Protocol:
CYN17-RF-CLINIC

CLINICAL STUDY TO ASSESS THE SAFETY, PARAMETERS AND EFFICACY FOR PROCEDURES USING A RADIOFREQUENCY DEVICE

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INVESTIGATIONAL PLAN

PROTOCOL #: CYN17-RF-CLINIC

CLINICAL STUDY TO ASSESS THE SAFETY, PARAMETERS AND EFFICACY FOR PROCEDURES USING A RADIOFREQUENCY DEVICE

CONFIDENTIAL

THIS INVESTIGATIONAL PLAN CONTAINS CONFIDENTIAL INFORMATION FOR USE BY THE INVESTIGATORS AND THEIR DISIGNATED REPRESENTITIVES PARTICIPATING IN THIS STUDY. IT SHOULD BE HELD CONFIDENTIAL AND MAINTAINED IN A SECURE LOCATION. IT SHOULD NOT BE COPIED OR MADE AVAILABLE FOR REVIEW BY ANY UNAUTHORIZED ENTITY.

CYNOSURE, INC.
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INVESTIGATOR AGREEMENT

I agree to conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in and institutional review board (IRB) review and approval are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigations. I have read and understand the information in the device manual, including the potential risks and side effects of the device.

I agree to personally conduct or supervise the described investigation. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study device the conduct of the study.

I agree to maintain adequate and accurate records and to make those records available for inspection. I further agree that Cynosure, Inc. or their designees shall have access to any source documents from which case report form information may have been generated.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators.

I will comply with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidance E6 during the conduct of this study.

_____ _____

Investigator's Signature Date

_____

Name of Investigator (Typed or Printed)

_____

_____

_____

Address of Investigator (Typed or Printed)

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1.0 BACKGROUND

Radiofrequency (RF) technology is commonly used in surgery, minimally invasive treatments and aesthetic applications. RF technology is a safe method for non-ablative (A nonwounding device treatment which stimulates collagen growth and tightens underlying skin) treatment because energy can be precisely delivered through the skin to the dermal tissue beneath without damaging the epidermis. The gentle heating of deep dermal tissue induces collagen denaturation, contraction, and subsequent synthesis. The collagen synthesis, in turn, creates a tightening effect that helps to eliminate mild to moderate facial wrinkles and rhytides (A wrinkle, typically a facial wrinkle secondary to muscular contraction patterns in the skin) and is used also for other cosmetic treatments on the body. Radiofrequency surgery is currently used to remove lesions such as moles, warts and skin tags and perform cosmetic surgeries such as, but not limited to; blepharoplasties, abdominoplasties, breast augmentations, face lifts, labiaplasties, and vaginoplasties. It involves the passage of radio waves into the skin to perform the removal or reshaping of a lesion. Different types of electrodes are used depending on the type of lesion (e.g. fine needle, wire loop, scalpel blade etc.).

In this study this family of generators will be tested for:
General surgical procedures such as (but not limited to);

- o Urologic, thoracic, plastic, reconstructive and gynecological
- o Electrosurgical coagulation (hemostasis or coagulating) of tissue
- o Epilation and telangiectasia

Non-ablative/aesthetic treatments such as (but not limited to);

- Facial wrinkles and rhytids
- Heating for the purpose of elevating tissue temperature for selected medical conditions such as temporary relief of pain, muscle spasms, and increase in local circulation
- Temporary reduction in the appearance of cellulite

2.0 DEVICE DESCRIPTION AND SPECIFICATIONS

The TempSure Class II Electrosurgical cutting and coagulation device and accessories used in this study received 510(k) clearance under K171262 on September 22, 2017 for:

- The 10mm, 15mm, and 20mm TempSure Envi handpieces are indicated for non-ablative treatment of mild to moderate facial wrinkles and rhytids.
- The 18mm, 25mm, and 30mm TempSure Envi handpieces provide heating for the purpose of elevating tissue temperature for selected medical conditions such as temporary relief of pain, muscle spasms, and increase in local circulation.
- The Massage device is intended to provide a temporary reduction in the appearance of cellulite.
- Coagulation/Hemostasis: Using the surgical handpieces and accessories, general surgical procedures including urologic, thoracic, plastic, reconstructive, and gynecological procedures where electrosurgical coagulation of tissue is performed.

And received 510(k) clearance under K182365 on October 24, 2018 for:

- Cutting: snoring. submucosal palatal shrinkage, traditional uvulopalatoplasty (RAUP), myringotomy with effective hemorrhage control, epistaxis treatment, turbinate shrinkage, skin incisions, biopsy, cysts, abscesses, tumors, cosmetic repairs, development of skin flaps, skin tags and blepharoplasty.

