
**A Split-Face Multi-Arm Randomized Clinical Trial
Showing the Efficacy & Safety of a Topical Mask After
Aesthetic Treatments**

Robyn Siperstein M.D.

A Split-Face Multi-Arm Randomized Clinical Trial Showing the Efficacy & Safety of a Topical Mask After Aesthetic Treatments.

Principal Investigator: Robyn Siperstein MD

9897 Hagen Ranch Road

Boynton Beach Florida 33472

Phone: 954-494-1400

Fax: 888-650-7801

Email Address: Doctorsip@Sipderm.com

Study Coordinator:

Stacy Stankiewicz

9897 Hagen Ranch Road

Boynton Beach Florida 33472

Phone: 561-364-7774

Fax: 888-650-7801

Email Addresses: Stacy@SipDerm.com

Sponsor: Velez

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6 and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Robyn Siperstein, MD

Title: A Split-Face Multi-Arm Randomized Clinical Trial Showing the Efficacy & Safety of a Topical Mask After Aesthetic Treatments.

Précis:

Subjects undergoing aesthetic facial treatments with either a fractionated non-ablative 1927nm Thulium laser (Sciton Moxi), ablative Erbium:Yag 2940nm (Sciton Contour), or Microneedling with Radiofrequency (Cutera Secret) will apply a face mask immediately after the procedure randomly on either their left or right side of their face with normal post-care on the other side of the face. Thirty minutes after the mask is applied to one side both regular photography and thermal photography will be done. In addition, subjects will fill out questionnaires and will be assessed by blinded evaluators for efficacy and potential side effects. Patients will wear the masks at home for at least two hours a day and return daily for photographs until deemed healed by the primary investigator (3-7 days). Patients will also fill out daily questionnaires.

Mask, Pain, Temperature, Post-Laser Care

Keywords:

Objectives:

Primary Objective: To assess the efficacy of a facial mask in decreasing facial skin temperature after three different aesthetic treatments

Important Secondary Objectives:

1. To determine the safety and incidence of adverse events when using a Velez face mask after 3 different aesthetic treatments
2. To assess the change in the level of pain when using a Velez face mask after aesthetic treatments
3. To assess patient satisfaction with use of a Velez face mask after aesthetic treatments
4. To assess erythema when using a Velez face mask after aesthetic treatments
5. To assess healing time when using a Velez face mask

Primary

Endpoints:

Primary Endpoint:

The difference between the temperature on the mid-cheek (point inferior to the lateral limbus).

Important Secondary Endpoints:

1. The difference in the number of adverse events between the two sides of the face
2. The difference in pain scores on each side of their face as rated by subjects
3. The difference in patient satisfaction scores when rating the procedure on the left and right side of their face
4. The difference in erythema on the left and right side of subject's faces as graded by blinded evaluators doing live assessments 30 minutes after the procedure
5. The difference in healing time on the left and right side of subject's faces as graded by blinded evaluators looking at daily photographs

Population: Healthy adults aged 21 and over living in Palm Beach County, Florida.
Sample Size: 15
Study Sites: 9897 Hagen Ranch Rd, Boynton Beach, Florida &
1401 N Federal Highway, Boca Raton, Florida
Duration: 7 days
Study Agent: Velez Intense Hydration Mask

SCHEMATIC OF STUDY DESIGN

- Total n=15
- Screen potential subjects by inclusion and exclusion criteria

Day 0 Randomization

- Obtain informed consent, randomize into one of the following two groups
- Treatment Group 1 Right Side Velez Intense Hydration Mask
- Treatment Group 2 Left Side Velez Intense Hydration Mask

