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A randomized trial of Clobetasol Proprionate Versus Fractional CO2 laser for the treatment of Lichen Sclerosus (CuRLS)

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1.0 PURPOSE and OBJECTIVES

The purpose of this study is to compare the safety and efficacy of clobetasol proprionate .05% ointment to fractional CO2 laser procedure for the treatment of vulvar lichen sclerosus.

Primary Outcome Measures:

- The primary outcome will be the subjective and objective cure of vulvar symptoms of itching, burning, dyspareunia at 12 weeks post treatment, or 6 months [Time Frame:12 weeks] using the SkINDEX-29 and Vulvar Symptom Visual Analog Scale (VAS)

Secondary Outcome Measures:

- Complications [Time Frame: 6 week, 6 months, 1 year] pain, infection, de novo or worsening dyspareunia, contact dermatitis and burns
- Subjective Vulvovaginal Symptoms Questionnaire (VSQ)
- Objective Cure of Lichen Sclerosus [Time Frame:6 months, 1 year] using PHOTO documentation, Vulvar Signs Visual Analog Scale
- Health Related Quality of Life (HRQOL) based on patient global impression of improvement and satisfaction as well as the Vaginal Health Index [Time Frame: 6 months, 1 year]

2.0 BACKGROUND and SIGNIFICANCE

Vulvar lichen sclerosus (LS) is a well-characterized dermatosis resulting in labial atrophy, synechiae and introital narrowing and can often cause dyspareunia, itching and co-existent vulvar pain. Biopsy is necessary to confirm the clinical diagnosis and the mainstay of treatment usually consists of topical steroid therapy. [1]

Clobetasol proprionate and mometasone furoate are potent topical steroids that have long been considered gold-standard treatment for vulvar lichen sclerosus and work through anti-inflammatory, anti-mitotic, and immunosuppressive effects. One of the complications of long-term steroid use, however, is potential thinning of the vulvar skin, therefore limiting long-term use. Other therapeutic options include topical calcineurin inhibitors, surgery including incision and skin graft treatment, cryotherapy and phototherapy. Table 1 summarizes current clinical comparative trials for lichen sclerosus involving topical steroid therapy. Clobetasol proprionate has a range of efficacy from 61-91% depending on the selected outcome criteria.

Table 1.

Author/year	Study Design	N	Outcome	Results
Bracco, GL 1993[2]	RCT Clobetasol vs. testosterone vs. progesterone vs. cream based therapy	79	-Subjective scaled symptom remission of vulval LS -Objective histologic and gross improvement	-75% remission with Temovate versus 10% Progesterone, 20%Testoterone, and 10% cream based treatments had subjective remission of LS -Only Clobetasol proprionate had significant histologic and gross improvement.
Terra S, 2014[3]	RCT clobetasol vs. phototherapy	15	-Mean relative reduction of total clinician's score (TCS): subjective pruritus and burning/pain VAS, Skindex-2, 20 MHz- ultrasonography, histopathological analysis	35.6% decrease in mean (total clinical score) TCS in UV-A1 phototherapy group -51.4% decrease in mean TCS for clobetasol proprionate group; Skindex-29, pruritus, burning/pain significantly decreased -Phototherapy group's only significant difference was with burning/pain -Significant difference in dermal density on ultrasound and histopathological reduction of

				inflammatory infiltrate in clobetasol proprionate group and not Phototherapy group
Lorenz B, 1998[4]	Retrospective	81	-Subjective patient improvement of symptoms (pruritus, irritation, burning and dyspareunia) -Subjective clinician improvement of appearance	-77% complete remission symptoms, 18% partial remission, and 5% no change after treatment with clobetasol proprionate -32% of patients had subjective complete remission of symptoms and 46% patients with subjective partial remission of symptoms
Funaro D, 2014[5]	RCT Clobetasol vs. tacrolimus	55	-Subject visual analog scale of symptoms (burning/pain, pruritus, and scaled improvement of condition) -Clinician cutaneous exam and photographs	-Clobetasol proprionate had 66% efficacy of complete removal of subjective clinical signs compared to 14% in the tacrolimus group. -Objective clinical exam revealed clobetasol proprionate group had more significant decreases in vulvar skin papules and atrophic patches than tacrolimus group.
Virgill A, 2014[6]	RCT clobetasol vs. mometasone	48	-Subjective (visual analog scale and gynecologic subjective scale) -Objective (four point scale and gynecologic objective scale) scores improvement by 75%	-59% of clobetasol group and 37% of mometasone furoate group had subjective score improvement. -67% of clobetasol and 48% of furoate group had objective score improvement
Ayhan A, 2007[7]	Retrospective	140	Subjective clinical response in six months	91.7% of clobestasol group and 77.5% of testosterone group reported subjective improvement

