Study Title: ***Clinical Study of the CO_2RE Laser Device for Treatment of Vulvar Lichen Sclerosus***

Protocol Number: DHF25211

IRB Revision Date: February 19, 2019

NCT#: NCT04148651

Study Type: Prospective Clinical Study

Device: *CO_2RE Laser*

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TABLE 1- STUDY SYNOPSIS

Short study name	Vulvar Lichen Sclerosus Treatment with CO_2RE
Proprietary name	Syneron Candela *CO_2RE Laser*
Intended Use	The CO_2RE laser system is a fractional CO_2 laser that is FDA-cleared under a 510(k) K151655 for laser incision, excision, ablation and/or vaporization and of soft tissue in gynecology (GYN).
Design	Prospective, non-randomized, single group assignment, interventional clinical trial
Study Population	Up to 45 female subjects from up to four investigational sites, age 18-80 years
Sites and Investigators	Up to 4 investigational sites
Treatment Duration	Eligible subjects, with a diagnosis of vulvar lichen sclerosus (VLS) supported by histologic findings on biopsy and/or clinical signs on physical examination and recalcitrant to mid- to high-potency steroid therapy, will undergo up to 5 treatments at 4±1-week intervals to the vulva with the CO_2RE device and External Intima disposable handpiece. Up to 10 subjects will have a biopsy taken at the baseline visit, at the 6-week follow-up and at the 6-month follow-up to evaluate histological markers compared to pre-treatment biopsy findings. A 1 week ± 2 days post first treatment phone call by a study nurse for safety evaluation will be performed. Subjects will return for 4 follow-up (FU) visits: at 6 weeks, 3 months, 6 months and 12 months after the final treatment. Methodology described in protocol to evaluate efficacy of treatments will be carried out at each visit at the clinic.
Primary Objective	Evaluate the efficacy of a series of CO_2RE treatments to improve the symptoms, clinical signs, and architectural changes associated with vulvar lichen sclerosus, at 6 weeks, 3 months, 6 months and 12 months after the final treatment.
Secondary Objectives	• Evaluate sexual function at the 3-month and 6-month follow-ups compared to baseline. • Evaluate histological markers at the 6-week and 6-month follow-ups compared to baseline. • Evaluate discomfort following each treatment. • Evaluate the safety of CO_2RE treatments for VLS during the study. • Evaluate subject satisfaction at the 6-week, 3-month, 6-month and 12-month follow-up visits.

Primary Endpoint	Change from baseline in presence and severity of symptoms (5-point severity scale), clinical signs (3-point severity scale) and architectural changes (3-point severity scale) at the 6-week, 3-month, 6-month and 12-month follow-up visits. (***Appendices I & II***).
Secondary Efficacy Endpoints	The following parameters will be measured during the study: • Sexual function, using the Female Sexual Function Index (***Appendix III***), at baseline and at the 3-month and 6-month follow-ups. • Histological signs (degree of hyperkeratosis, epidermal atrophy and dermal inflammation) at baseline and at 6 weeks and 6 months after the final treatment. • Subject satisfaction, using a 5-point Likert scale (-2=very dissatisfied; 2=Very satisfied), will be assessed at the 6-week, 3-month and 6-month follow-up visits.
Safety Endpoints	Evaluate the safety of the CO_2RE device for the treatment of VLS in female subjects: • Pain/discomfort level using a 10-point Numerical Scale Response (NSR) after each treatment. • Number, severity and type of adverse events recorded throughout course of the study. • 1 week ± 2 days post first treatment safety phone call to review 1-week patient diary.

INTRODUCTION AND RATIONALE

Background

Lichen sclerosus (LS) is a chronic, inflammatory skin disorder of genital and extragenital skin.[1] It most commonly affects the anogenital region of adult women.[2] Lichen sclerosus (LS) was described for the first time in 1887. Since then, many synonyms have been in use, notably 'Kraurosis vulvae,' 'vulvar dystrophy,' 'white spot disease,' and 'lichen sclerosus et atrophicus' or 'guttate scleroderma.[1] All of these terms have been abandoned and replaced by 'lichen sclerosus,' which is now used for genital and extragenital lesions. [1] LS is a chronically relapsing disease with a potential for atrophy, destructive scarring, functional impairment, and malignant evolution. [1,3,4] Therefore, early diagnosis, prompt treatment, and long-term follow-up of affected patients are mandatory. [1]

It is estimated that up to 20% of all women will experience significant vulvar symptoms at some point in their lifetime.[2] Although women's health is a topic of growing concern in today's society, conditions such as vulvar lichen sclerosus (VLS) are often underdiagnosed and undertreated. Most cases are diagnosed in postmenopausal women.[5] The involved skin becomes thin and white, with frequently present bruises or petechiae and anatomic changes. Symptoms include persistent itching and soreness or burning. At advanced stages of lichen sclerosus, scarring after inflammation may lead to severe damage by fusion of the labia, narrowing of the vaginal opening, burying of the clitoris in women and girls and risk of developing squamous cell carcinoma.

