Official Title: CYN20-FIRM-LIPO

CLINICAL STUDY TO ASSESS THE SAFETY AND EFFICACY OF THE TEMPSURE® FIRM FOR NON-INVASIVE LIPOLYSIS OF THE FLANKS

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INVESTIGATIONAL PLAN

PROTOCOL #: CYN20-FIRM-LIPO

CLINICAL STUDY TO ASSESS THE SAFETY AND EFFICACY OF THE TEMPSURE® FIRM FOR NON-INVASIVE LIPOLYSIS OF THE FLANKS

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CLINICAL STUDY TO ASSESS THE SAFETY AND EFFICACY OF THE TEMPSURE® FIRM FOR NON-INVASIVE LIPOLYSIS OF THE FLANKS

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 agree to personally conduct or supervise the described investigation.

I agree to inform any patients, or any persons used as controls if applicable, that the device(s) is/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 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 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, FDA Good Clinical Practice Regulations (21 CFR parts 50, 56, and 812), Declaration of Helsinki (DoH) and the Health Human Service (HHS) Belmont Study Principals and Guidelines during the conduct of this study.

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 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 will disclose financial arrangements and interests in accordance with Financial Disclosure Rules (21 CFR part 54) and FDA Form 3455.

_____ _____

Investigator's Signature Date

_____

Name of Investigator (Typed or Printed)

_____

_____

_____

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ATTACHMENTS/REFERENCES

I. Operator Manual for the TempSure®
II. Clinical Reference Guide for the TempSure®
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V. Advertisement
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PURPOSE

1.1 Name and Intended Use

The device used in this study is called the TempSure® Firm.

The intended use of the TempSure® Firm used in this study is for non-invasive lipolysis of the flanks.

1.1 Objectives

1. Primary Objectives:
    - Photographic evaluation with correct identification of pre-treatment images when compared to the 12 week follow up images performed by three independent reviewers.

2. Secondary Objectives:
    - Caliper measurements to show statistically significant improvement on treatment area versus control.
    - Subject satisfaction rates at 12 week follow up.
    - Safety assessment through the collection of Adverse Events.

1.2 Duration of the Investigation

The sponsor anticipates that all subjects can be enrolled within 3 months. If subject participates in all required visits, then the subject's participation in this study may last up to 6 months. It is anticipated that it will take approximately 3 months to analyze the data collected during this study. The total duration of this study is anticipated to last approximately 12 months.

2.0 PROTOCOL

2.1 Protocol Methodology and Analysis

Methodology:

Subjects are to be enrolled in this clinical study if they are 18 – 55 years old. A maximum of 68 subjects will be enrolled at up to 6 study centers. Subject will attend a screening/pretreatment visit which may be performed on the same day as the treatment visit. Subjects will receive up to 5 treatments with the TempSure® Firm on one flank. The other flank will be left untreated to serve a control. Subject will be required to return for follow-up visits at 6 weeks and at 12 weeks after the subject's final treatment. All subjects will receive a phone call 1 week (1-10 days) post each treatment. An unscheduled visit or phone call may be performed at any time during the study at the subject's request or as deemed necessary by the site Investigator.

Analysis:

Upcoming generations are proving to have an interest in non-ablative aesthetic treatments and will drive demand for innovated products, procedures, and practice design.[i] Due to this shift in patient base, practices need to evolve to adapt to the newer generational ideologies. There have been rapid advances in RF technology over the past few years and the nonsurgical treatment using this energy source offers great promise to our aging population.[ii] Radiofrequency technology for lipolysis needs to be further investigated to optimize treatment parameters for safe and effective non-ablative aesthetic treatments.

Relevance:

Non-invasive fat reduction is a commonly sought out procedure and continues to increase in demand (+3% from 2018 to 2019)[3] perhaps due to the fact that, according to the CDC, the prevalence of obesity in the U.S. was 42.4% in 2017-2018[4]. Currently, the treatments available for non-invasive lipolysis include, but not limited to, radiofrequency, cryolipolysis, laser lipolysis, HIFEM, and ultrasound. The limitations of current products on the market include different side effect profiles and modes of administration.