- Blended Cutting and Coagulation: snoring, submucosal palatal shrinkage, traditional uvulopalatoplasty (RAUP), myringotomy with effective hemorrhage control, epistaxis treatment, turbinate shrinkage, skin tags, papilloma keloids, keratosis, verrucae, basal cell carcinoma, nevi, fistulas, epithelidma, cosmetic repairs, cysts, abscesses, and development of skin flaps.
- Fulguration: basal cell carcinoma, papilloma, cyst destruction, tumors, verrucae, hemostasis.
- Bipolar: pinpoint precise coagulation, pinpoint hemostasis in any field (wet or dry). Snoring, submucosal palatal, shrinkage, traditional uvulopalatoplasty (RAUP), myringotomy with effective hemorrhage control, epistaxis treatment and turbinate shrinkage

The 60mm handpieces and flexible applicators used in this study are considered investigational in use because they have not been cleared by the FDA.

The Pellevé has been cleared (510(k) K123366) by the U.S. Food and Drug Administration (the FDA) for:

- Non-ablative treatment of mild to moderate facial wrinkles and rhytids for skin phototypes I-IV
- Cutting: snoring, submucosal palatal shrinkage, traditional uvulopalatoplasty (RAUP), myringotomy with effective hemorrhage control, epistaxis treatment, turbinate shrinkage, skin incisions, biopsy, cysts, abscesses, tumors, cosmetic repairs, development of skin flaps, skin tags and blepharoplasty.
- Blended Cutting and Coagulation: snoring, submucosal palatal shrinkage, traditional uvulopalatoplasty (RAUP), myringotomy with effective hemorrhage control, epistaxis treatment, turbinate shrinkage, skin tags, papilloma keloids, keratosis, verrucae, basal cell carcinoma, nevi, fistulas, epithelidma, cosmetic repairs, cysts, abscesses, and development of skin flaps.
- Hemostasis: control of bleeding, epilation, telangiectasia.
- Fulguration: basal cell carcinoma, papilloma, cyst destruction, tumors, verrucae, hemostasis.
- Bipolar: pinpoint precise coagulation, pinpoint hemostasis in any field (wet or dry), snoring, submucosal palatal shrinkage, traditional uvulopalatoplasty (RAUP), myringotomy with effective hemorrhage control, epistaxis treatment and turbinate shrinkage.

And under K132665 for indicated for non-ablative treatment of mild to moderate facial wrinkles and rhytids.

The devices used in this study may be considered investigational because they may not be used within the currently cleared indications for use.

The generators used in this study have multiple modes of operation and a selection of electrode tips and handpieces, the user can easily configure the system for a wide array of applications.

This device study does not meet the FDA definition for a Significant Risk Device study per 21 CFR 812.3(m). The sponsor determines that this is a non-significant risk device study.

Significant risk device means an investigational device that:
(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The Specifications for The Devices Are:

Surgical Connector	One bipolar and two monopolar surgical handpiece ports		
Neutral Connector	One universal neutral connector compatible with Cynosure neutral electrodes		
Smart Handpiece Connectors	One 4-pin circular connector for both RF energy delivery and temperature sensing (monopolar)		
Modes of Operation	The user can select between different modes of operation.		
Maximum Power	**TempSure Handpiece**		
	60mm, Flexible Applicator		300 Watts (+/- 20%)
	25mm, 30mm		165 Watts (+/- 20%)
	10mm, 15mm, 20mm		120 Watts (+/- 20%)
	Surgical	Cut	300 Watts (+/- 20%)
		Coag	120 Watts (+/- 20%)
		Blend	300 Watts (+/- 20%)
		Bipolar	40 Watts (+/- 20%)
	Pellevé Mode/Character		
	Cut		120 Watts
	Coag		60 Watts
	Blend		90 Watts
	Fulgurate		45 Watts
	Bipolar		120 Watts

3.0 INTENDED USE
The radiofrequency device used in this study is intended for tissue heating, coagulation, and cutting.

4.0 PROTOCOL
4.1 Purpose and Objectives
The purpose of this study is to develop parameters and assess the safety of the radiofrequency device for a variety of treatments. Treatment results may also be evaluated.

The Primary Objectives are:
- To develop treatment parameters.
- Assess the safety through recording of side effects during course of study.

The Secondary Objectives are:

- Subject satisfaction via continuous verbal feedback during the procedure and at follow up visits.
- Assess the ease of use, patient response, treatment time, functions of the new device.

4.2 Protocol Summary

Subjects are to be enrolled in this clinical study if they are 18 years of age or older. Up to 225 subjects will be enrolled at 8 study centers. All subjects may receive up to 10 treatments or multiple treatment areas. Subjects will receive a phone call or attend a visit at 2 days and/or 1 week post treatment to record side effects. If a side effect is tracked, the site will continue to call the subject until the event resolves. If deemed necessary by the investigator, the subject may attend an unscheduled visit for side effect assessment. The subject may return for optional follow up visits at 30, 90 and 180 days post last treatment for side effect and efficacy assessments.

4.3 Protocol Study Design

This investigation is a multi-center, prospective, open label study.

