

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

**TITLE: Safety and efficacy of human fibroblast lysate cream for vulvar lichen
sclerosus as compared to placebo**

SPONSOR: NEOCUTIS, Inc.
San Francisco, California

INVESTIGATOR: Andrew Goldstein, M.D.

SITE OF INVESTIGATION: Andrew Goldstein (M.D.)
The Centers for Vulvovaginal Disorders
3 Washington Circle NW, Suite 205
Washington, DC 20037
United States

**STUDY-RELATED
PHONE NUMBER(S):** Andrew Goldstein, M.D.
(202) 887-0568

PARTICIPANT'S NAME: _____

INTRODUCTION

You are invited to participate in a clinical research study. However, before you give your consent to be a volunteer, we want you to read the following and ask as many questions as necessary to be sure that you understand what your participation will involve.

NATURE AND PURPOSE

Lichen sclerosus (LS) is a skin condition of the external genitals (vulva) of women. LS causes vulvar itching, pain, and burning. In addition, LS causes scarring of the vulva which may cause significant sexual dysfunction or pain. Lastly, 4-6% of women with LS will develop vulvar cancer.

The current “gold standard” treatment for lichen sclerosus is ultra-potent topical corticosteroids. While effective, topical corticosteroids may have serious local and systemic side effects that include thinning of the skin, superimposed fungal infections, and suppression of the adrenal gland.

The study cream being tested contains the ingredient “cutaneous lysate”, which comprises a mixture of proteins obtained from cultured human fetal skin cells. The cells were obtained from a cell bank established for wound healing purposes. The cell bank was established with a single fetal skin biopsy obtained following a one-time medical intervention.

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The fibroblast lysate cream evaluated in this study may represent an effective alternative treatment to corticosteroids.

This study will also include the investigation lichen sclerosis histopathology and genomic profiling through patient skin biopsy samples. Genomic profiling allows us to identify the presence of specific genes and how these genes are expressed in the human body. In this study, genes related to inflammation will be investigated. Thus, genomic profiling for this study will allow us to determine how gene expression levels may change with treatment of the lysate cream.

This study is funded by a grant from Neocutis Inc., the company that makes and markets the study cream being studied. Dr. Andrew Goldstein is the sponsor of this study and he is being paid by Neocutis Inc. to conduct this research study. Dr. Andrew Goldstein does not have a financial interest in Neocutis Inc.

STUDY DURATION

The study will consist of three visits to the study center. Each visit is expected to last approximately one hour. The total amount of time you will participate in the study is 14 weeks, including a 2 week pretreatment period and a 12 week treatment period. You will fill out questionnaires at each visit and during treatment in the form of a diary with questionnaires. Your safety will be assessed for the entire 12 week treatment period.

Up to 30 women may participate in this study.

SUBJECT SELECTION

You *may* participate if you:

- are 18 years or older.
- have a diagnosis of active lichen sclerosis (Dr. Goldstein will cut off a pea size amount of skin (a biopsy) and will do a physical assessment of the vulva area at the beginning of the study to confirm this diagnosis).
- willing and able to comply with the study requirements.
- have a negative pregnancy test prior to enrolling in this study and will use at least two forms of birth control during the course of the study if you are sexually active and are fertile.

You *may not* participate if you:

- are immunocompromised (for example, you have been diagnosed with or have a history of lymphoma, AIDS, or Wiskott-Aldrich Syndrome), or have an uncontrolled malignant disease.

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- have a systemic or generalized infections (bacterial, viral or fungal), or obvious localized infections in the vulva area.
- have any active sexually transmitted diseases on the vulva (herpes, moluscum, condyloma)
- have been diagnosed with other vulvar dermatologic conditions including lichen planus, psoriasis, lichen simplex chronicus, candidiasis, intraepithelial neoplasia, or carcinoma.
- are pregnant or breastfeeding.
- if you become pregnant while on the study, you must withdraw from the study.
- have received an investigational drug within four weeks prior to the study or who plan to use other investigational drugs during the course of this study.
- have a hypersensitivity to the study product or any of the components of either cream.
- have severe medical condition(s) that in the view of the investigator prohibits participation in the study.
- have a history of substance abuse or any factor, which limits your ability to cooperate with the study procedures.
- are uncooperative or are not willing to attend regular visits.
- have received systemic immunosuppressants (e.g. corticosteroids), other systemic therapies or any other systemic therapies known or suspected to have an effect on vulvar lichen sclerosis within 4 weeks prior to participation in the study.
- have been treated with topical therapy (e.g., topical corticosteroids, pimecrolimus, tacrolimus, doxepin, phenol, menthal, camphor, pramoxine) or any other topical therapies known or suspected to have an effect on vulvar lichen sclerosis or its symptoms within four weeks prior to participation in the study.

