaginal Maturation Index quantifies the relative proportion of the vaginal parabasal (P), intermediate (I), and superficial (S) cells presented as % P / % I / % S. Vulvovaginal atrophy or estrogen deficiency will be demonstrated by a high percentage of parabasal cells, some intermediate cells and a paucity of superficial cells.

Vaginal pH: Vaginal pH > 4.6 as indication of atrophy, in the absence of infection or semen, of the vaginal epithelium using standard pH paper. Subjects will be asked not to have intercourse with semen deposited in the vagina 24 hours prior to their clinic study visit.

The schedule and activities of visits will be given to the subject, along with instructions about notification in case of untoward events.

WEEK		1	2	3	4	5	6	8
Pain level (NRS), SAL	X X	X	X	X	X	X	X	X
History, Exam, MI, pH, Q-tip	X			X			X	
FSFI, VVSQ, FSD-R	X			X			X	X

Patients will be enrolled in the study and randomized to treatment only after all the inclusion and exclusion criteria have been satisfied.

(Visit 1) Week 0

Patients will come to the study clinic to be screened according to the protocol inclusion/exclusion criteria at their first visit prior to randomization into the study. Site personnel must register the patient with the interactive voice response system (IVRS) at this visit to obtain a patient number.

After patients have signed the informed consent, site personnel will review the inclusion and exclusion criteria to ensure that the patient is eligible for the study. The following information will be recorded, or procedures performed for eligible patients. Verbal questioning is to be completed before any invasive procedures are undertaken.

1. Personal and demographic information.
2. Medical/gynecological history including year of last menstrual period to establish post-menopausal state.
3. Drug history (prescription/non-prescription/herbal supplements, including DHEA) for the previous 3 months.
4. Physical examination: The intake pelvic examination, including of the vulva and vagina, will be normal for a woman’s age and years since menopause.
5. Vaginal Maturation Index

6. Vaginal pH, bacterial screening swab
7. Q-tip Test to establish localization and rating NRS of vulvar, vestibular pain.
8. Vital signs including blood pressure and heart rate (after sitting 5 minutes) and body temperature, height and weight.
9. Assessment of acute life stress relating to any major life change that interferes with sexual function.
10. Status of patient's sexually functional, both psychologically and physically
11. Establishing that patient is sexually active with self (masturbation) and/ or with partner.
12. During the consent process, all of the questionnaires (including SAL, FSFI, NRS, VVSQ, FSDQ-R) will be reviewed with the patients to allow them to read what they will be expected to complete during their participation in the pre-treatment, treatment and post-treatment periods of the study.
13. At this visit, the study coordinator or other designated study personnel should read the SAL instructions to the patient and ask her if she has any questions. At the end of the initial visit, each patient will be given copies of the SAL or instructions that they will receive an email in order to fill out questionnaires online at the end of week 1, 2, 4, 5 and asked to complete one per week at home, at the end of Day 7, during the treatment period. They will receive a final email at the end of week 8 with instructions to fill out questionnaires anonymously online.
14. All questionnaires, both in clinic and at home, should be completed by each patient, on her own, in a private place. The patient will turn in the completed questionnaires over to the Investigator, with the option of inserting the questionnaire into an envelope which will be labeled with the patient number, name of the questionnaire and visit number. This will be done to enhance the confidentiality of questionnaires for the patient. The Investigator will fax the documents to the Sponsor via the IRIS Imaging System. Originals will be retained at the site. Alternatively, the subject may fill out the questionnaires on the secure, HIPAA compliant, website.
15. The vaginal pH, pH should indicate non-estrogenized vaginal epithelium according to the state criteria. bacterial screen results must be reviewed, signed, and dated by the Investigator prior to dispensing the study medication.

Patients will be enrolled in the study and randomized to treatment only after all the inclusion and exclusion criteria have been satisfied.

At the end of Visit 1, Week 0, site personnel will obtain investigational medication from IVRS and patients will receive a 3-week, 15 gram, supply of the investigational drug or the placebo ("the ointment"). They will be instructed on how to apply "the ointment". They will be given written instructions on how to apply the ointment.

*Instruction Sheet for Use of "The Ointment":*

- Use "the ointment" only on the area affected exactly as indicated by Drs. Harris or Nachtigall.
- Wash your hands before and after application of the ointment. A small amount (0.5cm) of the ointment should be applied to the affected area using your finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment as directed by Drs. Harris or Nachtigall.
- Apply the ointment once a day; if any irritation occurs stop using the ointment and notify Dr. Dena Harris at the telephone number (212-941-0011) or Dr. Nachtigall's office at 212-779-8353. Do not restart to use the ointment until your irritation completely resolves. You will then be instructed to reduce the frequency of application to twice per week or less depending on your discussion with and instructions from Drs. Harris' or Nachtigall's staff.