Testability:

The CoolSculpting device has been cleared for used for cold-assisted lipolysis(breakdown of fat) of bra fat, back fat, banana roll, submental area, thigh, abdomen, and flank, or "love handles" in individuals with a Body Mass Index

(BMI) of 30 or less (FDA K160259). The CoolSculpting study utilized the following evaluation methods: ultrasound and caliper measurements, circumferential measurements, 3D quantification of volume reduction, and blinded, independent review of clinical photographs. This particular study will utilize the collection of before and after photography for blinded, independent review of clinical photographs, caliper measurements, satisfaction scores, and safety data to evaluate the safety and efficacy of the treatment.

Compatibility:
Due to such a high prevalence of obesity in the U.S. and the increasing demand for non-invasive lipolysis treatments, there is a need to treat unwanted in its earlier stages to optimize treatment outcomes. As a subject gets older or the condition worsens, their treatment may need to be more aggressive to get their body to respond the same way that a younger subject or less severe case may be able to respond.

Predictive power:
While this study will observe the effects of the handpieces on lipolysis, results could potentially be applied to a variety of body areas and other potential applications. Assuming that there is significant improvement, it would be appropriate to expect results in different areas where other products and devices have significant results alongside reduction of unwanted fat.

2.2 Protocol Study Design

This is a prospective, open-labeled, randomized, multi-center clinical study to collect efficacy data on the TempSure® Firm.

2.3 Subject Selection Criteria

Subjects will meet the criteria described below:

Inclusion Criteria:

- A healthy male or female between the age of 18 – 55 years old.
- Willing to undergo treatments for fat reduction of the flank area (love handle)
- 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 childbearing 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 study.
- 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.
- The subject has a cut, wound, or infected skin on the area to be treated.
- The subject is on local, oral, or systemic anesthetic agents.
- 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.
- 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 (or at the discretion of the Investigator) prior to entering this study.

Cautionary Criteria:

- The subject has any embedded electronic device that gives or receives a signal, the device should be turned off or removed prior to treatment.
- The subject has an embedded pacemaker or implantable cardioverter defibrillator (ICD), the client's cardiologist must be consulted prior to treatment.

NOTE: This device has not been tested on patients implanted with electronic devices that receive or emit signals, such as: Pacemakers, Implantable Cardiac Defibrillators (ICD), or Cardiac Resynchronization Therapy (CRT) devices.

- If the neutral pad would need to be placed on a subject that has a metal plate, rod, or any metal implant that could conduct heat from the Smart Handpiece or surgical handpiece.
- The subject is allergic to adhesives, such as glues on medical tape, they should be alerted that a rash may occur on the neutral pad site and an over the counter solution may be used to treat the area.
- The subject is allergic to gold, such as the metallic covering of the TempSure handpieces.
- The subject is allergic to corn, such as the corn derivative ingredient in Parker Aquasonic Gel.
- If the subject has an unhealthy expectation of the results – this is not plastic surgery and all subject should be fully informed of the treatment's expected results.
- The subject has nerve insensitivity to heat in the treatment area.
- The subject has severe laxity or sagging that causes redundant folds of tissue or hanging skin in the area to be treated – this treatment will be ineffective.
- The subject has used Accutane (Isotretinoin) six to twelve months prior to treatment, as this can thin the skin and make it brittle.
- Studies of the use of the RF generator on subjects that have any of the following conditions is unknown:
    - Autoimmune Disease
    - Diabetic
    - Herpes Simplex
- Use caution when treating areas that have scars, tattoos, permanent makeup, and permanent brows.

Be sure to list and concomitant medications or procedures permitted before, during and after the trial

Subjects will be recruited for the study through the existing patient database and advertisements.

Subject populations will not be eligible to participate in the study if they are vulnerable populations such as; children, pregnant women, prisoners, institutionalized individuals, and any persons requiring a legally authorized representative as part of the consenting process.

Subject population characteristics that will not be eligible to participate in the study include non-English speaking individuals and people who cannot read or comprehend English. Employees of the Investigator will not be allowed to participate in the study.