The treatment of VLS aims at controlling the symptoms, stopping further scarring and distortion and reducing the risk of cancer. Previously, the gold standard in treatment was ultra-potent topical steroids (i.e. clobetasol propionate).[5] Currently, mid to high-potent topical steroids are a first-line therapy. The anti-inflammatory properties of clobetasol and other steroids have been most effective in managing associated symptoms, decreasing inflammation, and preventing progression of the condition and subsequent scarring.[6] Second-line treatments include calcineurin inhibitors, retinoids, and immunosuppressors. Surgery is used only for the treatment of complications associated with VLS.[5]

Contemporary VLS treatment modalities suffer from dependence on long-term patient compliance and high recurrence rates. The fractional carbon dioxide laser (CO_2) has been applied to treat skin disorders[7] and to induce vaginal rejuvenation[8], reconstitute normal vaginal flora[9] and to drive collagenogenesis tissue remodelling.[10] Although topical steroids are the gold standard treatment for VLS, fractional CO_2 resurfacing was successful in achieving remission for severe, hyperkeratotic VLS not responding to super-potent topical corticosteroids. In these patients, VLS was subsequently able to be maintained with topical corticosteroid treatment.[10]

The histological changes and relief of vaginal symptoms, such as itching and dryness, elicited with fractional CO_2 technology justify testing it as an alternative and/or adjunctive treatment for VLS. This clinical research will evaluate treatment efficacy of the CO_2RE CO_2 laser device with the External Intima fractional handpiece for improving the clinical signs of VLS and relieving symptoms associated with this condition.

CO_2RE Device Description

The CO_2RE laser system (Figure 1) utilizes a sealed-off, metal carbon dioxide gas tube that is radiofrequency (RF)-excited and air-cooled, emitting light at a wavelength of 10.6 µm with

programmable pulse duration and frequency. The system has a programmable 2-axis scanning laser beam device that allows the physician to select the skin area coverage from a selection of predetermined patterns in different sizes based on the skin area to be treated. The versatility of the fractional CO_2RE system enables precise, effective and simultaneous treatment of the skin's surface in the middle and deep dermal levels. The CO_2RE system consists of a treatment component and an internal control component. The treatment component consists of the laser delivery handpiece. A computer with a touch screen keyboard also provides controls for the fractionated delivery of the 10.6 µm beam.

Figure 1: CO_2RE device

In this study, the external fractional handpiece (Figure 2) will be used to perform treatments to the vulvar area affected by lichen sclerosus.

Figure 2: CO_2RE Intima External Handpiece

INTENDED USE IN GYNECOLOGY

The **CO_2RE** system device is FDA-cleared under a 510(k) K151655 - intended for laser incision, excision, ablation, and/or vaporization of soft tissue in gynecology (GYN) for the treatment of: conization of the cervix, including cervical intra-epithelial neoplasia (CIN) and vulvar and vaginal intra-epithelial neoplasia (VIN, VAIN); condyloma acuminate, including cervical, genital, vulvar, perineal, and Bowen's disease (Erythroplasia of Queyrat) and Bowenoid papulosa (BP) lesions; and leukoplakia (vulvar dystrophies).

STUDY DESIGN

Study Duration and Timelines

This study is a prospective, non-randomized, single group assignment, interventional clinical trial to evaluate the *CO_2RE* laser device for safety and efficacy for vulvar lichen sclerosus (vulvar dystrophy) treatment.

Up to a total of 45 female candidates, seeking treatment for vulvar lichen sclerosus from the participating investigator will be enrolled at a participating study site. Subjects will receive up to five (5) *CO_2RE* treatments.

A 1-week post first treatment safety call will be performed by a study nurse to review the patient daily diary.

Each subject will be followed for 4 additional post treatment visits (FU visits) that will be conducted at:

- 6 weeks post last treatment – 6wk FU ± 2 weeks (Efficacy & Safety).
- 3 months post last treatment – 3m FU ± 2 weeks (Efficacy & Safety).
- 6 months post last treatment – 6m FU ± 2 weeks (Efficacy & Safety).

- 12 months post last treatment – 12m FU ± 2 weeks (Efficacy & Safety).

STUDY OBJECTIVES AND END POINTS

Primary Objective

To evaluate the efficacy of a series of CO2RE treatments to improve the symptoms, clinical signs, and architectural changes associated with vulvar lichen sclerosus, at 6 weeks, 3 months, 6 months and 12 months after the final treatment.

Secondary Objectives

1. Evaluate sexual function at the 3-month and 6-month follow-ups compared to baseline.
2. Evaluate histological markers at the 6-week and 6-month follow-up compared to baseline.
3. Evaluate discomfort following each treatment.
4. Evaluate the safety of CO_2RE treatments for VLS during the study.
5. Evaluate subject satisfaction at the 6-week, 3-month, 6-month and 12-month follow-up visits.

Primary Endpoint

Change from baseline in presence and severity of symptoms (5-point severity scale), clinical signs (3-point severity scale) and architectural changes (3-point severity scale) at the 6-week, 3-month, 6-month and 12-month follow-up visits. (**Appendices I & II**).

Secondary Safety Endpoints

Evaluate the safety of the treatment:

1. Clinical evaluation of treated area at each study visit. Clinical photography will be performed for study documentation (**Appendix IV**).
2. Pain/discomfort level using a 10-point Numerical Scale Response (NSR) after each treatment (**Appendix V**).
3. Number, severity and type of adverse events recorded throughout course of the study.
4. 1 week ± 2 days post first treatment safety phone call (review of 1-week patient diary) – (**Appendix VI**).

Secondary Efficacy Endpoints

1. Sexual function, using the Female Sexual Function Index (***Appendix III***), at baseline and at the 3-month and 6-month follow-ups. *An overall score ≤ 26.55 is classified as Female Sexual Disorder (FSD)*.[15]
2. Histological signs (degree of hyperkeratosis, epidermal atrophy and dermal inflammation) at baseline and at 6 weeks and 6 months after the final treatment.
3. Subject satisfaction, using a 5-point Likert scale (-2=very dissatisfied; 2=Very satisfied), will be assessed at the 6-week, 3-month, 6-month and 12-month follow-up visits (**Appendix VII**).

SUBJECT POPULATION

Up to 45 female subjects who meet the following inclusion / exclusion criteria may be enrolled.