The vulvovaginal SmartXide[8] –V2-LR laser system by DEKA (Calezano, Italy) is a fractional C02 laser with maximum 40 Watt power and laser energy emission at 10,600 nanometer wavelength which is mainly absorbed by water in the underlying tissue. The SmartXide[8]–V2-LR system was first introduced in 2009 with DOT therapy distributing fractioned CO2 laser in small spots of 200 microns to the vulvar skin or vaginal epithelium, resulting in a portion of the skin remaining intact with less tissue destruction and faster healing. The device is cleared by the US Food and Drug Administration (FDA) for incision, excision, ablation, and coagulation of gynecologic soft tissues. The fractioned therapy has been shown to stimulate fibroblastic growth through activation and biosynthesis of collagen and restoration of the extracelluar matrix with collagen fibers.

D-Pulse DOT therapy involves two types of energy:

1) An initial high energy peak that allows laser energy removal of the superficial epithelial component
2) A second variable lower peak power that enables the laser energy to penetrate into the submucosa stimulating new collagen synthesis

The histopathologic changes associated with the CO2 laser treatment are supportive for reconstituting the vaginal epithelium back to physiologic function in patients with severe vaginal atrophy. The atrophic vaginal epithelium in GSM is thin with few cycles having glycogen storage rendering the vaginal pH less acidic and the epithelium completely atrophic. Two months after treatment, the epithelium is thickened with proliferating basal cells beneath. The structural integrity of the epithelium is enhanced with newly formed papillae and capillaries supporting the vaginal ecosystem. Epithelial cells have remarkably more glycogen forming the characteristic superficial, intermediate and deep layers. Fibroblasts undergo protein production to create the extracellular matrix including collagen.[9] The mechanism by which the carbon dioxide laser is hypothesized to work is by thermal energy creating heat shock of proteins. As a result of the damage, cytokines and growth factors are released signally molecules to recruit fibroblasts and increase cell division.[10] Table 2 includes prior

studies involving CO2 laser treatment for lichen sclerosus in both men and women. Studies are all retrospective and small in number with limited follow-up and only subjective outcome criteria.

Table 2. Prior studies using Fractional C02 laser for lichen sclerosus

Author and year	Trial Design	Primary Outcomes	Findings	Complications
Peterson C, 2004[11]	Case Report	Subjective symptoms Visual re-epithelization	All patients(N=2) with refractory anogenital lichen sclerosus had resolution of symptoms and re-epithelization after 2-3 years with CO2 laser therapy	None
Kartamaa M, 1997[12]	Case Series	Subjective assessment of lichen sclerosus (better, asymptomatic, some recurrence)	Among male and female patients (N=10) with biopsy proven refractory LS, 76% were asymptomatic after CO2 laser treatment with mean follow up of 32 months.	Three patients needed repeat treatment
Windahl T, 2006[13]	Retrospective cohort	Subjective patient assessment of recurrence of symptoms, any visible penile lesion, recurrence of meatal stenosis	In men with histologically verified penile lichen sclerosus treated with CO2 laser, 80% (N=50) had no local symptoms at mean follow up 14 years	Two patients required further treatment
Lee A, 2015[14]	Case Series	Subjective symptom resolution	In women (N=5) with biopsy confirmed severe vulvar LS recalcitrant to topical corticosteroid treatment; four of whom responded positively to fractional CO2 laser treatment, and one to ablative CO2 laser therapy	Two patients needed repeat treatment at 6-8 months Two patients reported discomfort with laser treatment
Ratz L, 1984[15]	Case Report	Subjective symptom resolution and re-epithelization	One case of balanitis xerotica obliterans refractory to topical treatments resolved after CO2 laser treatment	Syncopal episode after treatment