2.4 Screening

Subjects will be asked questions about their medical history, have their weight recorded, may have a limited physical exam, and their inclusion/exclusion criteria will be verified. Discontinuation of any concomitant medications will be discussed, and pretreatment instructions and post treatment instruction will be reviewed with the subject.

Procedure for the Limited Physical Exam:
If the investigator determines that a limited exam is necessary, the exam will be similar to 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, in addition to examining the throat, tonsils, teeth, ears, eyes and nose as well as a neurological exam such as testing muscle strength, reflexes, balance, sensory changes of the extremities and mental state.

The following pre-treatment instructions will be reviewed:

- Shave any dense hair on the area to be treated.
- Do not wear constrictive clothing. Treatment area must be accessible. The back for the neutral pad will also need to be accessed.
- The treatment area must be free of any open lesions or infections.

- For an optimum treatment, keep hydrated by drinking water (at least 8 cups daily) or hydrating fluids, such as Gatorade, and avoid drinking alcohol for 24 hours in advance.

The following post treatment instructions will be reviewed:

- 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.
- Soothing creams or moisturizers, such as Aveeno, may be used.
- Gently massage the treated area daily for 5 minutes for the duration of your involvement in the study.
- Use a sun block with UVA and UVB protection with SPF of 30 or greater for 2 – 3 weeks after each treatment to prevent sun damage.
- Maintain the same weight and exercise routine throughout the study.

2.5 Informed Consent Process and Enrollment

Subjects will be asked to review the pre and post treatment instructions prior to signing the informed consent form and their involvement in the study. Subjects who sign the informed consent will be screened to confirm eligibility and, if eligible, will 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. A subject will be considered enrolled in the study once they have signed the informed consent form.

2.6 Pre-Treatment Procedures

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, the date of their last menstrual cycle, and perform a urine pregnancy test. A urine pregnancy test will be performed on all women of childbearing potential prior to each treatment. A urine pregnancy test may also be conducted at the Investigator's discretion at any time during the study. If a urine pregnancy test is conducted, then a negative result must be obtained within 24 hours prior to the treatment.

Urine Pregnancy Test Procedure:

- A urine sample is tested mid-stream or by cup sample with an indicator stick.
- Negative results are indicated on the indicator stick.

- The area to be treated will be identified and may be marked with a surgical marker.
- Caliper measurements of both flanks will be taken prior to the first treatment and prior to treatment 4 and may be taken prior to other treatment visits as well.
- Photographs will be taken prior to the first treatment and prior to treatment 4 and may be taken prior to other treatment visits as well.
- The treatment area and the neutral pad area may be cleansed with water and soap and/or an alcohol wipe.
- The neutral pad will be placed on the back in an area determined by the Investigator to maintain standard energy settings and to require less power from the device during the treatment.

2.7 Treatment Procedures

- The Investigator will use the device as described in the TempSure Operator's Manual and Clinical Reference Guide.
- Gel will be applied to the treatment area.
- The TempSure® Firm handpiece (25mm, 30mm, 60mm) to be used and the limits of the area to be treated will be determined by the Investigator and will be used in accordance with the Tempsure Clinical Reference Guide.
- The handpiece will be placed in contact with the skin.
- The entire defined treatment area will then be treated by delivering energy to the skin.
- Parameters may be adjusted throughout the treatment to increase subject comfort.
- Subjects will be asked to report the general level of treatment discomfort/pain on a scale of 0 (none) to 10 (maximum intolerable pain).

- Temperature will be continuously monitored and recorded during treatment.
- Photographs may be taken at any time during treatment to document treatment area and any adverse events, if applicable.
- Subjects may receive up to 5 treatments every 1-2 weeks.
- The additional treatments will follow the same procedure.
- Adverse Events will be documented at all treatment visits.

2.8 Post Treatment Procedures

- Adverse events will be documented after treatment.
- Post treatment instructions will be reviewed.
- Photographs may be taken.

