Post-Market Clinical Follow Up Study to Collect Additional Data and Imaging

NCT04880070

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INVESTIGATIONAL PLAN

PROTOCOL #: SW-MCPM-2021

POST MARKET CLINICAL FOLLOW UP STUDY TO COLLECT ADDITIONAL DATA AND IMAGING

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SPONSOR:
CYNOSURE, LLC
5 CARLISLE ROAD
WESTFORD, MA 01886
PHONE: 800-886-2966
FAX: 978-256-6556

POST MARKET CLINICAL FOLLOW UP STUDY TO COLLECT ADDITIONAL DATA AND IMAGING

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)

_____

_____

_____

Address of Investigator (Typed or Printed)

SITE #1 CONTACT INFORMATION:
Principal Investigator Information:
Sean Doherty, M.D.
5 Carlisle Rd
Westford, MA 01886
Phone: 617-735-8735
Email: info@seandohertymd.com

SITE #2 CONTACT INFORMATION:
Principal Investigator Information:
David H. McDaniel, M.D., F.A.A.D.
McDaniel Institute of Anti-Aging Research
125 Market Street
Virginia Beach, VA 23462
Phone: 757-437-8900
Email: dhm@miaar.com

SPONSOR CONTACT INFORMATION:
Jennifer Civiok
Director, Clinical Development
5 Carlisle Road
Westford, MA 01886
Phone: 978-399-4343
Email: Jennifer.Civiok@cynosure.com

Alexander Denis
Clinical Research Supervisor,
Clinical Development
5 Carlisle Road
Westford, MA 01886
Phone: 978-895-9206
Email: Alexander.Denis@cynosure.com

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1.0 PURPOSE

1.1 Name and Intended Use

The device used in this study is called the SoftWave device.

The intended use of the SoftWave device used in this study is to assess the usability and tissue response to shock wave treatment and to support additional marketing claims.

1.2 Objectives

1. Primary Objective:
   - Collection of Treatment Discomfort/Pain Evaluation
2. Additional Objectives:
   - Evaluation of tissue response through Biopsies at multiple timepoints up to 30 days post treatment (optional):
     - Sample staining as appropriate, such as H&E
     - Nano-string for Gene Expression
   - Device comparison treatment with similar low-intensity shockwave device (optional).
   - Photographic evaluation with Vivosight imaging at the 30 and/or 90 day follow up compared to baseline (optional).
   - Photographic evaluation with 2D and/or 3D imaging at the 30 and/or 90 day follow up compared to baseline (optional).
   - Subject treatment assessment through questionnaires (optional):
     - Subject treatment experience questionnaire
     - Subject follow up questionnaire
     - Subject satisfaction questionnaire
   - Clinician treatment assessment through questionnaires (optional):
     - Clinician treatment questionnaire
     - Clinician satisfaction questionnaire
3. Safety Objectives:
   - Collection of Adverse Events

1.3 Duration of the Investigation

The sponsor anticipates that all subjects can be enrolled within 6 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 15 months.

2.0 PROTOCOL

2.1 Protocol Methodology and Analysis

Methodology:
Subjects are to be enrolled in this clinical study if they are a healthy male or female 18 – 65 years of age. Up to 50 subjects will be enrolled at 2 study centers. Subjects will attend a screening/pretreatment visit which may be performed on the same day as the treatment visit. Subjects may receive up to 5 treatments with the study device. Subjects may also receive treatment

with a similar shockwave device. Subjects may be consented to have biopsies collected at a specific time after their final treatment, which will occur up to 30 days post treatment. Follow up visits may occur 30 and 90 days post last treatment visit. An unscheduled visit or phone call may be performed at any time during the study at the request of the subject 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.[1] Due to this shift in patient base, practices need to evolve to adapt to the newer generational ideologies. This device will be using the SoftWave device to collect additional data and imaging. Although this device is cleared for use by the U.S. Food and Drug Administration, there is a need to collect additional data, images, and tissue response to expand marketing claims.

Relevance:
There is an increasing demand for new methods and additional cleared indications for non-invasive treatments using shockwave therapy. Another device currently on the market cleared for use is, but are not limited to, the dermaPACE®System.

Testability:
The SoftWave device, had been previously cleared for the activation of connective tissue (FDA 510(k) K182682), the treatment of chronic, full thickness diabetic foot ulcers (FDA 510(k) K191961), and the treatment of superficial partial thickness second degree burns in adults (FDA 510(k) K200926). This study will utilize the collection of data and imaging to support additional marketing claims.

Compatibility:
Although shock wave technology is a well-known and widely use technique for non-invasive treatments, there is still a need to collect additional data and images, and expand marketing claims and device use.