STUDY DESIGN

Both the study cream and placebo cream will be applied as a thin layer, twice a day to the affected area for 12 weeks. Treatment will not start until the wound at a biopsy site has closed completely. The study cream or placebo cream should always be applied once in the morning and once in the evening. At the Baseline Visit, the study nurse will demonstrate the application technique to the patient.

During treatment it is prudent for patients to minimize or avoid natural or artificial sunlight exposure. Patients will be instructed to wash their hands after applying either cream.

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The study cream contains the ingredient “processed human skin proteins”. Processed human skin proteins are a mixture of natural skin proteins obtained from cultured human fetal skin cells. The cells were obtained from a cell bank established for wound healing purposes. The cell bank was established with a single fetal skin biopsy obtained following a one-time medical intervention.

During the entire study, you will not be allowed to use other products (including moisturizers, emollients, etc.) on the affected area other than the study products.

SCREENING

This visit will include a detailed history and physical examination. You will fill out 2 questionnaires by recording an answer on a scale of 1 to 10. One form will ask you about the amount of itching you are feeling. The other form will ask you about the amount of vulvar burning/pain you are feeling. You will fill out a questionnaire called the Female Sexual Function Index. To see if you have vulvar cancer, Dr. Goldstein will put dilute acetic acid on your vulva examine your vulva with a microscope (colposcope). The acetic acid solution will be washed off with water after approximately 3 minutes. An 8 mm (about 1/3 inch) skin biopsy of the vulva will be taken. Prior to the biopsy, a numbing medication (lidocaine) will be injected in the biopsy site. After the biopsy, you will get one or two stitches at the biopsy site. These stitches dissolve and do not have to be removed. A digital photograph of your vulva will be taken. A urine pregnancy test will be performed.

STUDY PROCEDURES

The total treatment / evaluation period for each patient is 12 weeks. Scheduled clinic visits will be screening (day -15 to 0), baseline (day 1), and Week 12. There will be a total of 3 visits. You will fill out questionnaires at each visit and during treatment in the form of a diary with questionnaires.

Baseline Visit (Day 1)

You will return approximately 2 weeks after first visit. You will fill out the two questionnaires about your itching and burning/pain. You will have a limited physical exam. A digital photograph of your vulva will be taken. A urine pregnancy test will be performed.

Participants meeting inclusion criteria and not having any exclusion criteria will receive either the study cream or the placebo cream by the study nurse. You have a 50% chance of getting either the study cream or the placebo cream. You and Dr. Andrew Goldstein will not know which cream you are given. (This information will be available to Dr. Goldstein in case of any serious adverse event).

You will receive one tube of either the study cream or placebo that should last for the whole study. In case a tube is lost or the patient runs out of the cream, an extra tube will be kept for each patient at the doctor’s office. The cream should be applied as a thin

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film to the affected area. Instructions on how and when to use the cream will be given to you verbally and you will be given a copy of these instructions.

You are not allowed to use any other creams or emollients (including moisturizers, etc.) for lichen sclerosus.

You will be given a diary of the itching and burning/pain questionnaires to take home. You should record your level of itching and burning/pain on these forms once weekly at home. You will mail these questionnaires at Week 4 and Week 8 respectively, using pre-stamped envelopes provided to you. You will bring the diary for Weeks 8 to 12 with you to the final visit.

Final Visit (Week 12):

You will return approximately 12 weeks after the second visit. This will be your final visit for the study. You will fill out the two questionnaires about your itching and burning/pain. You will fill out another Female Sexual Function Index questionnaire. You will have a limited physical exam. A digital photograph of your vulva will be taken. You will tell the study doctor if you are having any side effects from the medication. An 8 mm (about 1/3 inch) skin biopsy will be taken. Prior to the biopsy, a numbing medication (lidocaine) will be injected in the biopsy site. After the biopsy, you will get one or two stitches at the biopsy site. These stitches dissolve and do not have to be removed. Your vulva will be examined with a microscope (colposcope) after application of a dilute acetic acid solution to make sure that you do not have vulvar cancer. The acetic acid solution will be washed off with water after approximately 3 minutes. A urine pregnancy test will be performed. Any unused cream will be collected. An exit interview will be conducted.

Withdrawal Procedures

If you do not complete this study for any reason, you may be asked to return to the clinic for assessment of your skin.

RESTRICTIONS

During treatment it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

Any topical therapies (e.g. corticosteroids, estrogen, or testosterone) at the lichen sclerosus treatment area or any systemic therapies (corticosteroid, immunosuppressive agent) will not be allowed during the study.