- Do not wash off the ointment from the treated area before the next application. When you wash the treatment area or bathe, apply the ointment afterwards, not before.
- Treatment with the ointment should be continued for a total of 6 weeks as instructed by Drs. Harris or Nachtigall. You will be seen at regular intervals during this time period by Drs. Harris or Nachtigall.
- the ointment is not a cure for any condition and your condition may reoccur during or after treatment and may need further treatment.

*What should I avoid while using catechins ointment?*

- Do not apply the ointment on open wounds.
- While being treated with the ointment, and you do choose to have sexual contact, (genital, anal or oral) note that the ointment may weaken condoms and vaginal diaphragms therefore you must wash off the ointment carefully before having protected sexual contact. Talk to your doctor about safe sex practices.
- Avoid contact with your eyes, nostrils and mouth while ointment is on your finger(s).
- Do not expose the genital area treated with the ointment to sunlight, sunlamps or tanning beds.
- Do not cover the treated area. Loose-fitting undergarments can be worn after the ointment

PLEASE NOTE• The ointment is naturally a light reddish-tan color and therefore may stain your light-colored clothes and bedding. It is recommended to wear darker colored undergarments or an unscented disposable cotton panty liner while using the ointment.

*How should I store catechins ointment?*

- Store the ointment refrigerated or up to 77°F (25°C). • Do not freeze the ointment.
- Make sure the cap on the tube is tightly closed.
- Bring the tube of the ointment when you come to your scheduled clinic study visits.

Keep all medicines out of the reach of children. Do not give the ointment to other people, even if they have the same symptoms.

All subsequent visit dates for the treatment period will be calculated from Week 0 (Visit 1) date.

Week 3 (Visit 2)

The following procedures will be performed at the study clinic at the end of Week 3:

1. Tubes of “the ointment” will be collected.
2. Update to medical/gynecologic/drug history.
3. Physical examination: An examination, including of the vulva and vagina.
4. Vaginal pH
5. Q-tip Test to establish localization and rating NRS of vulvar, vestibular pain.
6. Vital signs including blood pressure and heart rate (after sitting 5 minutes) and body temperature, height and weight.

7. Assessment of acute life stress relating to any major life change that interferes with sexual function.
8. Status of patient's sexually functional, both psychologically and physically
9. Establishing that patient is sexually active with self (masturbation) and/ or with partner.
10. Collection of completed SAL's or verifying that questionnaire filled out on secure website.
11. Distribution of new copies of the SAL or verifying that questionnaire to be filled out on secure website
12. Completion of the other questionnaires: FSFI, NRS, VVSQ, FSDQ-R
13. At the end of Visit 2, site personnel will distribute to the subject, a new 3-week, 15 gram, supply of the investigational drug or the placebo ("the ointment"). The subjects will be instructed on how to apply "the ointment". The subject will be given written instructions on how to apply the ointment.

### Week 6 (Visit 3)

The following procedures will be performed at the study clinic at the end of Week 6:

1. Site personnel will collect all tubes of "the ointment".
2. Update to medical/gynecologic/drug history.
3. Physical examination: An examination, including of the vulva and vagina.
4. Vaginal Maturation Index
5. Vaginal pH
6. Q-tip Test to establish localization and rating NRS of vulvar, vestibular pain.
7. Vital signs including blood pressure and heart rate (after sitting 5 minutes) and body temperature, height and weight.
8. Assessment of acute life stress relating to any major life change that interferes with sexual function.
9. Status of patient's sexually functional, both psychologically and physically
10. Establishing that patient is sexually active with self (masturbation) and/ or with partner.
11. Collection of completed SAL's or verifying that questionnaire filled out on secure website.
12. Completion of the other questionnaires: FSFI, NRS, VVSQ, FSDQ-R
13. The tubes of the investigational drug or placebo will be collected at this last clinic visit.

Distribution of new copies of the SAL, FSFI, NRS, VVSQ, FSDQ-R, a question about any change in medications, along with self-addressed envelopes which will be labeled with the patient number for their return to the Investigator. Instructions will be given to complete the questionnaires at the conclusion of week 8. Alternatively, subject will be filling out questionnaires on secure, HIPAA compliant, website.