Predictive power:
Assuming there is an acceptable side effect profile, it would be appropriate to expect results for other marketable indications.

2.2 Protocol Study Design

This is a prospective, open label, multi-center clinical study to collect additional data and imaging for the SoftWave device.

2.3 Subject Selection Criteria

Subjects will meet the criteria described below:

Inclusion Criteria:

- A healthy male or female 18 – 65 years of age.
- Willing to undergo treatments with the SoftWave device.

- 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 has a pacemaker or implantable defibrillator.
- The subject has a severe coagulation disorder.
- The subject has open epiphyseal plates.
- The subject has recently had a steroid injection.
- 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 to entering this study.
- The subject has any condition or is in a situation which, in the Investigator's opinion, may put the subject at significant risk, may confound study results or may interfere significantly with the subject's participation.

Be sure to list all concomitant medications taken or procedures performed before, during and after the trial.

Subjects will be recruited for the study through the existing patient database and may use 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 participate in the study include non-English speaking individuals and people who cannot read or comprehend English. Employees of the Investigator will be participating in the study.

2.4 Screening

Subjects will be asked questions about their medical history, may have a limited physical and their inclusion/exclusion criteria will be verified. Discontinuation of any concomitant medications, specifically pain killers, may be discussed and post treatment instruction will be reviewed with the subject. Subjects will be informed of standard COVID-19 procedures that adhere to federal and state guidelines.

Procedure for the Limited Physical Exam:
If the investigator determines that a limited exam is necessary, the exam will be like 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.

2.5 Informed Consent Process and Enrollment

Subjects will be asked to review the post treatment instructions prior to signing the informed consent form and their involvement in the study. They must also review the site's COVID-19 procedures and agree to follow protocols put in place at the site relating to COVID-19. 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.

The following post treatment instructions will be reviewed with subject:

- You can return to a normal lifestyle immediately after treatment including light athletic workouts but avoid extreme exercise or activities that may reinjure the damaged area through overuse. The inflammation may have eliminated pain but it takes time to heal.
- You can continue previously prescribed therapies, such as stretching.
- Avoid ice and anti-inflammatory medicine (i.e. NSAIDs, such as Ibuprofen) for several days after therapy as this may reduce outcomes.
- Drink lots of water.
- You may feel tired after a SoftWave treatment.
- You may experience a tingling sensation in the treatment area for several days after therapy. This is good.
- You may experience mild soreness or stiffness during the next 48 hours. This is normal.

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. At each subsequent treatment, subjects will be asked the date of their last menstrual cycle for pregnancy verification purposes. 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:

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

- Photographs will be taken prior to the first treatment and may be taken prior to each subsequent treatment.

2.7 Treatment Procedures

- Procedures for the shock wave treatment:
  - The defined study area will be identified and will be cleansed thoroughly using a facial cleanser or mild soap and water. The treatment area may be marked with a marker.
  - The device may be used in accordance with the Protocol Manual and Instructions for Use.
  - Test spots may be performed prior to treatment in an area, such as on the hand, or in or close to the treatment area or so the subject can get used to the sensation.
  - Ultrasound gel will be applied to the area to be treated.
  - The applicator will be placed on the skin and slowly moved over the identified treatment area administering pulses of acoustic pressure shockwaves.
  - 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).
  - Parameters and tissue response will be continuously monitored and recorded during treatment.
- The additional treatments will follow the same procedure.
- Subjects and Clinicians may be asked to complete treatment questionnaires.
- Subjects may receive up to 5 treatments. Treatments will be performed every 3 – 14 days.

2.8 Post Treatment Procedures

- Adverse events will be documented after treatment.
- Photographs may be taken post treatment.
- Post treatment instructions will be reviewed with the subject.

2.9 Follow Up

- Subjects will return for follow up visits at 30 and 90 days post last treatment.
- Photographs will be taken and adverse events will be documented and each follow up visit.
- Clinician and subject questionnaires may be performed at each follow up visits.
- Any subject affected by COVID-19 that is not able to attend their follow up visits to complete the study will be asked to return to the site for a final follow up visit within 1 year of last treatment.
- 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.

2.10 Biopsy Portion of the Study

- Subjects may enroll in the biopsy portion of this study. If the subject has signed the biopsy consent form and enrolled, the following will also be performed:
  - Biopsies may be taken from a treated area the day of treatment and/or may be taken 1, 3, 7 (+/- 1 day), 14 (+/- 2 days), 21 (+/- 2 days), and.or 30 days (+/- 3 days) post last treatment. A control will also be taken on the contralateral side of the treatment area.
  - Biopsy subjects may receive up to 6 biopsies.
  - A local anesthetic, such as lidocaine, may be injected to the area prior to biopsy.