2.9 Follow Up

- Subjects will receive a phone call 1 week (1-10 days) after each treatment to record side effects.
- The study subjects are required to return to investigator site for a follow up evaluation at 6 weeks and 12 weeks post last treatment.
- Photographs and caliper measurements of both flanks will be taken at all follow up visits.
- Subject's weight will be recorded at all follow up visits.
- Subject questionnaires will be performed at all follow up visits.
- Adverse events will be documented at all follow up visits.
- Some subjects may have an incomplete response or no response by the end of the study. After the subject has completed their participation in the study, a treatment on the untreated flank using the TempSure® Firm may be performed upon the subject's request at no cost.

2.10 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.

2.11 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.

2.12 Schedule of Visits and Procedures

	Visit #1*	Visit #2-6	Call	Visit #7	Visit #8
Procedure	Screening and Pre-treatment Procedures	Treatment Visit(s) 1-5 (1 – 2 Weeks Apart)	Phone Call 1 Week Post Each Tx (1-10 Days)	Follow Up 6 Weeks Post Last Tx (+/- 1 Week)	Follow Up 12 Weeks Post Last Tx (+/- 1 Week)
Medical History	X				
Weight	X	X		X	X
Pregnancy Verification**	X	X			
Informed Consent	X				
Photographs***	X	X		X	X
Caliper Measurement***	X	X		X	X
Treatment		X			
Treatment Discomfort/ Pain Evaluation		X			
Subject Questionnaires		X		X	X
Adverse Events Assessment	X	X	X	X	X

*Screening and Pre-treatment Procedures may occur at the same time as the Treatment Visit #1.
**Pregnancy verification required before each treatment only for women of childbearing potential.
***Photographs, caliper measurements, and weight will be taken prior to Treatment Visit #1 and prior to treatment on Treatment Visit #4 (post treatment 3) and at the 6 week and 12 week follow up visits.

2.13 Evaluation Methods

Photographs:
Photographs will be taken prior to treatment 1, prior to treatment 4 (post treatment 3), and at all follow-up visits and may be taken at each treatment and will be used to assess safety and efficacy of treatment.

Blinded Evaluation:
Three blinded independent reviewers will perform a photographic evaluation in which they will be asked to identify pre-treatment images when compared to post treatment images. The reviewers will be Board Certified Dermatologist and be chosen based on availability and have relevant clinical experience. They will attend a training session prior to grading.

Caliper:
Caliper measurements on both flanks will be taken prior to treatment 1, prior to treatment 4 (post treatment 3), and at all follow-up visits and may be taken at each treatment.

Caliper Procedure:
The caliper device is a hand-held instrument like a compass, that is used to measure the distance between two opposite sides. The clinician will measure the flank by using a diagonal fold directly above the iliac crest. The patient's skinfold will be pinched approximately 1 cm from the measurement spot and the caliper will be placed on the skinfold. The caliper provides a measurement (millimeters) of the thickness of skin and fatty tissue. Three readings should be taken and an average of all three sites should be calculated and documented.

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

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

2.14 Adverse Event Recording

All data captured must be supported by the Investigator's timely assessment and documentation of the adverse 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 TempSure 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 Gel:
The gel is a water-based gel that may be placed on the skin during the TempSure® Firm 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.

Adverse Events Pertaining to Neutral Pad:
Mild heat or hot spots may be felt during treatment by the subject. If the subject reports heat at the pad site, evaluate the site, check for epidermal injury. Skins burns may occur if subject does not report if the pad becomes too hot.

Adverse Events Pertaining to the 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.

Other Cautions:
Incomplete response or no response may occur since some subjects may not respond to treatment. After the subject has completed their participation in the study, a treatment on the untreated flank using the TempSure® Firm may be performed upon the subject's request at no cost.

2.15 Statistical Analysis

2.15.1 Hypothesis

For this study to be considered a success, the following criteria must be met:

1. Correct identification of pre-treatment images when compared to post treatment (12 week) images will be ≥80%.
2. Caliper measurements show statistically significant improvement on treatment area versus control.
3. The subject satisfaction rates at 12-week follow up visit will be ≥80%.
4. The side effect profile is acceptable to the Physician as it relates to this type of treatment.