Day 0 Baseline assessments/ Study Intervention

- Baseline Assessments:
 - Pre-procedure pictures taken with Canfield's imaging system (Front, Right and Left Views)
- Study Intervention:
 - 1st Arm (n=5)
Non-ablative fractionated Thulium laser (Sciton Moxi) will be performed on level 3 and an Intense Hydration Mask will be applied to one side of the face with nothing on the other side for 30 minutes. After photos and evaluation, a hydration serum will be applied to both sides and patients will be sent home with masks to be worn at least 2 hours every day until deemed fully healed by the investigator
 - 2nd Arm (n=5)
Ablative full Erbium:Yag laser (Sciton Contour) will be performed at 200 microns and an Intense Hydration Mask will be applied to one side of the face with nothing on the other side for 30 minutes. After photos and evaluation, Vaseline will be applied on both sides of the face and the patient will be sent home with masks to be worn at least 2 hours every day until deemed fully healed by the investigator
 - 3rd Arm (n=5)
Microneedling with RF (Cutera Secret) will be done with a non-insulated needle at a depth of 200 and an Intense Hydration Mask will be applied to one side of the face with nothing on the other side for 30 minutes. After photos and evaluation, a hydrating serum will be applied on both sides of the face and the patient will be sent home with masks to be worn at least 2 hours every day until deemed fully healed by the investigator
- All Arms
 - Post-procedure pictures and questionnaires to be completed by subjects 30 minutes after the procedure
 - Safety analysis and erythema scale to be performed by blind evaluators and a compliance analysis performed by study coordinator

Day 1-7 Follow-up assessments

- Daily in office follow-up assessments of study endpoints and safety until primary investigator deems patients healed from the procedure
 - 1st Arm (n=5) Non-ablative fractionated Thulium laser (Sciton Moxi)
Post-procedure pictures and questionnaires to be completed by subjects for 3-7 days as determined daily by the primary investigator
 - 2nd Arm (n=5) Ablative full Erbium:Yag laser (Sciton Contour)
Post-procedure pictures and questionnaires to be completed by subjects daily for 3-7 days as determined daily by the primary investigator
 - 3rd Arm (n=5) Microneedling with RF (Cutera Secret)
Post-procedure pictures and questionnaires to be completed by subjects daily for 3-7 days as determined daily by the primary investigator

1 KEY ROLES

Principal

Investigator

Robyn Siperstein,
M.D.

9897 Hagen Ranch Road
Boynton Beach, Florida, 33472

Study

Coordinators

Stacy

Stankiewicz,
9897 Hagen Ranch Road
Boynton Beach, Florida, 33472

Medical Monitor

Christopher Buckley
9897 Hagen Ranch Road
Boynton Beach, Florida, 33472

Blinded Evaluators

Elizabeth Nestor, MD
Suzanne Micciantuono-Meran, D.O.
Jennifer Richter, P.A.
Jeanelyn Berges, P.A.
Bridget Nolan, P.A.
Lainie Buck, P.A.
Kara Peck, P.A.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Aesthetic procedures are gaining popularity; however patients are always interested in less downtime and pain. With non-ablative laser and microneedling with radiofrequency, patients experience less, however even the few hours of pain and erythema may be decreased by post-procedure products making these treatments even easier to tolerate with less downtime. Additionally, ablative laser resurfacing still provides the best cosmetic results, however the pain and downtime often limits who is willing to do the procedure. Products that can decrease pain and erythema as well as quicken the healing phase are needed to enable more patients to undergo these cosmetic treatments.

While topical ice or a fan are sometimes used to decrease the pain and heat associated with procedures, these require the patient to remain in the office often in an exam room to either hold the ice or to utilize a specialized fan (Zimmer Chiller). This elongates the procedure time for both the patient and the treating provider. The advantage of the face mask is that it is self-adhering to the face and requires no additional time in the office or specialized planning since the masks do not need to be kept in a fridge. Velez intense hydration masks are made of bio cellulose material obtained from vegetable raw materials and are self-adhering providing mobility and immediate comfort.

2.2 RATIONALE

There are many different types of post-procedure masks that are reported to reduce pain and erythema, however none that have quantitative scientific data or publications to support their claims. This clinical trial will quantitatively show whether the Velez hydration masks are able to reduce post-procedure skin temperature, patient pain levels, erythema and healing time.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS & RISK ANALYSIS

Potential risk of the mask includes swelling, itching, pain, dermatitis, erythema, or hypersensitivity.

Potential risk of the cosmetic treatments include swelling, itching, pain, dermatitis, erythema, infection, bleeding or scarring.

To mitigate the risk, patients will be educated on how to properly care for their skin post-procedure and all patients in the ablative arm will be receiving oral antibiotics and antivirals for infection prevention.

2.3.2 KNOWN POTENTIAL BENEFITS

The laser treatment may improve the subject's aesthetic appearance and therefore the subjects' psychological well-being.