Very little is known about long-term effects of CO2 fractional laser therapy use in the vulva or vagina, although the treatment is widely accepted in plastic and cosmetic surgery and dermatology. Increased marketing for laser vaginal rejuvenation has spawned a proprietary female genital cosmetic surgery industry in the US with very limited published outcome data. SmartXide[8] –V2-LR has some established outcome data for treatment of genitourinary syndrome of menopause GSM, also known as vulvovaginal atrophy. Table 3 List outcomes of the SmartXide[8] –V2-LR system for treatment of vaginal atrophy.

Table 3 Outcomes of SmartXide[8] –V2-LR system for Vaginal Atrophy

Author and year	Trial Design	N	Primary Outcomes	Findings	Complications
Salvatore R, 2014[8]	Prospective	50	Objective vulvovaginal atrophy (VVA) symptoms- Vaginal Health Score Index (VHIS) Subjective VVA symptoms – 10 point visual analog scale	Fractional CO2 laser improved VVA all subjective symptoms in women; significant objective improvement VHIS (13.1+/- 2.5 at baseline vs. 23.1 +/- 1.9; p<0.001)	None

			(burning, vaginal itching, vaginal dryness, dyspareunia, and dysuria)		
SalvatoreR, 2015 [16]	Prospective	77	-Sexual function and quality of life (Female sexual function index and Short form 12) -Subjective symptoms (vaginal burning, dryness, dyspareunia, and dysuria with visual analog scale)	-85% normal sexual life after CO2 laser therapy in not sexually active group -Significant improvement in FSFI and VAS scores after treatment -Significant improvement in overall satisfaction with sexual life after laser treatment	None

3.0 STUDY DESIGN

Women presenting to the urogynecology clinic will be screened for lichen sclerosus. Vulvar biopsy will be performed for confirmation, and, if eligible, the patient will be consented to undergo baseline questionnaires, photodocumentation of vulvar lesions and randomization. Patient will be randomized to monthly LASER treatment for 3 months or topical STEROID therapy (temovate propionate .05% ointment nightly for one month, three times weekly for 2 additional months, then as needed) in a 1:1 ratio using a computer generated randomization schedule. Grouping assignments will be kept in sealed consecutively numbered, opaque envelopes. Because of the nature of the treatment, it will not be possible to blind patients but the assessor will be blinded to the intervention.

Patient questionnaires include multiple validated scales and surveys to provided reproducible measures of vulvar symptoms as primary and secondary outcomes. Questionnaires will be completed at the intake visit, repeated at 12 weeks after treatment is completed or 6 months from intake, and one year follow up. Subjective symptoms including vulvar itching, vulvar burning, vulvar irritation, pain with intercourse, tearing of the vulvar skin, painful urination, and painful defection will be rated with a validated visual analog scale (VAS), scaled 0-10, see appendix 1. Higher values correspond to more bothersome symptoms. The Skindex-29 questionnaire is a subjective measure of skin symptoms validated against the Medical Outcomes Study 36-item Short-Form Survey (SF-36)[17], appendix 2. The Skindex-29 was developed in dermatology and modified for use in vulvadynia[18]. The Skindex-29 is scored as a sum expressed on a 100-point scale with higher scores indicating lower quality of life. Validated quartiles are used to characterize disease symptoms, emotions, functioning, and overall score as either very little, mild, moderate, or severe[19]. Secondary outcomes of patient satisfaction and global impression of improvement will be collected using simple validated visual analog scale from 0-5, much worse to much better, appendix 4. A final subjective measure, the Vulvovaginal Symptoms Questionnaire (VSQ), a validated measure of vulvar symptoms, emotions, life impact, and sexual impact in postmenopausal women will be collected a secondary outcome[20], appendix 5. A higher total score on the VSQ corresponds to lower quality of life.