4.4 Criteria

Subjects will meet the criteria described below.

Inclusion Criteria:

- A healthy male or female 18 years of age or older.
- Understands and accepts obligation not to receive any other procedures on the treatment area through the length of the study.
- Understands and accepts the obligation and is logistically able to be present for all visits.
- Is willing to comply with all requirements of the study and sign the informed consent document.

Exclusion Criteria:

- Is pregnant or of child bearing potential and not using medically effective birth control or has been pregnant in the last 3 months, currently breast feeding or planning a pregnancy during the course of the study.
- The subject has active or localized systemic infections.
- The subject is currently enrolled in an investigational drug or device trial, or has received an investigational drug or been treated with an investigational device within in the area to be treated 6 months prior to entering this study.
- Any other types of cosmetic treatments in the area to be treated in the past 6 months are cautioned and determined at the discretion of the investigator.
- The subject has a history of keloids.
- The subject has evidence of active systemic or local skin disease that may alter wound healing.
- The subject has scarring or wounds in the treatment area that would interfere with study assessments.
- The subject has a metal implant (such as but not limited to; titanium orbit or metal chin repair) in the face or head that would interfere with study treatment, or subject

has an electronic implantable device (such as but not limited to; pacemakers and embedded defibrillators).
- The subject has any condition or is in a situation which in the investigators opinion may put the subject at significant risk, may confound study results or may interfere significantly with the subject's participation.

4.5 Screening

Medical history of each subject will be reviewed, and inclusion/exclusion criteria verified. Discontinuation of any concomitant medications or pretreatment instructions as determined by the investigator will be discussed. Pre and Post-Treatment instructions will be reviewed with the subject prior to signing the informed consent. Subjects will be asked questions about their medical history and may have a limited physical exam (no pelvic or and rectal exam will be performed).

Procedure for the Limited Physical Exam:
If the investigator determines that a limited physical is necessary, the exam will be similar to that of a basic annual physical exam performed by a primary care doctor to determine general overall health. The limited medical exam may include all or any of the following; vital signs such as blood pressure, heart rate, respiratory rate and body temperature, general appearance, listening to the heart, lungs and abdomen with a stethoscope, head and neck exam such as looking at the throat, tonsils, teeth, ears, eyes and nose and neurological exam such as testing muscle strength, reflexes, balance, sensory changes of the extremities and mental state.

4.6 Informed Consent Process and Enrollment

Subjects meeting the subject selection criteria for the study will sign the informed consent form and be assigned a subject identification number. Subjects will be de-identified through their subject identification number, which will be stored in a secure location. Subject identification numbers will be generated chronologically and assigned only to subjects who have met all the study selection criteria and have signed the informed consent form. The informed consent will be obtained prior to a subject's involvement in any study related procedures. Non-English speaking individuals cannot be enrolled in this study. Employees of the sponsor or the Investigator may be enrolled in this study. A subject will be considered enrolled in the study once they have signed the informed consent form.

4.7 Pretreatment

- Photographs, OCT, and Ultrasound measurements may be taken pretreatment.
- If the subject is of childbearing potential (i.e. females not post-menopausal or not surgically sterile) they will be asked if they are pregnant and the date of their last menstrual cycle. A urine or serum pregnancy test may be conducted at the Investigators discretion at any time. If the treatment area is on the abdomen, then urine or serum pregnancy test will be conducted. If a urine or serum pregnancy test is conducted, then a negative result must be obtained within 24 hours prior to the procedure.
- A treatment area will be identified by the investigator. Subjects may receive facial treatments or isolated areas of treatment on other areas of the body
- A marker may be used to define the area.

- Standard pre-treatment instructions will be reviewed, and the subject will be instructed to adhere to the following:
    - Do not receive other treatments within the study area for the duration of the study.
    - If treatment is on the face;
        1. Do not apply any products or makeup to general eye area for 12 hours (or more) prior to each study visit.
        2. Remove makeup and wash facial area prior to treatment.
    - Please remove all makeup, and any lotions or sun block from the treatment area. Any preparations left on the skin will act as impedance to the energy and will diminish the effects.
    - The treatment area must be free of any open lesions or infections.
    - For an optimum treatment, hydrate by drinking water or hydrating fluids several days in preparation. Avoid alcohol if possible. The same procedure should be followed prior to each visit.