You are not allowed to use any other creams or emollients (including moisturizers, etc.) for lichen sclerosus.

All concomitant medication and treatments must be documented. Patients will be given a diary on which they will record any concomitant therapy use (name of medication,

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treatment, dosage, and the reason [symptom] for its use) for the period between visits. The patient will be instructed mail the diary after 4 and 8 weeks, respectively, and to bring the diary with her to the final study visit.

RESEARCH PARTICIPANT RESPONSIBILITIES

As a research participant you will be asked to complete the study procedures for this study, come to the research unit for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

RISKS & DISCOMFORTS

Disease Specific or Genetic Testing

Disease testing and genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the nature and results of the research and whether there is a treatment or cure for a particular disease. Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job.

Even with special precautions, there is no absolute protection against discrimination on the basis of disease or genetic information. For this reason, the study Doctors will use the results of this study as research only and not include them in your medical record.

Study Products

Risks and side effects related to the human fibroblast lysate cream include: You could develop a rash or noticeable redness at the test site following application of the study cream. These signs and symptoms should disappear within a few days. The study cream may cause stinging, burning or itching sensations after application. These sensations are generally transient and should disappear within a short time after application.

Biopsy

Possible side effects from the vulvar biopsy include pain, bleeding, scarring, infection, and bruising at the biopsy site. Application of the dilute acetic acid solution usually causes mild or moderate stinging or burning depending on the presence of cracks or ulcers in the skin. The stinging or burning will usually stop within a few minutes after washing off this acid solution.

Pregnancy Risks

The effects of your participation in this study on the unborn are unknown and **therefore may be hazardous**. You must not be pregnant, nursing or planning a pregnancy during the study period. If you become pregnant during the course of this study your participation in the study will end and a final evaluation will be performed by the study

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doctor.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care and may request to track your pregnancy and will report the pregnancy to the Sponsor and the IRB.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks including allergic reaction associated with the use of the study products. You will be informed, in a timely manner, both verbally and in writing of any new information, findings or changes to the way the research will be performed that might influence your willingness to continue your participation in this study.

IN CASE OF INJURY

In case of a physical injury that was caused as a direct result of your participation in this research study, the study doctor will arrange for you to receive medical care. Your health insurance carrier or third party payer will be billed for the cost of this medical treatment. If you suffer any adverse event experience resulting directly from this system, the sponsor will provide reimbursement for the reasonable cost of medical treatment to the extent such costs are not covered by your medical or hospital insurance or by third party or government programs providing such coverage. No other form of compensation is routinely available. No compensation is provided for disability, lost wages or dissatisfaction with the cosmetic results.

You **do not** waive any of your legal rights by signing this form.

BENEFITS

There is the possibility that the itching, burning, pain, ulceration, and skin thickening from your lichen sclerosus might be decreased. There is the possibility that the study product will prevent further scarring of your vulva and may lower your risks of developing vulvar cancer. There is, however, no guarantee that you will benefit from your participation in the study.

COSTS

You will not be charged for any of the study product or procedures.

PAYMENT

You will not receive any monetary compensation to participate in this study, however, you may be reimbursed for up to \$300 dollars for travel related expenses if you provide receipts to Dr. Andrew Goldstein at the end of your participation in the study.

ALTERNATIVES

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The alternative treatments to the study cream are:

Clobetasol Cream is an FDA approved super-high potency corticosteroid indicated for the relief of the inflammatory and itching of steroid-responsive skin disorders. However, treatment beyond 2 consecutive weeks is not recommended.

Zonalon (Doxepin 5% cream) is an FDA approved treatments for vulvar itching. Common side effects associated with Zonalon include burning, crawling, or tingling sensation of the skin; swelling at the site of application; worsening of the itching, and sleepiness. Uncommon side effects associated with Zonalon include fever; abdominal pain and swelling; blurring of vision; convulsions (seizures); decreased awareness or responsiveness; difficulty in breathing; difficulty in passing urine; dizziness, fainting, or lightheadedness; enlarged pupils; excessive dryness of mouth; extremely low body temperature; fast heartbeat; increased or excessive unconscious or jerking movements; incurable constipation; irregular heartbeat; unconsciousness; vomiting; and weak pulse.

Emollients such as petrolatum (Vaseline) and topical estrogen and testosterone have been shown to decrease the symptoms of lichen sclerosus but they do not help the inflammation associated with lichen sclerosus. Therefore, they do not prevent further ulcerations, fissuring or scarring associated with lichen sclerosus.

Your other alternative is not to participate in this study.

OFFER TO ANSWER ANY QUESTIONS ABOUT THIS STUDY

If you have any questions or problems during this study, or if you think that you may have experienced a research-related injury, you should contact Andrew Goldstein, M.D. at (202) 887-0568.