Objective measures of the clinical appearance of vulvar lichen sclerosus will be completed by investigators at concurrent time points with the patient questionnaires. Non identifiable photo documentation of vulvar appearance will be completed using Fujifilm JX665 Digital Camera. Investigators blinded to treatment arm will complete visual assessment including white plaques/hypopigmentation, cigarette paper/thin skin, introital narrowing, perianal involvement (figure of eight shape), loss of labia minor, fusion of labia minora, philmosis of clitoral hood, vulvar fissure, and erosion scaled on validated visual analog scale, rated 0-10 from absent to severe, see appendix 1. Lower objective VAS scores corresponds to less severe Lichen Sclerosus disease. In addition, investigators will complete validated Vaginal Health Index (VHI) at all time points[21], appendix 3. The VHI evaluates vulvovaginal overall elasticity, fluid secretion type and consistency, pH, epithelial mucosa, and moisture on a scale 1-5 from none to excellent. A lower VHI score corresponds to greater urogenital atrophy.

The laser used in this clinical investigation complies with federal laser performance standards.

Fractional CO2 laser with 10600 um wavelength, 60 W pulse, continuous or pulsed with repetition rate, articulated arm with scanner hand-piece, 120 Vac power and 635 nm aiming beam. The laser power will be set at 26 W, dwell time of 800 microseconds, DOT spacing at 800 micro meters and normal scan mode. Vulvar lichen sclerosis will be treated except for the clitoris glans and clitoral hood which will be spared with at least 5mm margin. The procedure will be performed in the outpatient clinic at the National Center for Advanced Pelvic Surgery at MedStar Washington Hospital Center or Medstar Lafayette Center, and include 3 sessions, 4 weeks apart. A minimum of 2 weeks are required from the time of biopsy to treatment. Prior to treatment eutectic local anesthetic (EMLA) will be applied for at least 5 minutes up to 30 minutes and then wiped off prior to laser treatment. Photodocumentation will take place at baseline and at 6 months and one year following the last LASER or STEROID treatment. Interpretation of photodocumentation with clinical objective scale will be completed by blinded provider.

4.0 SUBJECT POPULATION and SELECTION CRITERIA

Patients presenting to urogynecology or gynecology clinic with vulvar symptoms and biopsy confirmed lichen sclerosus.

Inclusion criteria:

- Women
- Biopsy proven symptomatic vulvar lichen sclerosus
- Ability to understand the study, accept randomization and logistically follow-up with scheduled visits
- Post-menopausal

Exclusion criteria:

- Known vulvar malignancy
- Pregnancy or planning pregnancy or less than 3 months postpartum
- Current or prior diagnosis of any gynecologic malignancy
- Previous pelvic radiation therapy
- Allergy to topical steroid
- No active UTI, vulvar infection (candida, herpes, bacterial vaginosis, trichomoniasis or other infection)
- Pelvic organ prolapse > than Stage 2
- Treatment with systemic immunomodulators, topical calcineurin inhibitors (tacrolimus, pimecrolimus), or vulvar hormonal or vulvar topical steroid use within 2 months of enrollment
- History of vaginal mesh implant
- IUD (Intrauterine Device)
- Skindex-29 overall score <21, below mildly impaired health related quality of life threshold

5.0 SAMPLE SIZE CALCULATION

The study will consist of 2 study groups (LASER vs STEROID therapy). We expect improved subjective and objective results in the LASER group at 3 months post treatment or 6 months from enrollment compared with the STEROID group.

This study is designed as a two-group randomized clinical trial. Sample size calculations were conducted using the absolute change in the Skindex 29 as the primary end point. Out study will reach 80% power to detect a mean difference of 16 points on the Skindex 29 (sd=22 for both groups)[22] between the study groups with 24 patients in each group, or 48 in total based on a one-sided two-sample t-test with alpha=0.05. By accounting for 10% attrition, we propose to recruit 52 patients to the study to be randomized with a 1:1 ratio to each group, with a blocked component for those who used topical clobetasol in the past. The Skindex-29 has validated cutoff categories for mildly, moderately, and severely impaired health related quality of life scores, the mean difference between each quality of life measure overall score is between 6 and 7. Therefore, powering the study for a detection of mean difference of 16 points should measure significant quality of life improvement.[23,24]

Study Timeline:

	Intake Visit	Day 0	2 weeks	4 weeks-14 weeks	6 months	1 year
Vulvar biopsy (if never completed)	X					
Vaginal STEROID or LASER			STEROID daily x 4 weeks LASER monthly x 3 months	STEROID three times weekly x 8 more weeks, then as needed LASER STOP at 12 weeks		
Vaginal Health Index scale (VHIS)		X			X	x
SkIndex-29 Vulvar QoL Questionnaire Vulvovaginal Symptoms Questionnaire (VSQ)		X			X	x
Telephone call to check compliance and answer questions			X	X (8 weeks)		
Photodocumentation		X			X	x
Questionnaire of patient global impression of improvement and satisfaction PGI-I					X	x

6.0 DATA COLLECTION and TRANSMISSION

The data will be collected from study participants at MedStar Washington Hospital Center or other Medstar Urogynecologic Clinic. All data collection will be performed by research staff. The baseline, 6 month, and 1 year visits will be in-person and include clinic evaluations. The 2 week and 2-month telephone call will be performed by the research coordinator. At screening, each subject will be assigned a subject identification. Case report forms will be generated for each subject and completed by the investigator or study coordinator. Original case report forms will be securely maintained. Data will be entered into a secure RedCAPS Database which provides complete auditing for data management processes.

De-identified backup data will be kept in locked files at the participating site. Plans for publication will be handled by the investigators at MedStar Washington Hospital Center and will adhere to publication policies.

7.0 HUMAN SUBJECT RESEARCH and ETHICAL CONCERNS

Signed consent in English will be obtained from each participant / patient at the time of enrollment. The objectives of the study and the data collection procedures will explained to every prospective participant before study enrollment. An IRB-approved consent document will be used for protocols. Consent for the patients includes the right of the subject:

- To either withdraw or refuse participation without prejudice at any time during the study;
- To voluntarily participate in the research;

- To receive new information about the study as it becomes available;
- To understand the procedures, risks, and benefits;
- To maintain confidentiality of personal medical information.

8.0 PROTECTION AGAINST RISK

The proposed study involves changes in provision of program services to study participants. Description of random and blinded nature of the protocols will be explained by the physician in charge of the participant. To avoid or minimize potential risks, frequent monitoring for adverse events will be performed by study staff and the PI.

Risks of clobetasol proprionate include skin irritation, burning, rash and change in skin pigmentation.

Potential adverse reactions to laser use include ocular laser exposure which will be minimized with the use of protective eyewear with an optical density of 4x the treatment wavelength. Pain or mild to moderate discomfort, erythema, swelling, blistering, itching, numbness, change in pigmentation, scarring, and burns are other adverse events including as well as painful intercourse, change (postive or negative) in sexual response, including arousal around clitoris and orgasm. These risks will be minimized with laser use per manufacture instructions with trained personel and avoidance of laser treatment within 5mm of clitorial glans and hood. All known risks will be disclosed to the participants via the informed consent process. All study participants will be closely monitored post treatment for adverse events.

All known risks will be disclosed to the participants via the informed consent process. All study participants will be closely monitored post treatment for adverse events. All study investigators will receive extensive training on the study protocol. Attending staff/surgeons will also receive training on how to operate the laser and the appropriate settings for the vulvar treatment, supervised by the study mentor. Serious adverse events are defined as any untoward medical occurrence that (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization (4) results in persistent or significant disability or incapacity, (5) is a congenital anomaly/birth defect, or (6) is another medically important condition.

Data safety and Monitoring Board (DSMB) headed by Dr. Stephanie Wethington, Director of Gynecologic Oncology at MedStar Washington Hospital Center, will review all serious adverse events, including any untoward occurrence that (1) results in death, (2) is life threatening, (3) requires inpatient hospitalization, (4) results in permanent or significant disability or incapacity, and (5) is another medically important condition. All ongoing data will be analyzed once half of patients have been recruited and at completion of recruitment and study conclusion.

9.0 SOURCES OF MATERIALS

Medical record data and program records will be obtained for each participant. Demographic information and personal history will be obtained by interview. Study data, such as information obtained at follow-up assessment examination and interviews, will be obtained according to the time-frame specified in the protocol.