2.15.2 Sample Size Rationale

The primary outcome will be the change in the subjective assessment of the reduction in fat as assessed by blinded evaluation of photographs taken before and after treatments. The primary endpoint will be defined as the 12-week follow up post final treatment with an objective of 80% correct evaluation. The sample size was determined based on a two-sample t-test with a two-sided significance level of 0.05 and power of 95%. A hypothetical control group would assumedly result in correct identification of follow up pictures 50% of the time, with a standard deviation of 50% resulting from an equal amount of correct and incorrect answers. Our objective of 80% correct average evaluation of post treatment photos with a conservative 20% expected standard deviation. Based on these assumptions it was determined that a total of at least 43 patients would be required for the study to have a successful primary outcome.

One of the secondary outcomes will be the change in fat layer thickness as assessed by caliper measurements before and after treatments. Previous studies have shown a change in caliper measurements of 7.0mm in a treated flank, and 0.7mm change in the control. The maximum standard deviation seen for any measurements (treated or control, baseline or follow up) was 5.8 which is used as an assumed standard deviation for sample size calculations.[v] Assuming 0.05 significance level and adjusting for a power of 95%, it was determined that 14 subjects would be needed to have a successful secondary outcome measure.

Another secondary outcome is the subject satisfaction rate. The sample size is calculated similarly to the primary outcome and yields the same results.

Based on these assumptions it was determined that a total of 43 patients would be required for the study, which was the maximum calculated among all the study outcome measures. To allow for minor departures in these assumptions and to account of potential subject dropout it was decided to enroll 68 subjects.

2.15.3 Patient Populations
Interim results may be collected and reported. All data will be analyzed at the end of the study. The primary analysis will be performed by the intention-to-treat approach. Everyone who begins the treatment is part of the study whether he or she 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 trial's goals, endpoints and context.

The analysis of demographic, medical history, and efficacy variables will be based on all patients who are randomized and receive at least one treatment. The analysis of safety data will be based on all patients who are randomized, receive at least one treatment, and have at least some safety data.

2.15.4 Analysis of Demographic and Medical History Variables
Summaries will be prepared for all important demographic and medical history variables. For quantitative variables summaries will include the sample size, mean, median, standard deviation, minimum, and maximum. For these variables the treatment groups will be compared using either a t-test or a Wilcoxon Rank Sum test, as appropriate. For categorical variables the summaries will include the sample size and the number and percent of patients for each outcome. For these variables, the treatment groups will be compared using Fisher's Exact test. Statistical significance will be declared if the two-sided p-value is < 0.05.

2.15.5 Analysis of Efficacy Variables
The primary efficacy variable is blinded evaluation of photographs from baseline to Visit 8 (12-week follow up) with respect to fat reduction. Baseline is defined as the last assessment prior to the first treatment. Photos will be graded and the total and percentage of photos correctly identified will be compiled and analyzed. Correct identification percentages will be calculated for each individual reviewer as well as a summary for all three reviewers. Clinical success of grading will be declared if 80% independent reviewers achieve 80% correct identification of the photos.

The secondary efficacy variables are caliper measurements of fat thickness and subject satisfaction rates. As with the primary efficacy variable the assessment at Visit 8 (12-week follow up) will be primary. The analysis and summaries for caliper measurements will include a pairwise treatment group comparison as well as repeated measure ANOVA analysis. Statistical significance with respect to both the treatment and control group comparisons as well as repeated measures of the treatment group will be declared if the two-sided p-value is <0.05. For reach treatment group and timepoint of the caliper measurements a statistical summary will be completed. The summary will include sample size mean, median, standard deviation, minimum, and maximum. The statistical significance of the mean change from baseline to follow-up for each group as well between the treatment and control will be determined using a paired t-test. Subject satisfaction will be analyzed with standard descriptive statistics which include total number of responses in each category as well as the percentage of responses for each category. Clinical success of subject satisfaction surveys will be declared if at least 80% of subjects respond they are satisfied.

2.15.6 Analysis of Safety Variables
Safety will be assessed through the degree of pain/discomfort related to the procedure (universal pain scale) and the collection of Adverse Events throughout the course of the study. For each treatment group these variables will be summarized. The summaries will include the number and percent of patients for each outcome. No statistical comparisons will be performed for any of these variables.