### Consent Protocol:

Subjects will be given a written description of the study and possible untoward effects of the protocol. They will sign the IRB-approved informed consent.

Accepted subjects will be randomized and only a non-participant in the clinical trial will hold the code. Except for subjects who are excused from the trial prior to its completion because of any adverse reaction (i.e. irritation) the code will not be broken prior to the completion of the last subject's protocol.

Subjects will be consented at the initial study visit by Dr. Lila Nachtigall or Dr. Dena Harris. Drs. Nachtigall and Harris will be available for consent discussion.

The Study Treatment: Drugs – The 5% GTO (5% sinecatechins ointment, diluted Veregen ®) in petrolatum ointment will be furnished by Town Total Compounding Center Pharmacy (415 Crossways Park Dr Suite B, Woodbury, NY 11797), at week 0, in numbered, but otherwise unmarked compressible opaque, 15gram tubes that will be examined at each visit. The placebo will be petrolatum ointment with an inert vegetable dye to visually appear the same as the drug. Subjects will be instructed to bring in their tubes at their 3 and 6-week visits. The subjects will be instructed in the application of one 0.5cm strand of either the study drug: 5% (diluted Veregen) or placebo once daily to the vulvar vestibule. Application – Subjects will be instructed to apply a 0.5cm strand, lightly to painful or reddened areas of the vulvar vestibule. This is done daily for six weeks. Subjects will apply with a fingertip, taking care to avoid placing it into the vagina. (detailed instructions provided in this document) . Compliance - At each visit the tubes will be weighed.

6. Risks/Safety Information- The risks of full strength topical Veregen ® (15% sinecatechins ointment) are well known and well documented in the accompanying package insert. Veregen ® Medigene, (Green Tea ointment, (GTO), 15% sinecatechins) is a topical FDA approved drug (2006) indicated for the treatment of external genital warts, since 2006. The package insert specifies it to be applied to each and every visible wart three times a day. The safety profile for Veregen ® has been well established. The application of one 0.5cm strand of 5% (diluted Veregen) once daily to the vulvar vestibule does not cause the potential irritation that multiple 0.5cm strands of 15% (full strength Veregen) can cause.

The use of significantly lesser doses of the drug (one 0.5cm strand), once a day vs the use of multiple 0.5 strands three times a day and use of a lower concentration of the study drug 5% sinecatechins will significantly reduce the risk of adverse reactions to the drug as seen in the on-label use of the marketed drug Veregen ® 15% sinecatechins. In fact, the use of 5% sinecatechins, 0.5cm strand, topically applied, once daily to the vulvar vestibule was found to be soothing, and reduced or eliminated vulvar pain in post-menopausal women with secondary provoked vestibulodynia (SPVD).

In Phase 3 clinical trials, a total of 397 subjects received Veregen® (15% sinecatechins) three times per day topical application for the treatment of external genital and perianal warts for up to 16 weeks.

Local irritation is the main potential side effect and in fact the goal of treatment of external genital warts with full strength Veregen (15% sinecatechins ointment) by simultaneously applying a 0.5cm strand to each and every one of multiple visible genital warts three times daily for up to 16 weeks. The mechanism of action of Veregen in clearing genital warts is unknown. (see package insert for Veregen). It was discovered that the off-labeled use of diluted Veregen (5% sinecatechins ointment) applied as a single 0.5cm strand once daily was safe and effective in alleviating the pain from SPVD, as demonstrated in the off-labeled use of Veregen with patients in private practice (see US Patent 9750716). The mechanism of action of Veregen for treating secondary provoked vestibulodynia (SPVD) is unknown but may be due to Veregen's (sinecatechins, green tea extract) known action as an antioxidant/anti-inflammatory.

The study medication and placebo have a red brown color and may therefore stain underwear. Subjects will be advised to wear panty liners every day that they apply the study medication in order to avoid staining of their underwear with the medication or placebo

**7. Monitoring and Reporting of Adverse Events/Serious Adverse Events:** During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator, Dr. Dena Harris at the telephone number (212-941-0011) or Dr. Lila Nachtigall at the telephone number (212-779-8353) If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the Investigator, Dr. Lila Nachtigall.

Monitoring of Adverse Events will be done by patients reporting any adverse event to the Investigators, Dr. Dena Harris at the telephone number (212-941-0011) or Dr. Lila Nachtigall, at the office number provided (212-779-8353). No serious adverse events are expected.

**8. Study Oversight:** In the unlikely event of the need to prematurely terminate this study of 5% sinecatechins, Dr. Nachtigall will be the one to decide to terminate the study. The study will be made available for monitoring, auditing, IRB review and regulatory inspection by providing direct access to study related source data.