The mask may decrease the patient's skin temperature and therefore pain, erythema and healing time.

3 STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

- A Prospective, Multi-Arm, Split-Face, Randomized Clinical Trial
- 2 Study Centers
- Study agent: Velez Intense Hydration Mask
- Study Intervention on Day 0
- Live evaluations by Blinded Evaluators on Day 0
- Daily photographic evaluations by Blinded Evaluators

This will be a prospective, multi-arm, evaluator blind, split-face, clinical trial in which subjects will be randomized to 2 groups in 3 separate arms.

1st Arm (n=5) Non-ablative fractionated Thulium laser (Sciton Moxi)

2nd Arm (n=5) Ablative full Erbium:Yag laser (Sciton Contour)

3rd Arm (n=5) Microneedling with RF (Cutera Secret)

In each arm, there will be two groups

1st group: Velez Intense Hydration Facemask on the left side of their face and nothing on the right

2nd group: Velez Intense Hydration Facemask on the right side of their face and nothing on the left side

Both groups will be utilizing the same safety and comfort protocols established by the practice which include the use of topical numbing cream (B.L.T.) before the laser procedure and cleansing with a makeup wipe and alcohol.

After the procedure a blind evaluator will be grading the subjects' erythema, edema, and any side effects. A compliance analysis performed by study coordinator will be done each visit.

Thirty minutes after the laser procedure, digital photography using Canfield's imaging system, and a thermal camera will be done. In addition, a subject questionnaire on satisfaction, erythema, edema and pain levels after the procedure will be completed. Patients will then have the typical post-care treatment on both sides of their face such as Vaseline for laser resurfacing and a hydrating serum for the Moxi and Microneedling. They will apply the mask at home for at least two hours each day and then return to the office daily for questionnaires and photographs until deemed fully healed by the primary investigator.

3.2 STUDY OBJECTIVES & ENDPOINTS

STUDY OBJECTIVES

3.2.1

Primary: To assess the efficacy of a facial mask in decreasing facial skin temperature after three different aesthetic procedures

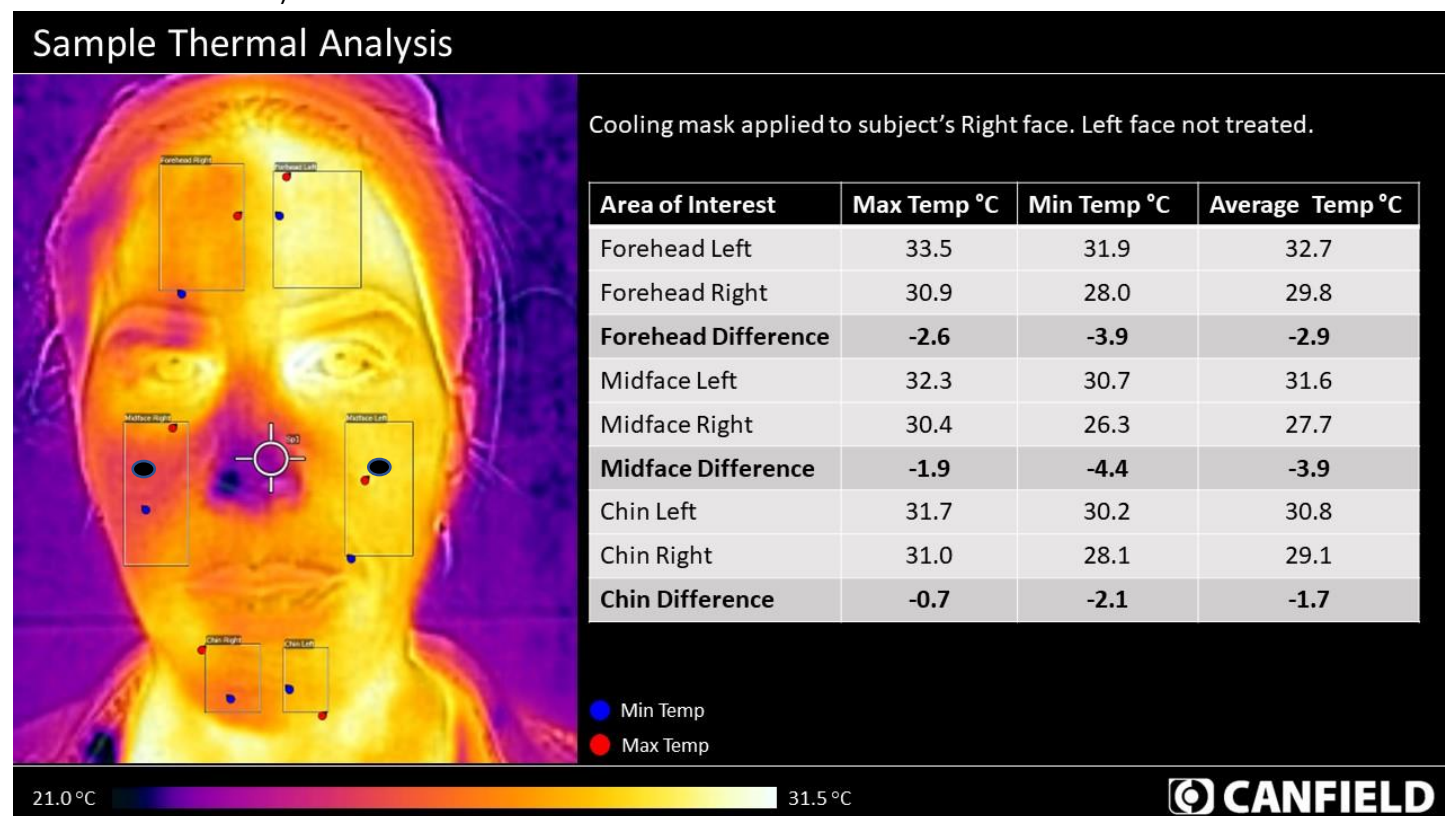
Secondary:

-To determine the safety and incidence of adverse events when using a Velez face mask after aesthetic procedures

- To assess the change in the level of pain when using a Velez face mask after aesthetic procedures
- To assess patient satisfaction with use of a Velez face mask after an aesthetic procedures
- To assess the reduction of erythema when using a Velez face mask after aesthetic procedures
- To assess healing time when using a Velez face mask after aesthetic procedures

3.2.1 PRIMARY ENDPOINT

The difference between the temperature as measured on each cheek at the level of the top of the alar rim and in between the lateral limbus. (The following is an example of a test subject before the trial to ensure the technology could measure what was needed in the trial – these are not results but an example of what the results would look like).



3.2.2 SECONDARY ENDPOINTS

- The difference in the number of adverse events between the two sides of the face
- The difference in pain scores on each side of their face as rated by subjects
- The difference in patient satisfaction scores when rating the procedure on the left and right side of their face
- The difference in erythema on the left and right side of subject's faces as graded by blinded evaluators doing live assessments 30 minutes after the procedure
- The difference in healing time in daily photographs as rated by blinded evaluators

These endpoints will show if the Velez Intense Hydration face mask decreases skin temperature after a cosmetic procedure, if subjects are happy with the use of the mask, and if they provide significant reduction in pain, erythema, and healing time.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all the following criteria:

- Provision of signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Male or female, aged 21 or over
- In good general health as evidenced by medical history
- For females of reproductive potential: use of highly effective contraception and a negative urine pregnancy test before laser treatment

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Subjects with active auto-immune conditions
- Subjects with a history of severe anaphylactic reactions
- Subjects with cancer, or other life-threatening medical condition
- Subjects taking prescribed anti-coagulants, chemotherapy, immunosuppressive agents, or immunomodulatory agents, in the 2 weeks prior to the study.
- Subjects with tattoos or many skin growths on the face that would obscure visualization of patient erythema
- Subjects with a history of keloid or hypertrophic scar on the face
- Subjects unwilling or unable to sit still while having the laser procedure, the mask application, or the photographs
- Subjects who are pregnant or nursing
- Subjects with any facial bruising, swelling, or erythema at baseline
- Subjects with current skin infections, tumors, herpes outbreak or dermatitis on the face
- Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

- Participants will be compensated for their participation in the study by having the opportunity to improve their aesthetic appearance without any cost to the subject.
- Subjects will receive both text, email, and phone call reminders for their scheduled visit.
- 5 subjects will be needed in each arm of the study to accommodate for a 10% expected dropout rate to have at least 4 subjects complete the study in each arm.
- The source of the subjects will be those who visited Siperstein Dermatology Group and allowed their information to be used to be contacted for promotions and trials. This list includes over 5,000 patients.