- A 2 mm or 3mm punch biopsy (based on Physician assessment) will be taken from the treatment area.
- Sutures may be uses to close the incision site.
- The subject may be asked to attend a 1 week (7-14 days) post each biopsy visit to remove the sutures and assess side effects.

- The following post biopsy treatment instructions will be reviewed:
  - Slight redness, initial tenderness to the wound site is normal; however, if you experience more redness, swelling, pain, pus, or drainage contact the study site immediately.
  - If the biopsy site begins to bleed, apply direct pressure for 10-20 minutes. If it continues to bleed, call the study site immediately.
  - Keep the wound dry today and remove bandage in 24 hours and leave off.
  - Avoid hot tubs, pools, and ocean until sutures are removed. Avoid soaking in water until 14 days after your biopsy.
  - When showering, wash carefully and do not scrub or traumatize the treated skin, or allow spray of shower to strike the skin directly. If the skin is treated harshly, this can increase the risk of scarring.
  - After showering, lightly pat dry the wound or let it air dry, then cover the biopsy site with an application of Vaseline (or petroleum jelly) at least 1-2 times daily. Keeping the wound moist reduces infection, minimizes scarring, and prevents crust formation over the wound.
  - Band-Aids (or any generic Adhesive Bandages) may be used for sleeping or in daily routines where the area may be rubbed/irritated. Whenever possible, keep Band-Aid (or generic Adhesive Bandage) off of the area and keep the area moist with Vaseline (or petroleum jelly) as previously described but do not allow drying out and forming a hard scab.
  - For any wound discomfort, you may take Tylenol as needed, or use cold compresses for up to 20 minutes hourly as needed. If using ice, it should be wrapped in a plastic and then a cloth to avoid burning your skin and wetting your bandage.
  - Avoid picking at the wound site, which increases risk of infection and scarring.
  - In order for the wound to heal properly and not leave bumpy scars, be careful not to overstretch the wound site area. As a wound heals, it will be weaker than the surrounding skin and can even "pop open" the sutures (stitches) if stretched too much. Sport or strenuous exercises that can pull at the wound site are best avoided for at least the next 3 days and up to one week.
  - Return for suture removal within 7 - 14 days as instructed per study protocol. If applied, Steri-strips must be kept dry as they are more likely to separate when wet. Steri-strips will usually fall off by themselves or you may be advised by the study doctor to remove them when the wound healed.
  - ONCE SUTURES ARE OUT: To minimize sore formation and to improve the final appearance of your skin, it is very important to keep the wound site area covered with the Vaseline for the next few days, until there is no more crust forming and the skin has completely healed.
  - Temporary discoloration at the wound site is normal and should gradually fade over the next few months. Please protect newly healed biopsied area with SPF and avoid sunburn.

2.11 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.

2.12 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

2.13 Schedule of Visits and Procedures

	Visit #1*	Visit #2-6	Visit #7	Visit #8	Visit #9
Procedure	Screening and Pre-treatment Procedures	Treatment Visit(s) 1-5 (3-14 days Apart)	Follow up and Biopsy 0, 1, 3, 7, 24, 21 or 30 days Post Last Tx (Optional)	Follow Up 1 Month Post Last Tx (+/- 1 Week) (Optional)	Follow Up 3 Months Post Last Tx (+/- 1 Week) (Optional
Medical History	X				
Pregnancy Verification	X	X			
Informed Consent	X				
Treatment		X			
Parameters		X	X		
Treatment Discomfort/ Pain Evaluation		X			
Subject Treatment Experience Questionnaire		X			
Clinician Treatment Questionnaire		X			
Biopsies			X		
Photographs (Vivosight)	X		X	X	X
Photographs (2D, 3D)	X		X	X	X
Subject Follow Up Questionnaire				X	X
Subject Satisfaction Questionnaire				X	X
Clinician Satisfaction Questionnaire				X	X
Adverse Event Assessment	X	X	X	X	X

*Screening and Pre-treatment Procedures may occur at the same time as the Treatment Visit #1.

2.13 Evaluation Methods

Photographs:
Photographs will be taken at all visits and will be used to assess efficacy and safety 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 and Clinician Satisfaction 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

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/or Surgeons and be chosen based on availability and have relevant clinical experience. They will attend a training session prior to grading.

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. All adverse events must be followed until their resolution.