## **9. Data Management- Preliminary Power Analyses and Sample Size Estimates**

### **Power Analyses**

#### **For Primary Outcome: Pain Score:**

Sample size was calculated to achieve at least 80% power with a significance level of 0.05 using a two-tailed, two-sample t test. A sample size of 56 subjects (28 subjects in treatment group and 28 subjects in the placebo group) was estimated to achieve 80% power to detect at least 2.0-points mean difference between treatment and placebo groups. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials suggests that reductions in pain intensity of at least 15–20%, or 2 points in the 0–10 scale, reflect clinically important changes (Dvorkin et al, Core Outcome Measures for Chronic Pain Clinical Trials:

IMMPACT Recommendations Pain: 2005 Jan; 113 (1-2) pp: 9-19)). The pain classification on a 0-10 scale will be as follows: 0 no pain; 1-3 mild pain; 4-6 moderate pain; 7-9 significant pain; 10 severe pain. To compensate for possible withdrawal of 15% of patients in the vulvodynia study, a total sample size of 64 participants (32 in the treatment group, 32 in the placebo group) will be required.

The power analyses were based on previous research data on the effectiveness of the off label use of dilute Veregen (5% sinecatechins ointment) green tea extract (GTE) for the treatment of significant to severe vulvar pain (Patent US 2016/0271102 A1).

### **Statistical Analyses**

Participants randomized to the dilute Veregen (5% sinecatechins ointment) green tea extract (GTE) arm will be compared to those randomized to placebo arm on demographic, descriptive and clinical variables at baseline using chi-square analysis for categorical variables, Student t test and ANOVA test for parametric data and Mann-Whitney U test for nonparametric data.

The ordinal variables (scores from the FSFI, Sexual Distress Scale revised, and the Sexual Activity Log questionnaires) will be analyzed using ANOVA test.

The nominal variables (binary categories from the Vulvovaginal Symptom Questionnaire, Erythema presence/absence and the Sexual Activities Log) will be analyzed using chi-square test. The p-values of less than 0.05 will be considered as statistically significant.

These measures will be analyzed at the following assessment points (baseline, 3-week visit, 6-week visit, and 8-week follow-up).

#### 10. IRB Review/Ethics/Informed Consent: Please see attached Informed Consent Document submitted.

##### IRB Review/Ethics/Informed Consent

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study will be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56 [add 312 for IND studies or 812 for device studies], applicable laws and the IRB requirements.

The Sponsor will submit any change to the protocol to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to subjects will be implemented immediately provided the FDA and the reviewing IRB are notified within 10 working days.

The investigator will provide each subject with full and adequate verbal and written information using the IRB approved informed consent document, including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent will be obtained prior to performing any study-related procedures, including screening and changes in medications including any washout of medications. A copy of the signed informed consent will be given to the study subject.

#### 11. Confidentiality:

- a) Records of the subject's participation in this study will be held confidential except when sharing the information is required by law or as described in the informed consent. The Investigator, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and

copy confidential study-related records which identify the subject by name. This means that absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subjects will not be identified.

- b) This study for which this IRB is submitted complies with all the requirements of the FDA under FDA regulation 21 CFR 312.2 to qualify for an IND exemption.
- c) The study will be made available for monitoring, auditing, IRB review and regulatory inspection by providing direct access to study related source data, medical records.
- d) All study-related records identifying the subject will be kept confidential and, to the extent permitted by applicable laws and/or regulations will not be made publicly available;
- e) If any results of the study are published; all subject's identities will remain confidential.
- f) In order to ensure strict privacy and confidentiality, subjects will not be identified by their name or other individual identifying characteristics. Each and every subject will be identified by a unique numerical code on all subject related study records.

12. Intended Use of the Data: Should the study confirm the efficacy of 5% sinecatechins ointment (diluted Veregen ®) in relieving or curing secondary provoked vestibulodynia in post-menopausal women without any significant effect on the maturation of the vaginal epithelium an excellent option will be available for women who suffer with this life altering condition. It would be a therapeutic option for postmenopausal women especially who because of a past history of gynecologic malignancy would be unwilling or unable to use estrogens A paper may be formulated and presented for publication in the medical literature.

The data is intended to test and therefore confirm the efficacy of local 5% sinecatechins ointment (Green Tea ointment) in the reduction or elimination of secondary provoked vestibulodynia with the added benefits of increasing lubrication and improving sexual function without demonstrable effects on the vaginal epithelium.