- The subjects on this list will first be contacted via email to see if they are interested in the trial. If they respond, they will then be sent a subject questionnaire to screen for those who satisfy the inclusion/exclusion criteria. The first 15 subjects that satisfy these criteria will be scheduled for the trial.

4.4 PARTICIPANT WITHDRAWAL OR TERMINATION

4.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- The participant's health declines requiring hospitalization
- The participant needs any surgery or other serious medical interventions
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The participant fails to show up for the visit.

4.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

The primary investigator will call, email, write or visit all participants that have withdrawn or terminated from the trial if they are unable to make their visits to ensure all safety parameters have been met.

4.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and Velez as well as provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements

Study may resume once concerns about safety, protocol compliance, or data quality is addressed and satisfy the IRB.

5.1 STUDY AGENT(S), ACQUISITION & STORAGE

5.1.1 ACQUISITION

Velez Intense hydration masks will be supplied by Velez.

5.1.2 FORMULATION

Velez intense hydration masks are made of bio cellulose material obtained from vegetable raw materials and are self-adhering providing mobility and immediate comfort.

5.1.3 PRODUCT STORAGE AND STABILITY

The product will be stored in its original package in an air-conditioned building with temperatures ranging from 72-78 degrees Fahrenheit. The product will remain in a locked cabinet until it is ready to be used on subjects.

5.1.4 PREPARATION

The subject's face will be cleansed with a cleansing cloth to remove all topicals such as make-up, sunscreen, and moisturizers. A topical numbing cream will be applied for 30 minutes and then removed before the subject's face will be cleansed with alcohol immediately prior to the laser procedure.

The product will be removed from original packaging, cut in half with a sterile scissor, and placed on the subject's assigned side within 5 minutes of the end of the procedure.

5.1.5 DOSING AND ADMINISTRATION

Each subject will receive half of the Velez Intense Hydration Mask on either their left or right side according to randomization.

5.1.6 ROUTE OF ADMINISTRATION

The mask will be placed topically on the skin

5.1.7 DURATION OF THERAPY

The subject will remain in the office for 30 minutes with the Velez face mask applied immediately after their laser treatment.

5.1.10 TRACKING OF DOSE

The study coordinator will check each package of the facemask to ensure it was used properly

5.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The product will be shipped from Velez. Once received the Study Coordinator will place the product in a locked cabinet until it is ready to be used on subjects. The Study Coordinator will oversee assigning the product to each subject and ensuring before the subject leaves that they had received the correct face mask on the correct side of the face.

6.1 STUDY PROCEDURE/EVALUATIONS

6.1.1 STUDY SPECIFIC PROCEDURES

- Medical history obtained from baseline subject questionnaire and verbally verified
- Examination by blinded evaluators
- Canfield photo imaging
- Counseling the subjects on the laser treatment and mask that they will be receiving
- Counseling the subjects that they will be given a facial mask on one side of their face only
- The study coordinator will check before the subject leaves that all appropriate photos and paperwork have been completed.

6.1.2 STANDARD OF CARE STUDY PROCEDURES

The *subjects'* skin will be wiped with a cleansing cloth and then alcohol prior to the laser procedure.

6.2

STUDY SCHEDULE

6.2.1 SCREENING

Screening Visit (Day -60 to 0)

- Send out and review subject questionnaires to determine eligibility based on inclusion/exclusion criteria.
- Schedule study visits for participants who are eligible and available for the duration of the study.
- Provide participants with specific instructions needed to prepare for first study visit and all subsequent visits.

6.2.2 ENROLLMENT/BASELINE

Enrollment/Baseline Visit (Visit 1, Day 0)

- Review in depth the study design with subjects and obtain informed consent of potential participants verified by signature
- Perform examination and verbally review subject's medications and medical history to determine eligibility based on inclusion/exclusion criteria.
- Verify all inclusion/exclusion criteria.
- Obtain demographic information
- Randomization
- Perform either a Sciton Moxi, Sciton Erbium, or Secret RF treatments to subject's face, and then apply a half mask on one side of the face according to randomized groups.
- Record adverse events as reported by participant or observed by investigator or blind evaluator.
- Perform protocol adherence check by study coordinator
- Collect post-procedure subject questionnaires
- Take post-procedure photos

- After photographs and blind evaluation both side of the face will be treated with the normal post-procedure care such as Vaseline for laser resurfacing and a Hydrating serum for Moxi and Microneedling. Additional masks will be given to patients to wear for 2 hours at home each day until deemed healed by the primary investigator.