2.16 Randomization
One flank will receive treatment with the TempSure® Firm handpiece and the other will not receive treatment to serve as a control. Randomization will occur using a validated method determined by the Investigator, such as flipping a coin or an electronic system such as Virtual Coin Toss (www.virtualcointoss.com).

3.0 RISK ANALYSIS AND MANAGEMENT

3.1 Risk Determination

This device study used in this study does or does not meet the FDA definition for a Significant Risk Device study per 21 CFR 812.3(m). Therefore, 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.

3.2 Risk Management

The Investigator in this clinical trial has been invited to participate based on his/her previous experience with the use of the system and/or similar systems and industry experience. Experience with treatments is the most critical element in managing subject risk in this trial.

In addition, as with any study, there is a risk of bias. To minimize/avoid bias subjects will be randomized and blinding will occur as determined by the study design. Objective evaluation methods may also be used in conjunction with subjective evaluation methods when feasible. The value of the compensation to the clinical investigator for conducting the study is not influenced by the study outcome. If photographic results are listed as the primary objective, they are to be evaluated by blinded evaluators who did not partake in the study. If information concerning investigator assessment of improvement or investigator satisfaction is collected, then it is not listed as an objective for the study.

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.

The risks to the subjects who participate in this study are the same as those for the subject undergoing similar noninvasive lipolysis treatment(s). It is possible to have an adverse reaction to the TempSure device use. There may be some side effects that we do not know about yet.

3.3 Risk Analysis

CONTEXT OF THE PROPOSED INVESTIGATION:
Radiofrequency (RF) technology is commonly used in surgery, non-invasive treatments and aesthetic applications. RF technology is a safe method for non-ablative (A non-wounding device treatment which heats underlying skin) treatment because energy can be precisely delivered through the skin to the subcutaneous adipose tissue beneath without damaging the epidermis.[vi]

According to published data, the elevation of tissue temperature between 42°C to 47°C can affect the cellular matrix of the adipose tissue creating injury to the adipocytes and prompt an inflammatory response.[vii] Gradually, the treated adipocytes will be removed by the human body through the inflammatory clearing process which takes weeks to months. The regeneration of adipose tissue is very slow (over years) and the total volume of the fat in treatment area will decrease due to the loss of adipocytes.

ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION:
There are two risks identified with the TempSure device used in this study. The first risk identified is the lack of clinical data for evidence of effectiveness of Envi handpieces for the treatment of lipolysis. Parameters need to be further investigated to be optimized for efficacious results. The second risk identified is the safety of treatment with the TempSure® Firm handpieces. Since the TempSure® Firm handpieces have not been cleared for use for lipolysis and has limited safety data for this indication, optimizing the safety profile is necessary.

The risk identified with the overall clinical investigation is the integrity of the data collected.

There are multiple clinical mitigation strategies for the risks identified. Proper training on the device and protocol will be performed. Data from prior investigations will be utilized to minimize side effects and optimize treatment outcomes. Monitoring of the study will be implemented to minimize subject and data risks.

ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION:
The subject may or may not have a reduction in unwanted fat.

CONSIDERATION OF PATIENT PREFERENCE INFORMATION:
Many physicians support the use of radiofrequency devices for non-invasive cosmetic treatments due to current patient satisfaction of cosmetic results with the currently available devices. However, there is still a level of interest in novel technologies that could reduce the need for invasive treatments for fat reduction.

ASSESSMENT OF UNCERTAINTY:
There is uncertainty of the efficacy of the treatment when TempSure® Firm is used for the treatment of unwanted fat.

CONCLUSION:
The TempSure® Firm handpieces used in this study have not been FDA cleared for use for the treatment of wanted fat (lipolysis) but pose no more risk than the currently cleared indications for use.

A previous safety study, CYN18-RF-TISSUE-RD, was conducted using excised human abdominoplasty tissue to test various radiofrequency parameters with the 60mm handpiece. Another safety study, CYN19-TS-ABDOM, was conducted using patients scheduled for an abdominoplasty surgery to use in-vivo tissue to test various radiofrequency parameters with the 60mm handpiece. Thermal measurements of treatment zones were collected to evaluate the depth of penetration and effects on human tissue.