Adverse Events Pertaining to the SoftWave Device:
Potential adverse effects associated with shock wave treatments include those listed below:

- Transient moderate increase in pain
- Redness and swelling
- Hematoma and petechial hemorrhage
- Headaches and fainting during extracorporeal shock wave treatments
- Short-term hypoesthesia
- Nausea during therapy
- Tingling during therapy

Adverse Events Pertaining to the Marker:
Using a marker has minimal risks and may produce effects on the body such as redness or a rash.

Adverse Events Pertaining to Ultrasound Gel:
The gel is a water-based gel that may be placed on the skin during 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.

Biopsies
Complication with biopsies can include pain, redness, swelling, infection, bleeding, scarring and skin texture irregularities.

Lidocaine
You may experience pain and numbness at the site of the injection. You may also experience redness, rash, infection, skin damage or nerve damage at the site of the injection. You may experience temporary loss of sensation and muscle function at the site of injection.

1% lidocaine (Lidocaine) with Epinephrine Injection
Lidocaine with epinephrine contains the preservative sodium metabisulfite which may cause allergic-type reactions 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.

Other Cautions:
Incomplete response or no response may occur since some subjects may not respond to treatment.

2.15 Statistical Analysis

2.15.1 Hypothesis
For this study to be considered a success, the average pain score is acceptable to the Physician as it relates to the type of treatment.

For additional objectives to be considered a success, the following criteria must be met:
- The side effect profile (adverse events) is acceptable to the Physician as it relates to the type of treatment.
- The subject satisfaction rates at the follow up visit will be ≥80% (optional).
- Correct identification of pre-treatment images when compared to post treatment (30 and/or 90 day) images will be ≥80% (optional).
- Successful collection of biopsies (optional).
- Successful collection of treatment assessment questionnaires (optional).

2.15.2 Sample Size Rationale
Based on the need for data collected from this study, it was determined that a total of 50 subjects will be required, including departures.

2.15.3 Patient Populations

Interim results may be collected and reported. All data will be analyzed at the end of the study on a per device basis as well as overall. 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 individual trial 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.

2.15.6 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.

3.0 RISK ANALYSIS AND MANAGEMENT

3.1 Risk Determination

This device study used in this study 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. Objective evaluation methods may 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 non-ablative shockwave treatment. It is possible to have an adverse reaction to the SoftWave device. There may be some side effects that we don't know about yet.

3.3 Risk Analysis

CONTEXT OF THE PROPOSED INVESTIGATION:
Shockwave is an effective approach to healing the human body using acoustic waves to stimulate the body's natural processes for self-repair. This technology is not new and although it has been in the marketplace for over 14 years in Europe, it just recently received FDA clearance in the US.

Shockwaves are created through the use of an electrode contained within a soft latex dome filled with water. When charged with electricity, the electrode creates a spark under the water. This spark creates a hot bubble of gas that expands into the surrounding water and produces the shockwave that travels out of the applicator and into the affected area being treated. These high energy acoustic waves penetrate deep into damaged tissue causing cellular walls to become permeable allowing exosomes to escape into the interstitial tissue mimicking cellular injury which triggers the migration of your body's own stem cells to the area for sustained long-term healing.

ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION:
The risk identified with the overall clinical investigation is the integrity of the data collected. There are multiple clinical mitigation strategies for the risk identified. Proper training on the protocol will be performed. 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 improvement for the indication treated.

CONSIDERATION OF PATIENT PREFERENCE INFORMATION:
Many physicians support the use of shockwave devices for non-invasive treatments due to current patient satisfaction with their results with the currently available devices. However, there is still a level of interest in expanding indications and marketing claims for shockwave devices.

ASSESSMENT OF UNCERTAINTY:
There is uncertainty of efficacy results for expanding marketing claims while using the SoftWave device in this study.

CONCLUSION:
This study is determined to be a non-significant risk study and the risks posed to the subjects and integrity of data are acceptable.

Patient population to be enrolled in this clinical study:
Total anticipated population: 50 Subjects
Age Range: 18 – 65 years of age
Gender: Male or Female
Condition: Conditions that may be treated with the activation of connective tissue.

4.0 DEVICE DESCRIPTION AND SPECIFICATIONS

The SoftWave device used in this study is cleared for use by the U.S. Food and Drug Administration (the FDA) for the following indications:
K200926:
The OrthoGold 100 is indicated to provide acoustic pressure shockwaves in the treatment of superficial partial thickness second degree burns in adults (22 years and older). The OrthoGold 100 is indicated for use in conjunction with standard of care burn treatment(s).