6.3.3 FOLLOW -UP

Follow Up Visits (Visit 2-8, Day 1-7)

- Record adverse events as reported by participant on side assigned the mask
- Photograph with both thermal camera and Canfield standardized photography
- Primary investigator to advise each day if they need to return the next day or are done with the study and completely healed

6.3.6 UNSCHEDULED VISIT

All unscheduled visits will be recorded

6.3.7 SCHEDULE OF EVENTS TABLE

| | Screening | Enrollment/Baseline Visit 1, Day 0 | Day 1 | , Day 2- | , Day 3- | , Day 4- | , Day 5- | , Day 6- | , Day 7- |
|----------------------------------|-----------|---------------------------------------|-------|----------|----------|----------|----------|----------|----------|
| Procedures | | | | | | | | | |
| Informed consent & Randomization | | X | | | | | | | |
| Demographics & Medical History | | X | | | | | | | |
| Aesthetic Treatment | | x | | | | | | | |
| Subject Questionnaire | X | X | X | X | X | +/-X | +/-X | +/-X | +/-X |
| Exam for Adverse Effects | | X | x | x | x | +/- x | +/- x | +/-x | +/- x |
| Exam by blinded Evaluator | | X | | | | | | | |
| Intervention with Face Mask | | X | x | x | x | +/- x | +/- x | +/- x | +/- x |
| Photos | | X | x | x | x | +/-X | +/-X | +/-X | +/-X |

6.3 Photography

Photographs will be taken 30 minutes after application of the intense hydration mask. Photographs may also be taken to document AEs at the treating investigator's discretion. Site personnel will be thoroughly trained in the photographic equipment and techniques before study start. A Photography Standard Operating Procedure will be provided in a separate user guide.

6.4 Subject Questionnaires

Subjects will be asked about their satisfaction with the facemask using a subject Satisfaction questionnaire.

6.3 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Treatment with any prescription oral anti-coagulants, corticosteroids, or immune-modulating medications are prohibited. In the event a subject takes these medications or has treatments or procedures before the laser treatment, the primary investigator will make the final decision regarding early termination from the clinical trial.

6.4 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

If the patient has a history of herpes simplex on the face, they will be allowed to use prophylactic anti-viral medications.

6.5 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

If patients develop an infection during the trial, they will be prescribed the appropriate anti-viral or anti-bacterial medication but will continue in the study.

7 ASSESSMENT OF SAFETY

Safety evaluations for this study include an interview of the subjects to obtain information about any medical occurrence that meets the definition of an AE. Each subject should be questioned about AEs at the study visit following the screening visit. The question should be asked: "Since your last clinical visit have you had any health problems?" Information on AEs can also be obtained from signs and symptoms detected during the examination by the evaluator, which should include visual inspection of the treatment area.

AEs must be documented in the source document without regard for cause or relation to investigational product. If in the process of the interview, additional information regarding medical history or preplanned medical or surgical procedures is revealed, it must be documented in the source documents.

It is the responsibility of the Investigator to determine severity of the AE and relatedness of the event to the study product.

7.1 ADVERSE EVENTS

7.1.1 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether considered intervention-related (21 CFR 312.32)

Serious adverse event or serious suspected adverse reaction.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.3.2 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

With these events the following will occur:

- *Modification of inclusion or exclusion criteria to mitigate the newly identified risks*
- *Implementation of additional safety monitoring procedures*
- *Suspension of enrollment of new participants or halting of study procedures for enrolled participants*
- *Modification of informed consent documents to include a description of newly recognized risks*
- *Provision of additional information about newly recognized risks to previously enrolled participants.*

7.4 CLASSIFICATION OF AN ADVERSE EVENT

7.4.1 SEVERITY OF EVENT

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.4.2 RELATIONSHIP TO STUDY AGENT

All AEs will have their relationship to study agent or study participation assessed.