10.0 CONFIDENTIALITY

This research staff will take every precaution to protect the confidentiality of the collected data. All personnel with access to data collected have completed the Program for Ethics Education in Research training with the appropriate HIPAA certification. Completed data forms will be placed in locked file cabinets, and only authorized staff members will have access to the data. The data will be compiled into a computerized database and will be stored on computers used exclusively for research studies and are safeguarded by passwords known only to authorized personnel. Photo documentation is to capture isolated vulvar and perineal area. Other identifiable body parts including patient's face will not be included in photographs. Photographs used as

part of photo documentation will be uploaded from digital camera after each encounter. The photograph file will be labeled with non identifiable patient number. Digital camera photo card will be cleared and photographs stored on research computers safeguarded by passwords. Fujifilm JX665 Digital Camera will be stored with storage card in locked file cabinets, and only authorized staff members will have access. Data are analyzed collectively. No personal identities are revealed to the statistician. The data used are obtained strictly for the purposes of the research in question. Any printout information and photographs will be destroyed once the project is completed and reports written.

11.0 TIMING OF STUDY and RECRUITMENT

The study investigators plan to start recruitment in August 2015. Study recruitment is expected to be complete within 5 years by August 2018. One year follow-up will be complete by August 2019. This study will be complete and the results analyzed by the primary investigator, Dr. Cheryl Iglesia.

12.0 STATISTICAL ANALYSIS

Statistical intention-to-treat and per protocol analysis will be completed in R (version 3.4, Vienna, Austria 2017) with demographic and questionnaire scores reported as means and standard deviations or medians and interquartile ranges. Chi square or Fisher's exact, two-sample t-test and Mann Whitney U will be used to compare categorical, continuous, and non-parametric variables, respectively. D-Agostino test will be used to assess normality. Two-way ANOVA analysis of mean Skindex-29 score improvement based on prior steroid exposure and treatment group will be performed.

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Appendix 1:

Subjective Symptoms VISUAL ANALOG SCALE (VAS)

Not bothersome									Most Bothersome	
0	1	2	3	4	5	6	7	8	9	10

SYMPTOMS
Vulvar itching
Vulvar burning
Vulvar irritation
Pain with intercourse
Tearing of vulvar skin
Painful urination
Painful defection

Objective Signs VISUAL ANALOG SCALE (VAS)

Absent			Mild			Moderate				Severe
0	1	2	3	4	5	6	7	8	9	10

SIGNS
White plaques/hypopigmentation
Cigarette paper, thin skin
Introital narrowing
Perianal involvement (figure of 8 shape)
Loss of labia minora
Fusion of labia minora
Phimosis of clitoral hood
Vulvar fissure
Erosion

Appendix 2: SKINDEX

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies . .	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition . . .	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition . . .	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love.	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition .	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands) .	☐1	☐2	☐3	☐4	☐5

17. My skin condition makes showing affection difficult . . .	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments.	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others . .	☐1	☐2	☐3	☐4	☐5

Please turn to next page

These questions concern your feelings over the past 4 week about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love .	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5

Chren MM, Lasek RJ, Quinn LM, Covinsky KE. Convergent and discriminant validity of a generic and a disease-specific instrument to measure quality of life in patients with skin disease. J Invest Dermatol. 1997 Jan;108(1):103-7

Appendix 3: Vaginal Health Index

	Overall elasticity*	Fluid secretion type & consistency	pH	Epithelial mucosa	Moisture
1	None	None	6.1	Petechiae noted before contact	None, mucosa inflamed
2	Poor	Scant, thin yellow	5.6 – 6.0	Bleeds with light contact	None, mucosa not inflamed
3	Fair	Superficial, thin white	5.1 – 5.5	Bleeds with scraping	Minimal
4	Good	Moderate, thin white	4.7 – 5.0	Not friable, thin mucosa	Moderate
5	Excellent	Normal (white flocculent)	≤ 4.6	Not friable, normal mucosa	Normal

*Lower score corresponds to greater urogenital atrophy

Appendix 4

Patient Global Impression of Improvement

Circle how you feel your symptoms are after treatment:

Much Worse	Worse	Same	Better	Much Better
1	2	3	4	5

Level of satisfaction after treatment

How would you define the level of satisfaction with the treatment?

Very Dissatisfied	Dissatisfied	Same	Satisfied	Very Satisfied
1	2	3	4	5

Appendix 5

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.

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