K191961:
The OrthoGold 100™ is indicated to provide acoustic pressure shockwaves in the treatment of chronic, full-thickness diabetic foot ulcers with wound areas measuring no larger than 16 cm2, which extend through the epidermis, dermis, tendon , or capsule , but without bone exposure. The OrthoGold 100 is indicated for adult (22 years and older), diabetic patients presenting with diabetic foot ulcers greater than 30 days in duration and is indicated for use in conjunction with standard diabetic ulcer care

K182682:
The OrthoGold 100 is intended for the activation of connective tissue.

The device used in this study is considered investigational because it may not be used in accordance with the currently cleared instructions for use and may use the data collected for additional marketing claims and indication.

SoftWave Technical Data:

Water System	• **Closed system** • **Content of the water cartridge: 450 ml Water (15.22 fl oz)** • **Adjustable water flow** • **Fill time of the reflector: Approx. 25 seconds**
Shock wave generator	• **The coupling to the treatment**

	area happens via water membrane. • **Principle: electro hydraulic, spark gap under water caused by discharge of high voltage condensers.** • **Shock wave release frequency: 0.5 to 8 Hz.**
Operation- and display elements	• **Operation monitor and touch wheel at the front side of the device** • **Power on / off, displayed by control lamp in switch** • **Footswitch to release shock waves**
Supply	• **Voltage supply: AC 100- 240 V, ± 10 %, 50/60 Hz** • **Single phase** • **Class I equipment** • **Type B** • **Power consumption: 100V/200VA 240V/200VA**

Changes to the SoftWave device are not anticipated during the investigation.

The comparison device that may be used is called the Eclipse Evive shockwave device. This is an FDA Class 1 device that falls under FDA code Sec. 890.5660 for marketing. You can find additional information on the device's website here: https://www.eclipsemed.com/evive/.

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 when 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 SoftWave 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.

Directions for use are contained in the SoftWave Instructions for Use

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
Post Treatment Instructions
Informed Consent Form

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.

IRB Contact Information:
IRB Name: Allendale Investigational Review Board
IRB Chairperson: Robert Staab
IRB Address: 30 Neck Rd. Old Lyme, CT 06371
Phone: 860-434-5872
Fax: 860-434-5892
Email: Rta1ali1@aol.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

If this is an IDE study, additional records and reports will be maintained on the investigation in addition to those prescribed in 21 CFR 812 sub-part G. If this is a non-IDE study, the study summary will be maintained on the investigation and may include those prescribed in 21 CFR 812 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, 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 the final follow-up visit. The Investigator may request to track the pregnancy and will report the pregnancy to the Sponsor and IRB.

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 photographs will be taken of the treatment area. 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. 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 SoftWave 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 1 working day 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, LLC, 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 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:

Device	Determination	510(k)
OrthoGold 100	Meets the criteria for exemption from IDE regulations, non-significant risk	K182682
OrthoGold 100	Meets the criteria for exemption from IDE regulations, non-significant risk	K191961
OrthoGold 100	Meets the criteria for exemption from IDE regulations, non-significant risk	K200926

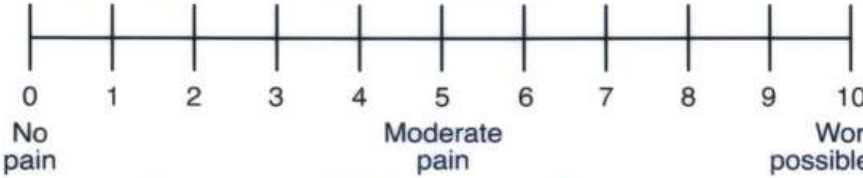
APPENDIX A:
Protocol Revisions Tracker

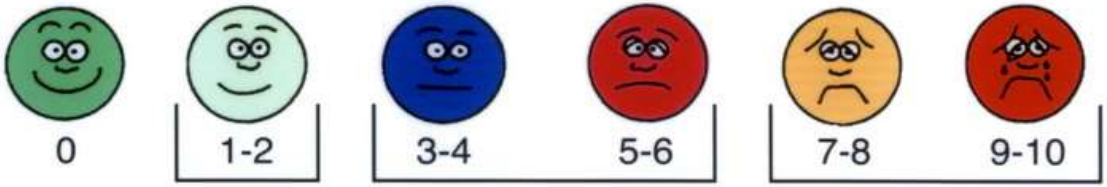
Version Date	Editor	Description
February 25, 2021	Kristy Luis	IRB Submission
March 10, 2021	Kristy Luis	IRB Response
March 11, 2021	Kristy Luis	Increased number of subjects to 50
April 7, 2021	Kristy Luis	Added use of comparison device. Added a control and 14 day biopsy.

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.





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

REFERENCES

[1] Sherber, N. S., MD FAAD. (2018). The Millennial Mindset. *Journal of Drugs in Dermatology, 17*(12), 1340-1342.