4.8 Treatment

- Radiofrequency Device Treatment:
    - The type of treatment will determine if gel should be applied to the skin prior to treatment. The gel is a conductive gel created for treatments that use radio frequency (RF) to ensure the proper connection between the hand piece and the skin.
    - A neutral pad will be used in accordance with the operator's manual for the device.
    - The hand piece, applicator or tip will be placed in contact with the skin.
    - The entire defined treatment area will then be treated by delivering energy to the skin.
    - The hand piece, number of passes and parameters used for the treatment will be determined by the Investigator.
    - Parameters may be adjusted throughout the treatment to increase subject comfort.
    - Contact cooling built into the 60mm handpiece may be used to increase subject comfort.
    - Nitronox may be used to increase subject comfort and will be determined by the Investigator.
- Procedural adverse events will be documented.
- Subjects will be asked to report the general level of treatment discomfort/pain on a scale of 0 (none) to 10 (maximum intolerable pain).
- Some subjects may have an incomplete response or no response by the end of the study. At the end of the study treatments using an FDA approved/cleared treatment method may be discussed with the subject and obtained at the cost of the subject.

4.9 Post-Treatment

- Photographs may be taken post treatment.
- Standard post-treatment care instructions will be reviewed and may be instructed to adhere to the following:
    - Wash skin with tepid water and a gentle cleanser.
    - If the skin is slightly pink or red in areas following the treatment, avoid hot water when washing or showering until any erythema (redness) has subsided.

- Makeup (preferably mineral-based) is not encouraged but may be applied immediately post-treatment.
- Soothing creams or moisturizers may be used.
- If the treatment area may be exposed to the sun; use a sun block with an SPF of 30 or greater to help prevent sun damage. This treatment does not cause photosensitivity.

- Subjects may be given a diary to assess recovery time to be completed during the week post the treatment.
- Subjects and clinicians may be asked to complete a treatment experience questionnaire.

4.10 Follow Up

- Subjects will receive a phone call or attend a visit 2 days and/or 1-week post treatment to record side effects. If a side effect is tracked, the site will continue to call the subject until the event resolves. If deemed necessary by the investigator, the subject may attend an unscheduled visit for side effect assessment.
- The subject may return for a follow up visit at 30, 90 and 180 days post last treatment for side effect and efficacy assessments.
- The assessments listed in the schedule of activities and observations table (Section 4.13) will be performed at all follow up visits.
- Adverse events will be assessed at all follow up visits.

4.11 Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the site Investigator. The date and reason for the unscheduled visit will be recorded in the source documentation.

4.12 Replacement of Subjects

Replacement of subjects who have withdrawn or been withdrawn from the study will be allowed to be replaced with prior approval from the sponsor and/or IRB.

4.13 Schedule of Activities and Observations

Procedure	Screening/ Pretreatment*	Visit 1-5: Treatment Visits	Visit 6: (optional) 2 Day Post Last Treatment Visit or Phone Call	Visit 7: 1 Week Post Treatment Visit or Phone Call	Visit 8: (optional) 30 Day Post Last Treatment Visit	Visit 9: (optional) 90 Day Post Last Treatment Visit	Visit 10: (optional) 180 Day Post Last Treatment Visit
Medical History	X						
Pregnancy Verification	X						
Informed Consent	X						
Treatment Discomfort/ Pain Evaluation		X					
Treatment		X					
Photographs	X	X	X	X	X	X	X
Subject Experience		X					
User Experience		X					
Diary***		X		X			
OCT***	X	X		X	X	X	
Ultrasound***	X	X		X	X	X	
Subject Satisfaction					X	X	X
Adverse Events Assessment **		X	X	X	X	X	X

* Screening/Pretreatment activities must be performed within 30 days prior to 1st treatment and may be performed on the same day as Visit 1.
** If deemed necessary by the investigator, the subject may attend an unscheduled visit for side effect assessment.
***Ultrasound (US), Optical Coherence Tomography (OCT), and the Diary are optional assessments.

The sponsor anticipates that all subjects can be enrolled within 6 months. The subject participation in this study will last approximately to 1-7 months. The total duration of this study is anticipated to last approximately two years.

4.14 Evaluation Methods

Photographs:
Photographs will be taken at all visits and will be used to assess safety and efficacy of treatment.

Treatment Discomfort/Pain Evaluation:
Subjects will be asked to report the general level of treatment discomfort on a scale of 0 (none) to 10 (maximum intolerable pain) using the universal pain assessment tool (Appendix B)

Subject Experience Evaluation:
Subjects will be asked to complete a questionnaire to assess their treatment experience.

User Experience Evaluation:
The clinician will be asked to complete a questionnaire to assess the usability of the device.

Diary:
A subject diary may be collected to assess the recovery time of the treatment for 7 days post treatment.

Subject Satisfaction:
The subject will be asked their level of satisfaction using a 6-point Likert scale that ranges from “extremely satisfied” to “extremely unsatisfied.”

Rating	Description
6	Extremely Satisfied
5	Satisfied
4	Slightly Satisfied
3	Slightly Unsatisfied
2	Dissatisfied
1	Extremely Unsatisfied

Ultrasound (U/S):
An ultrasound scan is a medical test that uses sound waves to capture live images from the inside of the body. The subject will most likely be lying down on a table with a section of their body exposed for the test. A special lubricating jelly will be applied to their skin. This prevents friction between the ultrasound transducer—similar in appearance to a microphone— and the skin. The jelly also helps transmit the sound waves. After the procedure, the gel will be cleaned off the subject. The whole procedure typically lasts less than 30 minutes. Following it, the subject will be free to go about their day and normal activities.