Subject Withdrawal and Replacement

Subjects enrolled in the study can discontinue their participation at any time for any reason without prejudice or reduction in the quality of their medical care. The investigator or sponsor can terminate a subject's participation in this study to protect the subject's health or if the subject fails to follow directions resulting in noncompliance to study procedures. Subjects who withdraw or are terminated from the study may be replaced to allow up to 45 subjects to complete the study. Subjects who fail to complete the treatment will be replaced and will not be evaluable.

Inclusion Criteria

1. Able to read, understand and sign informed consent for study participation;
2. Female subjects with age 18-80 years;
3. Biopsy demonstrates biopsy-proven lichen sclerosus and/or there are characteristic changes for vulvar lichen sclerosus on physical examination;
4. Treatment of LS has been recalcitrant to mid to high-potent topical corticosteroid treatment or subject refuses topical corticosteroid treatment. Recalcitrance to therapy is defined as no response to topical corticosteroids of an adequate potency (i.e. clobetasol propionate 0.05% ointment or other steroids) and a sufficient duration (12 weeks of use) or lack of symptomatic control of the disease with a maintenance therapy;
5. Topical corticosteroid treatment, if any, will be continued during the study period;
6. Exogenous hormone treatment, if any, will be continued during the study period (type and dose must stay consistent throughout the study);

7. One or more of the following symptoms: itch; pain unrelated to intercourse; pain, skin tearing or bleeding with intercourse; changes/decrease in sexual function;
8. Characteristic changes for vulvar lichen sclerosus on physical examination;
9. No breaks, tears or lesions, malodorous discharge or strawberry cervix present on gynecological exam.

Exclusion Criteria

1. Presence of clinically atypical appearing nevi in the area to be treated;
2. Unexplained vaginal bleeding;
3. Active infection, specifically: urinary tract infection, vulvar or vaginal infection (candidiasis, genital herpes/HSV, bacterial vaginosis, trichomonas);
4. History of vulvar or any gynecological malignancy, as well as history of pelvic radiation therapy or stem cell transplant;
5. Pelvic organ prolapse > stage 2;
6. Pregnancy or planning pregnancy during the study;
7. Systemic treatment with immuno-modulatory drugs.
8. Use of vaginal dilators during study.

STUDY PROCEDURES

Enrollment and Screening

During the first visit, the investigator will screen the subject for eligibility to participate in the clinical study. The inclusion/exclusion criteria will be reviewed, the subject's medical history, an examination of the subject's treatment areas will be conducted.

The subject will review the informed consent form (ICF) and the study will be explained to the subject including all risks, potential benefits, procedures, visit requirements, and other alternative treatment options. If the subject qualifies and wishes to participate they will complete the ICF with a signature and date. The original will be retained with subject's records and a copy will be provided to the subject.

The following measurements will be performed and recorded at the specified times throughout the study (as specified in Error! Reference source not found.).

Table 2. Study Measurements

Assessment	When to conduct	Method
Complete the Inform Consent form and Eligibility Screening and Medical History	During the screening visit / prior to the 1st treatment	Physician or staff will complete the form with the study subject
PAP smear if not up-to-date (within 3 years according to ACOG guidelines)		Patient should provide lab results of up-to-date normal cell cytology
Urine pregnancy test for women capable of becoming pregnant		Patient should have a negative pregnancy test
Gynecological exam		Physician will examine the vulvar and vaginal area for any signs of active infection or atypical nevi
Vulvar biopsy of treatment area (optional)	Prior to the 1st treatment and at the 6-week and 6-month follow-ups	Biopsies will be obtained from up to 10 subjects to conduct histological assessment. Lab reports will be provided to show changes in markers compared to baseline.
Subject assessment of symptoms	• Baseline or pre-Tx. 1 • At the 6-week, 3-month, 6-month and 12-month follow-up visits	Subjects will complete the Symptom Severity Questionnaire, according to the pre-defined scales (**Appendix I**)
Physician assessment	• Baseline or pre-Tx. 1 • Prior to treatments • At the 6-week, 3-month, 6-month and 12-month follow-up visits	Physician will assess clinical signs associated with VLS, according to the pre-defined scales (**Appendix II**)
Subject assessment of sexual function	• Baseline or pre-Tx. 1 • At the 3-month and 6-month follow-up visits	Subjects will complete the Female Sexual Function Index (FSFI) – **Appendix III**
Clinical evaluation and photographs of treated area	• Baseline or pre-Tx. 1 • Prior to treatments • At the 6-week, 3-month, 6-month and 12-month follow-up visits	Physician will evaluate the treatment area. Physician or staff will take photographs of the treatment area (**Appendix IV**)
Treatment pain assessment	Immediately after each treatment	NSR Scale (**Appendix V**)
Subject 1-week daily diary - reviewed at the 1wk FU after the first treatment	The daily diary will be provided at the 1st treatment visit and reviewed by phone during the 1-week safety evaluation	Subjects will be requested to complete a daily diary with data regarding their comfort, AE, and activity (7 days of follow-up post 1st treatment) – **Appendix VI**

Subject satisfaction rating	At the 6-week, 3-month, 6-month and 12-month follow-up visits	Subject will complete the Subject Satisfaction Questionnaire, according to the pre-defined scale – **Appendix VII**
Adverse Events and Serious Adverse Events	During the entire study period: prior to and immediately after the treatments, during all follow-up visits, and whenever a safety concern is reported by the subject	Examination of the treated area, interview subjects for Adverse Events

Pre-Treatment Procedures

Screening procedures may be conducted on a separate day prior to the 1st treatment, but preferably within 2 weeks.