Evaluation of relatedness will consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The clinician’s assessment of an AE’s relationship to study agent is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

7.4.3 EXPECTEDNESS

The primary investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.5 RECORDING INSTRUCTIONS

Investigators, or other study site personnel, shall record all AEs including:

- a) Event term (recorded in standard medical terminology and avoiding abbreviations)
- b) Affected area
- c) Start date (first day with symptoms)
- d) Stop date (last day with symptoms)
- e) Intensity (mild, moderate, or severe)
- f) Seriousness (serious or not serious)
- g) Causal relationship to study product or study product injection procedure (yes or no)
- h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
- i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

All AEs, non-serious as well as serious, are to be reported as an AE. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 14 days (for SAEs) after the last study intervention. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.6 REPORTING PROCEDURES

7.6.1 ADVERSE EVENT REPORTING

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review of subject questionnaires. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The FDA and IRB will receive notification of any UP or SAE within 24 hours of discovery by the primary investigator. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life---threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 7 working days after the investigator first learns of the effect. The study sponsor is responsible for investigating and reporting the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect.

A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

The following information should be provided when reporting an AE:

- Subject identification (subject number and initials)
- Event description including observed symptoms
- Medical history related to event
- Event onset date and time
- Depth of injections
- Interventions implemented to treat event
- Event outcome (with resolution date and time if applicable)
- Relatedness to study product or procedure
- Seriousness of event
- Study treatment information such as number of injections, date of injections, name of product injected, volume injected, injection tool (needle) etc.

7.6.2 REPORTING OF PREGNANCY

If it is discovered that a subject is pregnant, the subject will discontinue any interventions.

7.7 STUDY HALTING RULES

Administration of the study agent will be halted when two SAEs determined to be related are reported. The primary investigator will notify the IRB and FDA and investigators immediately when the second

serious adverse event is reported, and enrollment screens will stop accepting new study participants. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.

Additionally, enrollment and treatment into the study will be temporarily halted if the Sponsor receives a SAE for a vascular embolic event that lead to skin necrosis, vision loss, stroke, pulmonary or cardiac complications or death and is determined by the Investigator to be directly or possibly related to the study device or injection procedure. The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes:

- The SAE was unanticipated, directly related to the study product or device injection procedure, and presents an unreasonable risk to study subjects, the study will be terminated. The IRB and FDA will also be notified if the study is prematurely terminated due to safety concerns.
- If the SAE does not meet the above criteria, then enrollment in the study will continue.

7.8 SAFETY OVERSIGHT & CLINICAL MONITORING

An independent medical expert (medical monitor) will advise the study investigator and monitor participant safety. The role of the Medical Monitor is to 1) Review all AEs on a regular basis throughout the trial; 2) be available to advise the investigators on trial-related medical questions or problems, and 3) evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. The Medical Monitor will remain blinded throughout the conduct of the clinical trial unless unblinding is warranted to optimize management of an adverse event or for other safety reasons. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

An assessment of pain as a safety endpoint will be done using a quantitative tool to assess pain 30 minutes after treatment, and during the follow up visits.

An independent medical expert (medical monitor) will advise the study investigator and monitor participant safety. The role of the Medical Monitor is to 1) Review all AEs on a regular basis throughout the trial; 2) be available to advise the investigators on trial-related medical questions or problems, and 3) evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. The Medical Monitor will remain blinded throughout the conduct of the clinical trial unless unblinding is warranted to optimize management of an adverse event or for other safety reasons. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

8 STATISTICAL CONSIDERATIONS

8.1 DESCRIPTION OF STATISTICAL METHODS

This is a randomized clinical study. Continuous data will be expressed as means with standard deviations. The p-value for statistical significance will be 0.05. For the primary objective, the test is one-tailed.

Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

Demographic endpoints, baseline assessments, and subject characteristics will be presented using descriptive statistics by treatment, as appropriate.

The Dataset will be comprised of 15 subjects

8.2 STATISTICAL HYPOTHESES

Primary Endpoint

- The alternative hypothesis is the difference in the mean temperatures on each side of the face is greater than zero
- The null hypothesis is the difference in the mean temperatures on both sides of the face is zero.

Secondary Endpoints

1.

- The alternative hypothesis is the difference in the mean pain, erythema, and comfort scores from one side to the other side is greater than zero
- The null hypothesis is the difference in the mean pain, erythema, and comfort scores from one side to the other side is zero.