Studies CYN17-RF-CLINIC and CYN19-TS-ENVI-ABD collected safety and efficacy data using the 25mm, 30mm, and 60mm handpieces on various body areas, including the abdomen.

Patient population to be enrolled in this clinical study:
Total anticipated population: 68 Subjects
Age Range years old: 18 – 55 years old
Gender: Male or Female
Condition: Unwanted fat on flanks

4.0 DEVICE DESCRIPTION AND SPECIFICATIONS

The TempSure® device used in this study is currently cleared by the U.S. Food and Drug Administration (the FDA). The TempSure® device 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 handpiece of the TempSure® device received 510(k) clearance under K190678 on July 24, 2019 to 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 TempSure® device is considered investigational because TempSure® Firm handpieces used in this study are not cleared for use for lipolysis.

Changes to the TempSure® device are not anticipated during the investigation.

The TempSure® Device Specifications are:

Surgical Connector	1 surgical monopolar port
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	Select the Smart Handpiece or Surgical mode of operation
Maximum Power	**Temperature-Sensing Handpieces** ⚠ 10mm, 15mm, and 20mm handpieces have a maximum GUI setting of 70, which provides output power of 120 Watts (+/- 20%). ⚠ 18mm handpiece has a maximum GUI setting of 25, which provides output power of 25 Watts (+/-20%). ⚠ 25mm and 30mm handpieces have a maximum GUI setting of 80, which provides output power of 165Watts (+/- 20%). ⚠ 60mm handpieces have a maximum GUI setting of 100, which provides output power of 300 Watts (+/- 20%). ⚠ FlexSure applicators are controlled by setting the temperature. During treatment, power can reach a maximum output of 300 Watts (+/- 20%). Ensuring that the neutral pad recommended for use with the 60mm handpiece and flexible applicator has sufficient current carrying capacity so as to assure that there is no unacceptable temperature rise under the pad is an essential performance of the TempSure platform.

The TempSure® device Operator Manual: Attachment I

The TempSure® consumables are: Handpieces, NEM Pads, Gel

5.0 MONITORING PROCEDURES

The Sponsor Standard Operating Procedure (SOP) for monitoring the investigative site will be followed. The sponsor will train the site following sponsor SOP's and may be present at initiation of treatment. The sponsor will also monitor the site periodically. The Investigator/Institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source documents. 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.

The monitoring plan for this study is outlined in the Cynosure Monitoring Plan.

ASSIGNED CLINICAL RESEARCH MONITOR:
Monitor #1
Name: Kristy Luis
Institution: Cynosure, LLC
Address: 5 Carlisle Rd. Westford, Ma

6.0 LABELING

Sample labeling will follow FDA regulations and the sponsor standard operating procedure.
If applicable the TempSure® device label will include, (in accordance with 801.1):

Statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use."

Additionally, the label or other labeling will describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

7.0 CONSENT MATERIALS

Forms and informational materials which are provided to the subject during the informed consent process are listed below:

Form/Informational Material Description
Pre and Post Treatment Instructions
Informed Consent Form
Universal Pain Assessment Tool

8.0 INSTITUTIONAL REVIEW BOARD INFORMATION

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. Any action taken by any IRB will be recorded in the study file.

IRB Contact Information:
IRB Name: New England Independent Review Board
IRB Address: 197 First Avenue, Suite 250, Needham, MA 02494
Phone: (617) 243-3924
Fax: (617) 969-1310
Email: info@neirb.com

9.0 OTHER INSTITUTIONS

If a part of the study is conducted by an institution that has not previously been identified within the Investigational plan each institution's contact information will be documented below;

No other institutions will be part of this study.

10.0 ADDITIONAL RECORDS AND REPORTS

Additional records and reports will be maintained on the investigation in addition to those prescribed in 21 CFR 812.25 sub-part G.

Additional Records and Reports:

Report	Submit To	Description/Constraints
N/A	N/A	This is a non-IDE study; no additional records or reports will be maintained.

11.0 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 study.

If the subject thinks they have become pregnant during the study, they must 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.

12.0 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.