Screening / Initial Evaluation and Baseline

1. ICF - Prior to any study procedures, written informed consent will be obtained. Once the subject fully understands the possible benefits and risks of the study, the subject will be asked to sign and date the informed consent form (ICF). The subject will be given a copy of the signed ICF.
2. Subject ID - Prior to treatment, the subjects will be assigned a study subject number.
3. Medical History - A medical history will be obtained to determine if the subject meets the study criteria, including a list of all prescribed and over-the-counter medications taken within the previous 6 months will be recorded.
4. PAP smear – each patient should provide up-to-date results of PAP smear with normal cell cytology.
5. Gynecological exam – The study physician will examine the vulvar and vaginal area for any signs of active infection, atypical nevi, or breaks, tears or lesions.
6. Urinalysis - Negative urine pregnancy test for women capable of becoming pregnant.
7. Patients will complete questionnaires (Subject assessment of symptoms & FSFI).
8. For up to 10 subjects, a vulvar biopsy will be taken at baseline.

Vulvar Biopsy Procedure

For subjects participating in the biopsy subset of the study, a punch, or scissor snip, biopsy will be obtained prior to the first treatment and again at the 6-week and 6-month follow up visits. The study patient should be informed on the benefits and risks of the procedure and written consent obtained. The risks include pain, bleeding, infection, scarring, inadequate sample possibly requiring another biopsy procedure, or allergic reaction to anesthetic.

The biopsy specimen should be taken from the area of the vulva or peri-anal skin that clinically appears to have the most active or developed VLS changes. A 3-mm or 4-mm punch can be used in most cases. A 3-mm punch biopsy is generally thought to be the smallest size that will provide an adequate sample of tissue for pathologic analysis. However, certain locations where there is little subcutaneous adipose tissue, such as the labia minora and the clitoral hood, may be best sampled by scissor snip technique. The chosen location and biopsy technique should be based on the provider's best judgment of potential histological change as well as patient comfort and healing. Adjacent skin of the same area should be sampled for post-treatment follow-up biopsies.

Mark the biopsy site with surgical skin marker and photograph the marked location. To minimize patient discomfort, apply topical anesthetic prior to injecting local anesthetic. Then, draw 1ml of 1% lidocaine with 1:100,000 epinephrine into a 1ml syringe. Slowly inject the anesthetic with a 30-gauge needle. While this amount of local anesthetic is adequate for the majority of patients, additional anesthetic can be injected as clinically warranted. When anesthetizing the area, insert the needle and withdraw the plunger to decrease the chance that injection occurs into a vessel. Inject slowly at the base of and underneath the lesion, injecting enough to create a wheal. If possible, only penetrate the skin once. The wheal should be larger than the biopsy instrument that will be used. Adequate anesthesia for the procedure should be present in 1-2 minutes. Test for appropriate anesthesia prior to making any incision. As in most clinical situations, biopsy is performed shortly after injection.

Once an adequate biopsy sample has been excised, the specimen should be placed carefully in a fixative solution, such as 10% formalin. Confirm that the sample is in the container after closing the lid. The tissue should to be sent to pathology along with the properly completed pathology forms. Insurance information should not be included on the form, as study subjects will not be billed for biopsies. Patient Initials and Subject Code should be included on the specimen labels (i.e. 001_AMK).

Hemostasis may be achieved with pressure only for small specimens. In addition to pressure, bleeding also may be controlled with suture or gel foam for punch biopsies or with aluminum chloride or silver nitrate for scissor snip biopsies.

Petrolatum jelly should be applied to the healing wound after the procedure and at least twice daily. Petrolatum jelly promotes healing and acts as a protective barrier preventing irritation from contact with urine, sweat, and friction. Given the location and difficulties in keeping a dressing in place, most vulvar biopsies are not bandaged. Use of a pad or pantyliner may be needed for a few days after the biopsy. Mild spotting can be expected for the few days following a vulvar biopsy and if bleeding occurs, it can generally be stopped by direct pressure from the patient.

Showers are permitted 24 hours after biopsy and the biopsy site should be cleansed once daily with a gentle cleanser. Alternatively, the patient may take sitz baths. The use of washcloths, buff puffs, soaps, and any type of vigorous cleaning should be avoided while the biopsy site is healing. Swimming and hot tub baths should be avoided until healing is completed.

Prior to Each Treatment Procedure

1. Hair that exists in the treatment area can be removed by shaving, using a razor or an electric razor, or alternatively, hair can be wetted with saline. Hair can also be removed by waxing 72 hours before treatment.
2. Pre-treatment photographs of the treatment area should be taken.
3. Clinical signs of VLS will be reported.
4. The device arm should be thoroughly cleaned and washed.
5. A new disposable external handpiece should be used for each treatment and disposed of following the treatment.

Treatment Procedure (Tx.1 – Tx.5)

The treatment procedure should be conducted according to the following guidelines, as described in the *CO_2RE* User's Manual:

Pre-Treatment Instructions

1. Prior to beginning treatment, a topical anesthetic may be applied to the external labia and introitus. EMLA or a compounded formulation can be used. Duration of application and anesthetic type is at the discretion of the investigator. Topical anesthetic must be thoroughly removed, and the area cleaned prior to beginning treatment.
2. Dedicated eye protection must be worn during treatment by both the subject and staff.
3. Care must be taken to avoid unintended exposure of the treatment beam to the subject's eye or surrounding skin. Such exposure can cause possible damage. Accordingly, the eyes should be protected with non-reflective eye shields.

4. Treatment should be performed while the subject is lying down comfortably; the operator should have easy access to the subject's treatment area.
5. Affected areas of the vulva (vestibule, introitus, medial labial majora, intralabial sulcus, labia minora and clitoral hood) will be treated.
6. Subject should remove their pants and underwear.
7. Prepare the CO_2RE device for the treatment procedure, including cleaning the handpiece's reflecting mirror (wiped and dried well with ≥70% alcohol).
8. Turn the CO_2RE device on and select the treatment parameters.