Optical Coherence Tomography (OCT)
An OCT device uses a very low power laser that is directed at the skin. The reflected light is captured by the device to provide images of the skin layer down to 1 millimeter depth. It may be used to help evaluate the effect of RF exposure on the skin. The subject will be asked to lay down and the device’s arm will be brought into contact with the skin area of interest. Depending on the area of skin to be measured, the exam will take 15 to 30 minutes to perform.

4.15 Adverse Event Assessment

Recording of adverse events will take place at all visits.

4.16 Adverse Event Recording

All data captured must be supported by the Investigator's timely assessment and documentation of the event in the case report forms or source documents. All documented adverse events will be reviewed by the Sponsor or designee to determine whether the adverse event meets regulatory reporting requirements and to ensure timely adverse event reporting to meet local and global regulatory requirements.

Adverse Events Pertaining to the Radiofrequency Device:
Mild discomfort during treatment may be experienced by the subject. Typically, the discomfort is temporary and localized within the treatment area. Mild edema (swelling) and erythema (redness) may occur. Initial studies indicate that these side effects typically resolve within 2 to 24 hours.

Other anticipated side effects may include; pain, skin burns, bleeding, scarring, crusting, bruising, infection, itching, prolonged edema (swelling), and erythema (redness), hardness, and nodules. Loss of hair pigment may also occur within and adjacent to the treatment area.

Adverse Events Pertaining to Surgical Marker:
Using surgical marker has minimal risks and may produce effects on the body such as redness or a rash. Markings may remain visible for a few days or may be removed with alcohol.

Adverse Events Pertaining to Gel:
The gel is a water-based gel that may be placed on the skin during an RF treatment. No known adverse events are documented. However, an allergic reaction is always possible when placing a topical gel onto the skin. Allergic reaction may include a mild reaction such as skin redness, irritation or hives.

Eye injury due to direct ocular Radiofrequency exposure may occur:
Corneal Eye Shields (sterile, plastic, non-conductive) must be used for any radiofrequency surgical procedure being performed over the globe of the eye.

Adverse Events Pertaining to Cooling:
Anticipated transient side effects associated with cooling may include tingling, itching, decreased sensation, numbness, redness and pain.

Adverse Events Pertaining to Anesthetic:
1% lidocaine (Lidocaine) with Epinephrine Injection
Pain and numbness may be experienced at the site of the injection. Redness, rash, infection, skin damage or nerve damage at the site of the injection may also be experienced. Temporary loss of sensation and muscle function at the site of injection may be experienced. Lidocaine with epinephrine contains the preservative sodium metabisulfite which may cause allergic-type reactions or intolerances including anaphylactic symptoms such as itching, hives, swollen areas of the body, and/or trouble breathing and life-

threatening or less severe asthmatic episodes in certain susceptible people.

Adverse Events Pertaining to Nitronox:
May experience nausea, vomiting, excessive sweating, euphoria, excitement, deep sedation, drowsiness, sleep, dizziness, lightheadedness, dysphoria, amnesia, and headaches.

Adverse Events Pertaining to Ultrasound:
Ultrasound imaging has minimal risks and may produce effects on the body such as redness and pockets of gas. Skin rashes from use of the ultrasound gel may also occur.

Other Anticipated Adverse Events:
Incomplete response or no response is relatively common since some subjects may not respond to treatment.

5.0 PREGNANCY

Females may not participate in this study if they are pregnant, breastfeeding, were pregnant within the last three months or are planning a pregnancy during the course of the study.

If the subject thinks they have become pregnant during the study it is important that they inform the Investigator immediately. If she becomes pregnant or thinks that she may be pregnant, she will be removed from the study and will be asked to perform a final evaluation similar to that of the final follow-up visit. The Investigator may request to track the pregnancy and will report the pregnancy to the Sponsor.

6.0 SUBJECT WITHDRAWAL

The subject is free to withdraw from this study at any time. The subject must inform the Investigator immediately if they intend to withdraw. To terminate the subject's participation in this study, they must contact the Investigator at the contact information listed on page one of the informed consent form. They will be asked to come to the study clinic or Investigators office to complete a final follow up visit and may be asked to perform end of study procedures. Their decision to participate in this study or to withdraw from this study will not influence the availability of their future medical care and will involve no penalty or loss of benefits to which they are otherwise entitled.

The Investigator in charge of the study can remove the subject from this study without their consent for any reason, including, but not limited to:
a. His/her judgment that any condition or circumstance may jeopardize their welfare or the integrity of the study.
b. Their failure to follow the instructions of the Investigator(s).
c. If the study is stopped by the sponsor and/or Investigators participating in the study prior to completion.