Data collected prior to withdrawal will be used in data analysis but after withdrawal no further data will be collected.

13.0 PHOTOGRAPHY

Standardized and 3D photographs will be taken of the treatment area. 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. Photographs will be taken of the treatment area for study purposes. If the subject does not wish to have their photographs taken, they cannot be in the study.

14.0 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 and Case Report Forms (CRF).

Adverse Events (AE) 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 TempSure® Firm 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 study file.

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.

Reporting Adverse Events:

Report	Submit To	Description/Constraints
Adverse Events, Unanticipated Adverse Device Effect	IRB and Sponsor	If an unforeseen complication is determined to be an unanticipated adverse device effect, the investigator's report must be submitted within 10 working days after the investigator first learns of the effect.
Serious Adverse Events	IRB and Sponsor	The sponsor must be notified within 24 hours of serious adverse events. The IRB must be notified within 10 working days of serious adverse events as defined by FDA guidelines.

15.0 PROTOCOL DEVIATIONS

All requests for protocol deviations by the Investigator must 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.

16.0 CONFIDENTIALITY AND DISCLOSURE OF MEDICAL INFORMATION

As part of this study the Investigator and the team at the research facility 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 test 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 your study information and photographs may be used.

The research facility 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 research facility 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, subject study information and photographs may be used.

Study records will be kept at the research facility 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.

17.0 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.

18.0 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.

Study Summary Reporting:

Report	Submit To	Description/Constraints
Deviation from Investigational Plan	IRB and Sponsor	A deviation performed in an emergency to protect the life or physical well-being of a patient necessitates notification of the IRB and sponsor. The investigator's report must be submitted within 5 working days after the emergency occurred. Deviations in a non-emergency situation require notification to sponsor prior to implementation
Failure to Obtain Informed Consent	IRB and Sponsor	The investigator must make notification within 5 working days after device use, using the Protocol Deviation CRF. The report must include a brief description of the circumstances justifying the failure to obtain informed consent.
Final Report	IRB and Sponsor	The investigator must submit a final report within 3 months after termination or completion of the investigation.
Withdrawal of IRB approval	Sponsor	The investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	IRB, Monitor and Sponsor	The investigator must submit progress reports at regular intervals, and as required by the IRB, but in no event less than annually.

19.0 DISCLOSURE

The Principal Investigator and Cynosure employees and consultants 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.

20.0 RESPONSIBILITY OF THE INVESTIGATOR

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) guidance E6, FDA Good Clinical Practice Regulations, Declaration of Helsinki (DoH) and the Health Human Service (HHS) Belmont Study. Investigators will supply information to the sponsor such that the sponsor can comply with the Financial Disclosure Rules.

21.0 PROCEDURE FOR AMMENDMENTS TO 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.

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 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.

24.0 REPORT OF PRIOR INVESTIGATIONS

The report of prior investigations or predicates are:

Protocol	Device	IRB Name	Determination	Initial IRB Approval Date
CYN17-RF-CLINIC	TempSure/Pelleve	Allendale Investigational Review Board	Meets the criteria for exemption from IDE regulations, non-significant risk	01/12/2017
CYN18-RF-TISSUE-RD	TempSure/ Radiofrequency Devices	Allendale Investigational Review Board	Meets the criteria for exemption from IDE regulations, non-significant risk	08/15/2018
CYN19-TS-ABDOM	TempSure	Allendale Investigational Review Board	Meets the criteria for exemption from IDE regulations, non-significant risk	04/11/2019

CYN19-TS-ENVI-ABD	TempSure	New England IRB	Meets the criteria for exemption from IDE regulations, non-significant risk	03/25/2019

APPENDIX A:
Protocol Revisions Tracker

Version Date	Editor	Description
June 25, 2020	Kristy Luis	IRB Submission
July 9, 2020	Kristy Luis	Response to IRB
August 7, 2020	Kristy Luis	Removed Dr. Bass as an investigator and add Dr. Saluja, increased number to subjects from 50 to 55.
September 24, 2020	Kristy Luis	Increased number of subjects to 66. Added weight to be collected at treatment 4 visit.
May 10, 2021	Kristy	Increased number of subjects to 68.

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