Treatment

1. The distal part of the External handpiece should be clean and dry. The handpiece should be held perpendicular to and in close contact with the skin. In the same manner, the distal end of the handpiece should be moved to the designated spot.
2. Prior to treating the entire area, several test spots should be performed in a small section within the area to assess the skin for unwanted effects.
3. The choice of treatment settings should take into consideration the subject's skin type, tendency to bruise, and the specific anatomical location (vulva).
4. Set the CO_2RE treatment parameters according to investigator decision taking into consideration the necessary ablation depth (which is influenced from the amount of water in the vaginal tissue).
5. Single pass laser exposures will be performed at a Repeat Rate of 0.5 – 1 seconds, using the following parameters:

   Deep Mode
   - Core (mJ): 40 – 50
   - Fractional Coverage: 3 – 5%
   - Pattern size (mm): 7.8 X 7.8 (Square)

   And/or

   Fusion Mode
   - Core (mJ): 40 – 70
   - Pattern size (mm): ANY, except 7.8 X 7.8
   - Ring Fluence (J/cm^2): 46 – 87.3
   - Fractional Coverage: 20 – 30%

6. Consider dialing down the energy or changing the fractional density if more than pin-point bleeding occurs.
7. Do not use pulse stacking or more than a single pass.

8. Once the user has selected the laser operating parameters and had located the handpiece at the proper treatment area, he / she can use the footswitch to activate the laser treatment.

Immediately Post Treatment

1. The immediate responses, for the desired effect, are erythema, edema and a distinct stippled gray fractional epidermolysis pattern that aids in visualization of treatment progress. The treatment parameters and treatment response should be noted in the CRFs.
2. Subject will be given a pain (NSR) scale to record the pain level they felt during the treatment.

Post-treatment Instructions for Subject

Subject will be provided with the following instructions for care of the treated areas as described in the informed consent form.

Following the first treatment:

1. Subjects will receive a daily diary, which they will be requested to complete, regarding their comfort and any adverse events for the 7-day period following treatment.

Following each treatment session

1. If the subject experiences itch or discomfort after treatment, ice packs may be applied to the treatment area.
2. Temporary erythema (redness) and edema (swelling), as well as heat and tightening sensations, may occur up to a few hours after the treatment. If the subject feels significant discomfort longer than a few hours, an over-the-counter pain medication such as Tylenol® (Acetaminophen) may be used. Nonsteroidal anti-inflammatory drugs (NSAID), such as aspirin, Ibuprofen (Advil, Motrin), naproxen (Aleve, Anaprox, Naprelan, Naprosyn), etc. should be avoided unless the patient does not experience symptomatic relief with or is contraindicated to acetaminophen.
3. On the evening after the treatment, subjects should wash the treated areas gently with lukewarm water and avoid very hot or cold water in these areas. Generally, subjects may use their regular cleanser after treatment, as long as these are not mechanical scrubs or exfoliants.
4. Subject should refrain from sexual activities for a period of 7 days.
5. Any pain, fever or unusual discharge should be immediately reported.

Follow-up Visits

1. All subjects will be requested to return to the clinic at the following time-points during the study to assess the clinical safety and performance of the device:
   - 6 weeks post last treatment – 6wk FU ± 2 weeks.
   - 3 months post last treatment – 3m FU ± 2 weeks.
   - 6 months post last treatment – 6m FU ± 2 weeks.
   - 12 months post last treatment – 12m FU ± 2 weeks.

2. At the follow-up visits, the following assessments will be performed, and data recorded:
   - Review changes in medication, medical history and AE, if applicable, from last visit.
   - Photographs of treated area.
   - Optional biopsy of treated area (6-week and 6-month follow-up only).
   - Subject assessment of symptom severity.
   - Investigator assessment of clinical signs.
   - Subject Satisfaction.

DATA ANALYSIS

Recording

All data will be recorded on Case Report Forms (CRFs) or transcribed from source documentation, where applicable (i.e. lab reports). The site will be monitored by Syneron Candela staff or designees to assure adherence to the clinical trial requirements, subject safety, protocol procedures, and for data accuracy. The Case Report Forms and images will be reviewed and retrieved during the monitoring visit. All source documentation will remain in the subject's files at the site.

Review and Analysis of all data collected will be conducted by the Sponsor or designee as described for this protocol with the following data:

Demography and Baseline Measurements

Demographic and baseline/screening measurements (e.g., age, weight, clinical VLS signs and digital images) will be collected and descriptively presented.

Treatment Visits

Clinical VLS signs as assessed by the study investigator, photographs of the treated region, and NSR scores will be collected and compared to baseline to assess efficacy and safety. Any potential adverse events will be documented.

Follow-up Visit Measurements

Follow-up measurements, efficacy and satisfaction assessment scores, and digital images will be used for comparative measurements with their respective data at baseline. Primary endpoints will be evaluated at the 6-week, 3-month, 6-month and 12-month follow-up visit.

Safety

Safety of device procedure will be evaluated throughout the study. Any side effects to the treated area will be reported by the subject, the study investigator and the research staff. The occurrence and severity of all complications from the start of the study will be recorded.

ADVERSE EVENTS (AE)

An adverse event (AE) is any adverse change in health or side effect that occurs in a study participant during their participation in the study.

Anticipated Adverse Effects

An adverse event (AE) is any undesired clinical occurrence in a study subject as indicated by signs, symptoms, illnesses, events that develop or worsen in severity in association with the study when deemed by the Investigator to be related to use of the device or study procedures.

Anticipated post-treatment adverse effects which could result from the *CO_2RE* treatment include pain, swelling, bruising (ecchymosis), blistering, burn, and infection.

The Investigator will document all adverse signs and symptoms regardless of severity or frequency that are either volunteered by subjects or observed during the course of the study that are related to the device. The Investigator will also record adverse experiences of subjects resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states that the Investigator deems related to the device. Included in the description will be the nature of the sign or symptom, the date of onset, whether the event was serious, the severity, the relationship to study procedures or investigational device, the action taken, the date of resolution, and the outcome. The Principal Investigator will determine the relationship of the adverse device effect to the investigational device.