7.0 PHOTOGRAPHY

Standardized photographs may be taken of the treatment area. If photographs are taken of the face the subject will be asked to remove jewelry, make up and lotions prior to each photo session. Photographs will be taken with an appropriate high resolution digital camera. Camera settings (lighting, distance, background, polarization, etc.) will be reproduced at each visit, so that photographs are suitable for comparison.

8.0 RISK ANALYSIS AND MANAGEMENT

The Investigator in this clinical trial has been invited to participate based on his/her previous experience with the use of system, similar systems and industry experience. Experience with treatments is the most critical element in managing subject risk in this trial. All other known risks will be disclosed to the subject via the informed consent process. Since this is an elective procedure and the subjects are volunteers, it can be assumed that their signature on the informed consent is indicative of their agreement to accept the risks involved.

In addition, as with any study, there is a risk of bias. To minimize/avoid bias objective evaluation methods may also be used in conjunction with subjective evaluation methods when feasible.

9.0 ADVERSE REACTIONS DEFINITIONS AND REPORTING REQUIREMENTS

All adverse events that occur, starting from the time of the first treatment, will be recorded in the source documents.

Adverse Events occurring will be captured and followed until the condition resolves, stabilizes, is otherwise explained, or the subject is lost to follow-up. Subjects will be instructed that they may contact the Investigator at any time throughout the course of the study.

The Investigator and/or designated study staff will review each event and assess its relationship to the study device (not related, unlikely, possible, probable, and highly probable). The following definitions will be used for rating relationship to the device treatments:

- Not related – The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Unlikely – The event was most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or a concomitant medication administered to the subject; and does not follow a known response pattern to the investigational product.
- Possible – The event follows a reasonable temporal sequence from the time of investigational product administration; **and/or** follows a known response pattern to the study sampling sessions; **but** could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Probable – The event follows a reasonable temporal sequence from the time of investigational product administration; **and** follows a known response pattern to the investigational product; **and** cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Highly Probable – The event follows a reasonable temporal sequence from the time of investigational product administration; **and** follows a known response pattern to the investigational product; **and** cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; **and** either occurs immediately following investigational product administration, **or** improves on stopping the investigational product, **or** reappears on repeat exposure, **or** there is a positive reaction at the application site.

  Each adverse event reported will be graded on a 3-point severity. Using the following definitions for rating severity will be used:

- Mild – easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities.
- Moderate – sufficiently discomforting and may interfere with normal everyday activities.
- Severe – incapacitating and/or preventing normal everyday activities.

A Serious Adverse Event (SAE) is any adverse device experience that results in any of the following outcomes: death, a life-threatening adverse device experience, in-patient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition

If any of the above adverse events are serious as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All serious adverse events will be reported within 24 hours of acknowledgment to the Sponsor whether or not the serious events are deemed sampling session-related. All serious event reporting will adhere to 21 CFR part 812 and the IRB will be notified accordingly.

The SAE information will be entered into the database and a desk copy of the complete SAE report will be submitted to the files.

Adverse events, whether serious or non-serious, will be followed until the condition is resolved, stabilized, otherwise explained or the subject is lost to follow-up. Adverse events will be captured throughout the study and where appropriate, medical tests and examinations will be performed to document the resolution of event(s). Outcomes may be classified as resolved, improved, unchanged, worse, fatal, unknown or lost to follow-up. Following the resolution of any study-associated adverse events there will be no further adverse event reports for that subject.

10.0 PROTOCOL DEVIATIONS

All requests for protocol deviations by the Investigator have to be communicated to the sponsor in writing and if accepted by the Sponsor must be approved by the IRB. If a deviation occurs, the Investigator must inform the Sponsor as soon as possible. The Sponsor will notify the IRB in accordance with IRB specific policies.

11.0. DATA RECORDING, COLLECTION AND MONITORING

The sponsor will train the site and may be present at initiation of treatment. The sponsor will also monitor the site periodically. The sponsor may request intermediate data following each visit to evaluate treatment progress. Case Report Forms will be reviewed for current data and Regulatory Binders will also be reviewed for correct documents. The sponsor will collect data at the end of the follow up period. The sponsor will list the study on clinicaltrials.gov as required by FDA regulations.

12.0 CONFIDENTIALITY AND DISCLOSURE OF MEDICAL INFORMATION

As part of this study the Investigator and the team at the study center will keep records of subject participation in the study. These study records will include personal information that the subjects provide including age, sex, etc., the results of the study, information about response to treatments,

photographs taken during the study and other medical information relating to participation in the study.

Under federal law the study records cannot be used or disclosed by the Investigator for research purposes unless subjects sign the informed consent authorization.