If you have any questions regarding your rights as a research participant, please contact Kim Lerner, Chair of the Independent Investigational Review Board, Inc. at toll free 1-(877) 888-iirb (4472) during regular working hours. You can also contact the Independent Investigational Review Board, Inc. if you would like to report problems in a research study, express concerns, ask questions, request information, or provide input. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of participants in a research study. For more information about your rights and role as a research participant you can visit the Research Participant section of the IIRB, Inc. website at www.iirb.com.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in the study is voluntary. You understand that you are free to withdraw from this study at any time, and you agree to inform the physician immediately if you intend to withdraw. It is understood that your decision not to participate in this study or to withdraw from this study will not influence the availability of your future medical care and

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will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time.

You agree that the physician in charge of the study or the Sponsor can remove you from this study without your consent for any reason, including, but not limited to:

- a. His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study.
- b. Your failure to follow the instructions of the investigator(s).
- c. If the study is stopped by the sponsor and/or doctors participating in the study prior to completion.

If you are asked to leave the study, you will not lose any benefits to which you are otherwise entitled. If you are asked to leave the study, the doctor may examine you and do some final tests.

USE AND DISCLOSURE OF MEDICAL INFORMATION

As part of this study Dr. Andrew Goldstein and his team at the research facility will keep records of your participation in the study. These study records will include personal information that you provide including your age, sex, etc., the results of procedures and tests you undergo during the study or had before the study, information about your response to treatments you receive while participating in the study, photographs taken during the study and other medical information relating to your participation in the study. Under federal law your study records cannot be used or disclosed by the research clinic for research purposes unless you sign this authorization. You may not participate in the study unless you sign this authorization. If you sign this informed consent form, you will be agreeing to the disclosures described below:

- a. Some or all of the test results, photographs and other information will be reported to NEOCUTIS, Inc., the sponsor of this study, and consultants (including monitors and auditors) that are helping conduct the study. The Sponsor and its consultants will analyze and evaluate these results and information and may report them to the U.S. Food and Drug Administration (the FDA) or other regulatory agencies in the United States and/or foreign countries. Your study records will be assigned a code number by the study team and you will ordinarily not be identified by name in the study records that are sent to the Sponsor and its consultants. However, The Sponsor and its consultants will have the right to see your complete study records, including your name, and might choose to do so.
- b. In addition, personnel from the Sponsor and its consultants will be visiting the research facility to monitor the conduct of the study, and they will be reviewing your study records and your medical records for this purpose.
- c. Your study records and medical records may also be reviewed by the Independent Investigational Review Board, Inc., which is an ethics committee that reviews the conduct of human research studies.

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The research facility and the Independent Investigational Review Board, Inc., will review and use your study records only for purposes of this study. They will keep your identity confidential and, except for the disclosures described above, will not disclose your study records to other parties unless disclosure is required by law. Once the research facility discloses information in your study records, photographs or medical records to the Sponsor or its consultants, the information will no longer be protected by federal law. Because of the need to release information to these parties, absolute confidentiality can not be guaranteed. However, the Sponsor and its consultants will only use your information for purposes of the study and will not disclose your study records to parties other than the FDA and similar government agencies, unless disclosure is required by law. If reports or articles are written about the study, you will not be identified by name in them. Your study records may be retained at the research facility indefinitely following the completion of the study. You will not have the right to review your records while the research is in progress. However, you will be able to review your records after the research has been completed.

This authorization does not expire. However, you have the right to revoke this authorization at any time. You can do this by giving written notice to the study doctor, informing him that you are revoking your authorization to use and disclose medical information. The study doctor's contact information is listed on page 1 of this consent.

If you revoke this authorization to use and disclose your medical information, you will not be permitted to continue your participation in the study after the revocation. If you drop out of the study, you do not have to revoke your authorization to use and disclose your medical information. However, if you drop out of the study and do decide to revoke your authorization to use and disclose your medical information, the information that has already been collected in your study record may continue to be used and disclosed as described above, however, no new information will be obtained or added.

CLOSING STATEMENT

You have read and understood the information which has been stated above and have received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent. You hereby consent to be a participant in this study.

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SIGNATURES

I have read in a language that I understand well, the above information. The content and meaning of this information has been explained to me. I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

Date/Time _____
Print Subject Name _____
Subject Signature

Date/Time _____
Name of Person conducting
the Informed Consent
discussion _____
Signature of Person
conducting the Informed
Consent discussion

Date _____
Print Investigator Name _____
Investigator Signature

Copy of consent form given to subject on (date) _____ by (initials) _____

Independent Investigational Review Board, Inc.
Approved:

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