Unanticipated Adverse Device Effects

For device studies, part 21 CRF 812.3(s) uses the term unanticipated adverse device effect which is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

All unanticipated adverse effects will be graded as follows:

Mild: Sign or symptom, usually transient, non-life-threatening requiring no special treatment and generally not interfering with usual activities.

Moderate: Sign or symptom, non-life-threatening which may be ameliorated by simple therapeutic measures and may interfere with usual activity.

Severe: Sign or symptom that is intense or debilitating but non-life-threatening and that interferes with usual activities. Recovery is usually aided by therapeutic measures and the discontinuation of the study device may be required.

Serious: Any untoward medical occurrence that at any time results in death or life-threatening illness, resulting in persistent or significant disability/incapacity.

The relationship of the adverse effect to the study is defined as follows*:*

Probable: An adverse event has a strong temporal relationship to study device, and another etiology is unlikely or significantly less likely.

Possible: An adverse event has a strong temporal relationship to the study device, and an alternative etiology is equally or less likely compared to the potential relationship to study device.

Probably not: An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.

Not related: An adverse event has no temporal relationship to study device or has a much more likely alternative etiology.

Reporting Adverse Events (AE) and Serious Adverse Events (SAE)

The Investigator must report all unanticipated adverse device events that are serious in nature to the clinical study monitor immediately or within twenty-four hours by telephone (see below). If such an unanticipated adverse device event is reported after normal working hours, the

Investigator will leave a voice message at the monitor's telephone number with accompanying report of the unanticipated adverse device event sent to the e-mail address below:

Sharon Timberlake, Global VP of Clinical and Regulatory Affairs
Candela Corporation
Telephone Number (mobile): +1 (617) 957-1434
Email: sharont@syneron-candela.com

A written report prepared by the Principal Investigator must follow within five working days to both the IRB and to Candela Corporation and should include a full description of the event and sequence.

Research records will be available to study personnel, the sponsor, Ethics Review Committee/Institutional Review Board (IRB) and regulatory agencies as required. Research records may be used for purposes of medical education, after removal of subject names or other identifying information. In the Informed Consent, the subjects will be informed that the photographs and video taken of them during the study may be made available to the sponsor for marketing and instructional purposes, after removal of identifying information. All images collected will be stored without personal subject identifiers at the site and at Syneron Candela.

Device Failures and Malfunctions

Definitions of Device Failure

Device Failure: A device has failed if it is used according to the Sponsor's instructions but has failed to perform as expected.
Device Malfunction: A device malfunction is an unexpected malfunction of the device that is contrary to expectations when operated according to the Sponsor's instructions.
Device Misuse: A failure of a misused device, namely one that is used by the Investigator in a manner which is contradictory to the Sponsor's instructions, will not be considered a device malfunction.

Precautions to Minimize Complications

Every precaution should be taken pre-, during and post-procedure to minimize technical and procedural complications.

- All conventional precautions relating to this type of procedure must be taken, as with any other procedure.

- All failures and malfunctions of the device will be documented in the database, and the device MUST be returned to the Sponsor for analysis. Device failures and malfunctions should also be documented in the subject's medical record. (NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded accordingly).

RISK/ BENEFIT ANALYSIS

Risks

Candela Corporation has determined that the CO_2RE system is a non-significant risk in accordance with 21 CFR 812.3 for the intended use in this study.

During design and development of the mentioned device, design measures were taken, and tests were performed to ensure treatment safety. These included selection of biocompatible materials, directions for appropriate cleaning to prevent cross-infection, electromechanical safety testing and electromagnetic compatibility testing. A large amount of clinical data (clinical studies and post-marketing data) using different devices for dermatological and gynecological procedures, including Syneron Candela devices, which are like the CO_2RE device, demonstrate a very good safety and efficacy profile. Nevertheless, potential risks for adverse effects of the treatment procedure include, but are not limited to pain, swelling, bruising (ecchymosis), blistering, burn, and infection.

Potential benefits to participating individuals and to society

Subjects may or may not benefit from improvement in lichen sclerosus. All subjects in the study are expected to have some benefit from the treatment procedures. Subject will receive treatment procedures at no cost. This study will benefit the advancement of medicine by generating data on safety and efficacy that will aid in the development of an alternative treatment options to ultra-potent topical corticosteroids (such as clobetasol propionate). This study will benefit the advancement of medicine by generating data on safety and efficacy that will aid in the development of an alternative or adjunctive treatment option for female patients who do not improve with topical corticosteroid use for vulvar lichen sclerosus.

Payment for Participation

Subjects will be paid a total of up to $200 for up to 10 study visits ($20 per visit) for all study visits and evaluations. Subjects will not pay for office visits, examinations or procedures that are part of this clinical study. Subjects who do not complete all study-related procedures and requirements will receive partial payments according to the treatment and follow-up visits that were completed ($20 per visit). Subjects who are biopsied at baseline, at the 6-week follow-up and the 6-month follow-up will receive an additional $200 (~$67 per visit). Payments will be issued upon study completion.

ETHICS AND GOOD CLINICAL PRACTICE

This study will be carried out in compliance with the following:

- Syneron Candela's Standard Operating Procedures (SOPs).
- Declaration of Helsinki (current version).
- US Code of Federal Regulations (Title 21CFR including parts 50, 56 and 812 governing informed consent and IRB regulations).
- International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), 1996.

QUALITY ASSURANCE AND STUDY MONITORING

Study Monitoring/Auditing/Inspection

The Study Monitor will be responsible for monitoring the study sites to review the data being collected. The sponsor shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the trial is being conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements. Visits will be made prior to the initiation of the study, at scheduled intervals throughout the study, and at termination of the study.