Some or all of the test results, photographs and other information will be reported to Cynosure, Inc. the manufacturer of the device (Sponsor), and consultants 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 Administration and the FDA, Institutional Review Board or other regulatory agencies in the United States and/or foreign countries. The subject's study records will be assigned a code number by the study team and they will ordinarily not be identified by name in the study records that are sent to the Sponsor and its consultants. However, The Sponsor, the Institutional Review Board and its consultants will have the right to see the complete study records, including the subject's name, and might choose to do so. If reports or articles are written about the study, the subject will not be identified by name in them however their photographs and study information may be used.

The study center will review and use the study records only for purposes of this study. They will keep the subject's identity confidential and, except for the disclosures described above, will not disclose the study records to other parties unless disclosure is required by law. Once the study center discloses information in the 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 cannot be guaranteed. However, the Sponsor and its consultants will only use information for purposes of the study and will not disclose your study records to parties other than; the FDA or other regulatory agencies in the United States and/or foreign countries, unless disclosure is required by law. If reports or articles are written about the study, subjects will not be identified by name in them however their photographs and study information may be used.

Study records will be kept at the study center according to applicable regulations and policies and may be kept indefinitely following the completion of the study. Subjects will not have the right to review their records while the research is in progress. However, they will be able to review their records after the research has been completed.

13.0 LABELING

Sample labeling and directions for use are contained in the Operators Manual for the device.

14.0 CLINICAL RESEARCH CONDUCT

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. The investigator must ensure that the study is conducted in accordance with the provisions as stated in the FDA regulations and complies with the applicable local or regional regulatory requirements.

15.0 INFORMED CONSENT

During the screening, the investigator or a representative on their behalf will perform the informed consent process and discuss all aspects of the study. A signed informed consent form

(ICF) shall be obtained from the subject, clearly indicating his/her understanding of the study requirements, as well as the possible risks involved with study participation.

16.0 DATA ANALYSIS

All data will be analyzed at the end of the study. The primary analysis will be performed by the intention-to-treat approach. All subjects who begin the treatment is considered to be part of the study whether the subject completes the study or not. Additional per-protocol analysis may also be performed on subjects who complete the entire clinical trial according to the protocol. The most appropriate method of handling missing values will be chosen based on the particular trial's goals, endpoints and context.

Endpoints will be summarized with descriptive statistics. Continuous variables will be summarized with n, mean, standard deviation and range. Frequency counts and percentage of subjects within each category will be presented for categorical data. If applicable, Student's t-test may be used to determine if two sets of data are significantly different from each other and p-values will be reported. If the calculated p-value is below the threshold chosen for statistical significance (0.05, or 0.01 level) then the null hypothesis is rejected in favor of the alternative hypothesis. Subgroup analyses may be performed to identify a subject population that achieves the most benefit. Interim results may also be collected and reported as deemed necessary.

17.0 REPORTING FOR THE STUDY

A study summary report will be generated. It will include a description of the clinical conduct of the study and results.

18.0 DISCLOSURE

The Principal Investigator and Cynosure employees have signed confidentiality agreements with the sponsor. This confidentiality agreement ensures that all information provided to the Investigator or Data Management and Statistics group dealing with the study and information obtained during the course of the study will be regarded as confidential.

19.0 RESPONSIBILITY OF THE INVESTIGATOR

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000 including notes of clarification, Washington, 2002 and Tokyo, 2004) and FDA Good Clinical Practice Regulations (21 CFR parts 50, 56, and 812). Investigators will supply information to the sponsor such that the sponsor can comply with the Financial Disclosure Rules (21 CFR part 54).

20.0 PROCEDURE FOR AMMENDMENTS TO THE PROTOCOL

No deviations from this protocol will be permitted, except in a medical emergency, without the approval of the Sponsor. Any amendment to this study will be discussed by the Investigator and the Sponsor. If agreement is reached concerning the need for modification, this will be made in a formal amendment to the protocol.

All revisions and/or amendments to the protocol must be approved in writing by the appropriate Institutional Review Board.

21.0 INSTITUTIONAL REVIEW BOARD

This protocol, informed consent forms, and any amendments to the protocol will be reviewed by the appropriate Institutional Review Board prior to initiation. The study will not be initiated without the approval from the Institutional Review Board.

22.0 TERMINATION OF STUDY

The Sponsor reserves the right to discontinue this study for administrative reasons at any time. The Investigator reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.

23.0 STUDY RECORDS

All records and documents pertaining to the study will be maintained in appropriate permanent files as per the ICH guidelines for Essential Documents for the Conduct of a Clinical Trial and 21 CFR 11, and will be available for inspection by the Sponsor, Sponsor designee, the U.S. Food and Drug Administration or applicable regulatory body at any time.

24.0 DATA SECURITY

To ensure the privacy and confidentiality of data for this protocol, the data will be stored on a restricted access location on a company server. Access to the project directory containing the data will be limited to the Investigators and research staff. Information about data security awareness is promoted through user training and education, supplemented by policies and procedures. Password protection will be used for all transactions that allow viewing, editing, and analysis of data, or that provide access to data fields derived from the original source documents.