All other secondary effectiveness analyses will be done descriptively as appropriate.

8.3 SAFETY ANALYSIS

Safety analysis will be descriptive only.

The number and percentage of subjects reporting each post-treatment symptom will be presented in total and by maximum severity.

A summary of all AEs will be provided, which will include:

- number of subjects with at least one AE and number of events (in total as well as serious AEs)
- number of subjects with at least one related AE and number of events (in total as well as serious AEs)
- number of subjects with at least one mild, moderate, and severe AE and number of events (in total as well as serious AEs)
- number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs)
- number of subjects who did not have an AE

The number of subjects with AEs related to the study product as well as the number of events will be summarized, and action taken for related AEs will also be summarized. Serious AEs will be listed.

8.4 DROPOUTS & MISSING DATA

Number of missing values will be summarized and reported as appropriate.

8.5 WITHDRAWALS AND DEVIATIONS

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the population analyzed.

8.6 SAMPLE SIZE

According to a pilot study with 5 subjects at Siperstein Dermatology Group who were receiving the Sciton Moxi treatment, the standard deviation in the differences on cheek temperatures was 1.76, μ_1 was 30.7 and μ_2 was 26.3

Sample size calculation where $\alpha = 0.05$, $\beta = 0.2$, $\sigma = 1.76$, $\mu_1 - \mu_2 = 4.4$ equals 4.343

$$2(1.96 + 1.282)^2$$

$$\frac{4.4^2}{21.021128/4.84} = 4.343$$

$$(4.4/2)^2$$

Therefore not only by combining data in each subgroup but also each subgroup with 5 patients will still achieve significance considering a 10% dropout in which case $n=4.5$ which is above 4.3 calculated above.

Outcome measure used for calculations: The mean absolute change in a validated scale between baseline and 90 days after the last injection of Juvéderm Vollure.

- Test statistic: t - test
- Type I error rate (alpha) 0.05
- Power level (e.g., 80% power) 80%

The primary endpoint will be the mean change. A Paired t---test will be used to analyze the primary endpoint. The results of the statistical analysis will be presented as an odds ratio with 95% Confidence intervals. A Shapiro---Wilk Test will be used to assess the normality of data.

A Paired t---test will be also be used to analyze the two secondary endpoints. The results of the statistical analysis will be presented as an odds ratio with 95% Confidence intervals. A Shapiro---Wilk Test will be used to assess the normality of data. All other secondary effectiveness analyses will be done descriptively as appropriate.

8.7 MEASURES TO MINIMIZE BIAS

8.7.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

To avoid bias, the subjects will be randomized to receive the treatment on one side. All evaluators will be blinded as to which side received the active intervention. The blinded evaluators will observe the subjects, but both the evaluator and subjects will be told that no discussions are to take place between the two and that the subjects are to remain silent during the evaluator examination.

To ensure only the clinical investigator performing the procedures and the study coordinator know the assignment, each subject will have an envelope assigned to them to be held by the study coordinator with the subject's name on the outside and the assignment on the inside. Only after the laser treatment does the study coordinator allow the clinical investigator to see the inside of the envelope with the randomized group assignment.

9 ETHICS/PROTECTION OF HUMAN SUBJECTS

9.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and the ICH E6.

9.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.3 INFORMED CONSENT PROCESS

Informed consent is required for all participants. In obtaining and documenting informed consent, the investigator will comply with applicable regulatory requirements and should adhere to 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and ICH GCP. Prior to the written informed consent, the consent forms will be provided to the participants. Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to think about being a participant prior to agreeing to sign. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Siperstein Dermatology Group Boynton research office. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Siperstein Dermatology Group research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Siperstein Dermatology's Boynton Beach research office.

9.4.1 RESEARCH USE OF STORED HUMAN DATA

Pictures and data collected under this protocol may be used in future publications. Access to stored pictures and data will be stored using codes assigned by the investigators. Data will be kept in password protected computers. Only investigators will have access to the samples and data.

10 DATA HANDLING AND RECORD KEEPING

10.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the formal discontinuation of the clinical study. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the IRB and sponsor. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

10.4 PUBLICATION

The PI will be responsible for submitting the data to a peer-reviewed journal within 6 months of the end of the trial.

11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.