Once enrollment and treatments have begun, monitoring visits will take place more frequently pending enrollment and study activities.

The sponsor and site will maintain regular phone and e-mail correspondence throughout the study to confirm compliance of study procedures.

The investigator/institution agrees to allow the study monitor and other authorized personnel direct access to source data/documents for trial related monitoring, the clinical supplies

storage/dispensing area and to provide all documents in the Investigator Regulatory Binder for review, and to assist site auditors in their activities if requested. Requests by the United Stated Food and Drug Administration (FDA) or regulatory agencies of other countries to inspect the study site may be made after adequate notification. The investigator may be required to assist the regulatory inspectors in their duties, if requested.

ADMINISTRATIVE PROCEDURES

Supply and Disposition of Study Devices

The *CO_2RE* Intima disposable external handpieces will be supplied to the participating clinics. Unused equipment will be returned to the sponsor at the end of the study.

Control & Disposition of the Investigational Device

The *CO_2RE* system will be used according to the instructions of the Sponsor, Candela Corporation, and the manufacturer, Syneron Medical Ltd. At the end of this study, any materials provided specifically for use in this study must be returned to the Sponsor, as described in the Clinical Trial Agreement and study budget.

Informed Consent

The Study Personnel will obtain written Informed Consent prior to the subject's participation in any study procedures. The Study Personnel will inform the subjects of the experimental procedure to be utilized and assure the subjects that their decision regarding participation in the study will have no bearing on the quality of medical care received and that their decision whether to participate in the study is strictly voluntary.

During the initial interview, the subject will be assured that they are free to change their mind and will be allowed to participate in the study or withdraw from the study with no adverse effect on their standard medical care.

Monitoring Plan

At least 3 monitoring visits are projected during the whole study. The frequency of which will be based on enrollment, study activities and the study visit scheduled. The first visit is scheduled at the initiation of the study prior to the first subject treatment in the study. The second visit is scheduled after enrollment and treatment has been initiated and a third visit will be for a close-out visit for the study. Interim visits may be conducted as needed to assure compliance to the study protocol and regulatory requirements. The number and frequency of monitoring visits may also be increased per the sponsor decision to collect data and images post treatment.

Case Report Forms

Paper case report forms will be used in this trial. All protocol-required information collected during the study must be entered in the appropriate field of the case report form (CRF). The investigator, or designated representative, should complete the appropriate CRF fields as soon as possible after information is collected. The information must match the information that exists as source documents in the clinic chart, hospital chart, and/or investigator's files. An explanation should be given for all missing data.

It is the investigator's responsibility to assure the accurate completion, review, and approval of all CRFs and the timely completion and submission of all adverse event forms.

Record Maintenance

The investigator shall retain a copy of all study documents in accordance with FDA regulations which specify that records should be kept for a period of two years: 1) following the date a marketing application either is approved or disapproved for use, or 2) following notification to the FDA that no application is being filed and/or that the study has been discontinued.

If an investigator leaves the study site before record retention obligations have expired, the sponsor should be notified in writing of the person designated to retain the study documents during and after the study.

Handling of clinical data. The data are entered into a secure database to which only the Sponsor has access. Admission to the database should require access to a password-protected network secured by the Sponsor. This database is maintained by Syneron Corporation who performs backups, data verification, and application upgrades. All equipment housing the clinical data should be located in locked rooms or a secure computer network. The only individuals, who view, extract and analyze data for protocol reports and publications are physicians and nurses who are members of the study team or sponsors. Only authorized personnel of the sponsors will have access to databases.

Any paper copies of subject medical records or research records should be stored in secure cabinets at the study site.

PUBLICATION POLICY

The investigator will not publish the study results and will not disclose confidential information received from Candela Corporation without prior written agreement from Syneron. Such confidential information shall include any and all information relating to this study as described in the Clinical Trial Agreement. In the event that Candela Corporation consents to the publication of data from this study, the investigator will provide Candela Corporation manuscripts for review sixty (60) days before submission for publication. Candela Corporation

will have no editorial rights over manuscripts. The investigator will also provide Candela Corporation with advance notice of at least sixty (60) days, of any presentation, lecture, abstract session, etc., in which any results from the study will be disclosed.

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APPENDIX I – SUBJECT SYMPTOMS SEVERITY SCALE*

At baseline and at the four follow-up visits, the study subject will complete assessments for severity of the following symptoms associated with their vulvar lichen sclerosus.

Subject Symptoms

Symptom	**Presence of symptoms**	**Severity**
Itch	Yes / No	1, absent/never 2, sometimes/occasionally 3, often 4, most of the time 5, all the time
Pain unrelated to intercourse (burning, soreness, discomfort, etc.)	Yes / No	1, absent/never 2, sometimes/occasionally 3, often 4, most of the time 5, all the time
Superficial (introital) dyspareunia (pain occurring at the moment of penetration)	Yes / No	1, absent/never 2, sometimes/occasionally 3, often 4, most of the time 5, all the time

Skin tearing or external bleeding with intercourse	Yes / No	1, absent/never 2, sometimes/occasionally 3, often 4, most of the time 5, all the time
Quality of life	Yes / No	1, no impact 2, barely affected 3, slightly affected 4, moderately affected 5, strongly affected
Decrease in sexual function – desire to have sexual intercourse is decreased due to physical appearance or self-esteem	Yes / No	1, no impact 2, barely affected 3, slightly affected 4, moderately affected 5, strongly affected

*Based on: Sheinis M, Selk A. Development of the Adult Vulvar Lichen Sclerosus Severity Scale-A Delphi Consensus Exercise for Item Generation. J Low Genit Tract Dis. 2018 Jan;22(1):66-73. doi: 10.1097/LGT.0000000000000361.