25.0 CONFIDENTIALITY OF SUBJECT IDENTIFICATION

After the informed consent has been signed, each subject will be entered on a screening/enrollment log, which will be kept with the study records. Once a subject is consented, a unique subject identification number will be assigned. No two subjects will have the same subject identification number. This subject identification number will identify the subject throughout the study and will be used for all source documents, and Data Collection Forms. The subject identification number will be held confidential so far as permitted by law. Investigative site staff, the Sponsor or its designee, and, under certain circumstances, the FDA and Institutional Review Board (IRB) will be able to inspect and have access to the subject identification number and the confidential data that it links to. Any publication or presentation of data will not contain any identifiable subject information.

APPENDIX A:

Protocol Revisions Tracker

Version Date	Editor	Description
January 6,2017	Jennifer Civiok	Initial Submission to the IRB
January 12, 2017	Jennifer Civiok	Response to IRB conditional approval;
May 3, 2017	Jennifer Civiok	Add Raminder Saluja, MD as a study center, increase # of study centers from 1 to 5, increase number of subjects from 50 to 150
November 17, 2017	Jennifer Civiok	Add Barry DiBernardo, MD as a study center Updated FDA clearance, Clarify that the Pelleve and/or TempSure RF Device may be used, update treatment to list that a neutral pad will be used in accordance with the instructions for use, minor administrative edits.
January 19, 2018	Jennifer Civiok	Add Edward Jaccoma, M.D. as a study center.
April 9, 2018	Kristy Maxfield	Add Jeffrey Dell, M.D. as a study center, add 60mm handpiece as investigational, expansion of subject enrollment (150 to 200) and number of sites (5 to 8), minor administrative edits.
April 25, 2018	Kristy Maxfield	Add adverse event of hardness and nodules.
July 12, 2018	Kristy Maxfield	Added contact cooling may be used during treatment. Added adverse events pertaining to cooling.
October 11, 2018	Kristy Luis	Updates/edits to device specifications. Added follow up visits at 2 days and 7 days. Added anesthesia may be used and adverse events. Added additional evaluation methods (user and subject experience, optical coherence tomography, ultrasounds, and a diary). Minor administrative edits
November 12, 2018	Kristy Luis / Jill Ashley	Update FDA clearance. Update 2 day visit as either a visit or phone call. Add the use of Nitronox and adverse events. Minor admin edits.
November 16, 2018	Kristy Luis	Increase number of treatments from 5 to 10. Update to include side effect of loss of pigment in hair.
February 4, 2019	Kristy Luis	Add satellite site for Dr. Doherty. Increase number of subjects from 200 to 225.

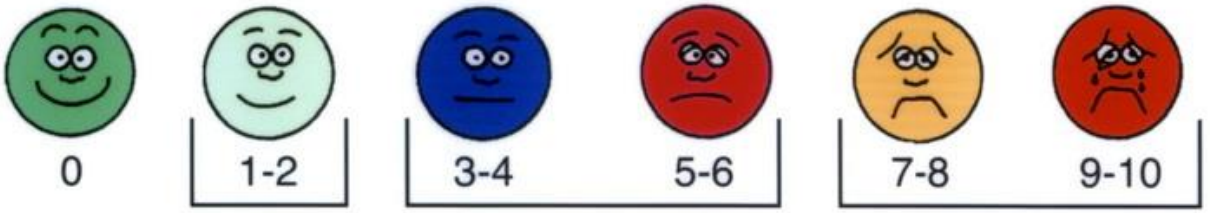
March 20, 2019	Kristy Luis	Added flexible applicator may be used. Updated TempSure Specifications chart. Admin edits.

APPENDIX B:

UNIVERSAL PAIN ASSESSMENT TOOL

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.

WONG-BAKER FACIAL GRIMACE SCALE



ACTIVITY TOLERANCE SCALE	NO PAIN	CAN BE IGNORED	INTERFERES WITH TASKS	INTERFERES WITH CONCENTRATION	INTERFERES WITH BASIC NEEDS	BEDREST REQUIRED
SPANISH	NADA DE DOLOR	UN POQUITO DE DOLOR	UN DOLOR LEVE	DOLOR FUERTE	DOLOR DEMASIADO FUERTE	UN DOLOR INSOPORTABLE
FRENCH	AUCUNE DOULEUR	LÉGÈRE DOULEUR	DOULEUR MODÉRÉE	FORTE DOULEUR	TRÈS FORTE DOULEUR	DOULEUR EXTRÊME
GERMAN	KEINE SCHMERZEN	LEICHTE SCHMERZEN	MÄSSIGE SCHMERZEN	STARKE SCHMERZEN	SEHR STARKE SCHMERZEN	EXTREME SCHMERZEN
JAPANESE	痛みなし	軽い痛み	中程度の痛み	ひどい痛み	非常にひどい痛み	最悪の痛み