APPENDIX II – CLINICAL SIGNS AND ARCHITECTURAL CHANGES SEVERITY SCALE*

At baseline, prior to treatments and at the four follow-up visits, the study investigator will complete assessments for severity of the following clinical signs associated with vulvar lichen sclerosus.

Sign	**Presence of signs**	**Severity**
Fissures	Yes / No	1, mild 2, moderate 3, severe
Whitening	Yes / No	1, mild 2, moderate 3, severe
Crinkly/fine wrinkling of skin/parchment-like skin	Yes / No	1, mild 2, moderate 3, severe
Extent of disease (figure of eight vs localized to labia, localized to clitoris, localized to perineum or combined)	Yes / No	1, mild 2, moderate 3, severe
Erosions	Yes / No	1, mild 2, moderate 3, severe
Ulcerations	Yes / No	1, mild 2, moderate 3, severe

Hyperkeratosis	Yes / No	1, mild 2, moderate 3, severe
Excoriations	Yes / No	1, mild 2, moderate 3, severe
Lichenification	Yes / No	1, mild 2, moderate 3, severe
Elasticity (or loss of elasticity)	Yes / No	1, mild 2, moderate 3, severe
Sclerosis	Yes / No	1, mild 2, moderate 3, severe
Telangiectasia	Yes / No	1, mild 2, moderate 3, severe

Architectural changes	**Presence of changes**	**Severity**
Clitoral hood fusion	Yes / No	1, mild 2, moderate 3, severe
Labial fusion/resorption	Yes / No	1, mild 2, moderate 3, severe

Narrowing of the introitus	Yes / No	1, mild 2, moderate 3, severe
Anterior changes (fusion anteriorly below the clitoris, causing	Yes / No	1, mild 2, moderate 3, severe
urethral occlusion at its extreme)	Yes / No	1, mild 2, moderate 3, severe
Perianal involvement	Yes / No	1, mild 2, moderate 3, severe
Formation of posterior commissure bands/fourchette webs	Yes / No	1, mild 2, moderate 3, severe

*Sheinis M, Selk A. Development of the Adult Vulvar Lichen Sclerosus Severity Scale-A Delphi Consensus Exercise for Item Generation. J Low Genit Tract Dis. 2018 Jan;22(1):66-73. doi: 10.1097/LGT.0000000000000361.

APPENDIX III – FEMALE SEXUAL FUNCTION INDEX*

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low
   - ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Very high confidence
   - ☐ High confidence
   - ☐ Moderate confidence
   - ☐ Low confidence
   - ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

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* Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000 Apr-Jun;26(2):191-208.

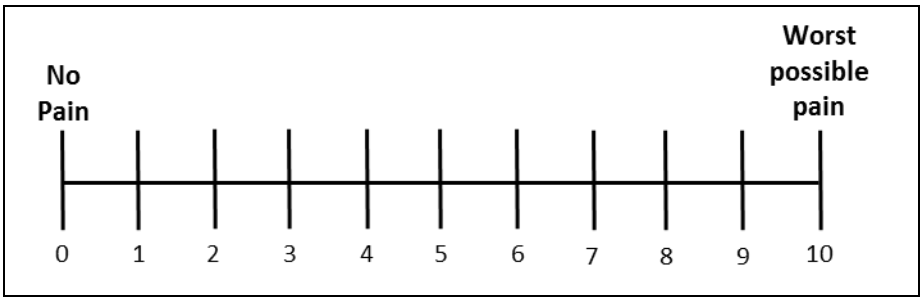
APPENDIX IV – PHOTOGRAPHY GUIDELINES

At each time point (before the treatments and at the follow-up visits), photographs of the treated area should be taken in a standardized manner.

- Photographs should be taken in a private room or area of the clinic under controlled conditions, including the distance from the camera to the subject, height of the camera, background, camera positioning, subject's positioning and lighting in order to achieve high quality before & after sets.
- For consistency purposes, the same person should ideally take all study photographs, especially per subject.
- Small plain labels (with the date, subject ID, subject initials, Investigator name, and identity of the specific area photographed, if necessary) should be placed in the same location within each frame at each photography timepoint. The presence of the label should not impair the photo's desired effect or obscure the treated area.
- The digital files should be labeled in a standardized manner (subject number, subject initials, study visit). For example: 001JS_Tx1, 001JS_FU1, etc.

APPENDIX V – TREATMENT-ASSOCIATED PAIN ASSESSMENT

Immediately after each treatment, the subject will be asked to rate pain/discomfort associated with the treatment, based on the following Numerical Scale Response (NSR). The subject will be given a horizontal line scale and asked to make a mark along the scale. The subject will be asked to rate pain from 0 to 10, with 0 equaling no pain and 10 equaling the worst possible pain. A number is obtained by measuring up to the point the subject has indicated.



APPENDIX VI – SUBJECT POST-TREATMENT DAILY DIARY QUESTIONNAIRE

At the 1st treatment study visit, subjects will be provided with a 1-week daily diary and instructed to rate the discomfort they experienced on the day of treatment and each day following treatment, according to the following scale:

	Score and Rate
❑	0 - No Discomfort
❑	1 - Mild Discomfort
❑	2 - Moderate Discomfort, but tolerable
❑	3 - Very Painful, barely tolerable

Additionally, subjects will be instructed to report any adverse (side) effects during the first week post-treatment and to describe the event on the questionnaire.

APPENDIX VII – SUBJECT SATISFACTION SCALE

Subject satisfaction will be assessed at the 6-week, 3-month, 6-month and 12-month follow-up visits, according to the following scale:

Score	**Improvement Rate**
-2	Very dissatisfied
-1	Dissatisfied
0	Uncertain
1	Satisfied
2	Very satisfied