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Clinical assessment of skin tightening and contour change of submental tissue using bipolar radiofrequency microneedling

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1. Background:

The human skin aging process is characterized by thinning dermis, atrophy of the extracellular matrix, and reduced collagen synthesis[1]. Loss of collagen in the dermis is of aesthetic concern, as it is the main structural support in the dermis and its loss results in skin laxity. Photo-damaged skin, mostly due to UVR, causes degradation of elastic fibers. This is histologically seen as disorganized tangles of elastin. Additionally, as we age, skin tends to appear more dry due to its poor hydration and turgor capacity[1]. The use of minimally invasive aesthetic treatments in reducing signs of aging has been gaining in popularity over surgical treatments in recent years[2]. Several energy types including, laser, radiofrequency, infrared, and ultrasound, have been developed for facial rejuvenation[3]. These treatments induce controlled thermal damage into the dermis and cause collagen contraction and neocollagenesis resulting in skin tightening over several months[2]. The effects of facial rejuvenation treatments on collagen have been well defined in literature, however, the role of elastin in facial rejuvenation has not been well studied.

In facial skin aging, the skin loses elasticity and begins to sag. Minimally invasive bipolar radiofrequency produces a controlled thermal injury in a fractional manner without damaging the dermal-epidermal junction, epidermis or subcutis[5]. Radiofrequency, unlike lasers, are chromophore-independent providing better penetration than lasers, and spare sweat glands, sebaceous glands, and hair follicles[5,6].

The Profound System is a bipolar fractional radiofrequency device which uses microneedles and thermal heat to stimulate neocollagenesis and neoelastosis.

This study intends to evaluate the safety and effectiveness of the Profound System on submental tissue and its effect on skin tightening and lift, as an exploratory evaluation. This device has been FDA cleared and commercially available since 2016 for treatment of facial wrinkles and improvement in the appearance of cellulite. This device is well-studied and frequently used on facial skin.

There are alternative treatments that have demonstrated a decrease in laxity of the facial skin. We feel that the Profound System may be able to produce clinically significant improvement in laxity of the neck skin. This device has been used in the Department of Plastic Surgery clinic off-label for over three years for this purpose. Additionally, our research team conducted a study using Ulthera, an ultrasound device, approximately 10 years ago; the results of this study led to its FDA approval for the treatment of lax neck skin. Therefore, our experience with this device and with treating lax neck skin have guided our decision to conduct this study.

2. Purpose:

The purpose of this study is to evaluate the safety and efficacy of bipolar fractional radiofrequency treatment via use of the Profound System to achieve skin tightening and contour change in lax submental (beneath the chin) tissue.

Overall assessment of clinical outcome and safety will be based on clinic visits and measurements of volume difference and lift obtained by the Vectra H2 3D Imaging System and Stand-up Vectra (Canfield Scientific, Parsippany, NJ). Additionally, evaluation of pre- and post- procedural photos/video obtained via the 3D Imaging Systems will be performed comparing Baseline and 180 Days by blinded raters. These photos will be identifiable full-face photos, and subjects will be adequately informed of such. Two unblinded clinician's assessments of satisfaction will be characterized using the five-point Global Aesthetic Improvement Scale (GAIS) at the final follow up visit, one based on a live assessment and one based on photos. Subjects will also undergo high-resolution ultrasonography, optical coherence tomography, transepidermal water loss measurements, and/or BTC 2000 measurements for exploratory purposes. Additionally, consenting subjects will undergo two skin biopsies at the treatment site. Micro-biopsies using 0.33mm size punches will be used to extract core tissues before and after treatment for histological evaluation (tissue structure, elastin, collagen and hyaluronic acid expression) and gene expression assessment (elastin, other major extracellular matrix (ECM) molecules and elastin related genes).

From these exploratory procedures the improvement in laxity of the submentum can be evaluated in comparison to pre-treatment assessments.

3. Study Design

This is a single-center, unblinded, non-randomized, non-controlled study designed to follow a total of up to 15 qualified and consenting subjects to receive one bipolar fractional radiofrequency microneedling treatment under an IRB approved protocol. The Principal Investigator(s) have been selected based on his expertise, qualifications (credentials, training, and medical specialty), subject access, previous clinical research, facilities, and interest in this particular field of research.

4. Study Population

Up to 15 subjects will be enrolled and treated at UT Southwestern in the Department of Plastic Surgery. Subjects will be identified from the clinical practice of Dr. Jeffrey Kenkel, Department of Plastic Surgery.

Subjects who present for treatment with the Profound System will have the study explained to them, will be asked about their willingness to be involved in the study, and their willingness to sign an informed consent form. Included in this interview will be questioning from the investigator or staff member about any privacy concerns the individual may have.

Prior to any study procedures each Subject will read and sign an Informed Consent Form, explaining the purpose, design, risks and duration of the study. By signing the consent form, subjects indicate that they are willing to have their full-face photograph and acknowledge that these photos may be used for scientific publication. If the subjects decline permission to be photographed, they may not participate in the study since the photographic documentation of treatment outcome is an important measure of evaluation.

Subjects should abstain from undergoing any dermatological treatments during entire study duration.

5. Inclusion/Exclusion Criteria

5.1 Inclusion Criteria

a. Healthy male and female adults between ages 21-70 years of age.
b. Desire skin laxity lift of the submental region.
c. Confirmed BMI ≤ 35.
d. Subjects who can read, understand, and sign the Informed Consent Form.
e. Subjects willing and able to comply with all study requirements.
f. Fitzpatrick skin type I-VI.
g. Submental fat graded by the Investigator as ≥ 1 using the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS, see Appendix D).
h. Subject is willing not to undergo any type of aesthetic procedure that could confound the study device treatment effects until he/she completes the study.

5.2 Exclusion Criteria:

a. Active localized or systemic infections, that may alter wound healing.
b. Immunocompromised subjects.
c. Subjects with coagulation disorder.
d. History of skin photosensitivity disorders, or use of photosensitizing drugs (e.g., tetracycline or sulfa drugs).
e. Pregnant and/or lactating (All female volunteers will be advised about using birth control during the period of study).
f. Excessive skin laxity on the submental and neck (Submental Skin Laxity Grade: SMSLG 4, Appendix E), or other anatomical feature for which reduction in SMF which may, in the judgment of the investigator, result in an aesthetically unacceptable outcome.
g. Scarring in areas to be treated.
h. Tattoos in the treatment areas to be treated.
i. Significant open facial wounds or lesions.
j. Severe or cystic acne in treatment areas.
k. Current active smoker.
l. Use of Accutane (Isotretinoin) within the past 6 months.
m. Use of topical retinoids within 48 hours.

n. Use of prescription anticoagulants.
o. Pacemaker or internal defibrillator.
p. History of skin disorders resulting in abnormal wound healing (i.e. keloids, extreme dry and fragile skin).
q. Subjects on current oral corticosteroid therapy or within the past 6 months
r. Metal implants in the treatment area.
s. In the opinion of the investigator, subject is unwilling or unable to adhere to all study requirements, including application and follow-up visits.
t. Subjects with a history of radiation therapy to the treatment area.
u. Subject has a history of allergy to lidocaine or ester-based local anesthetics.
v. Subjects with significant cardiac history or rhythm disturbance who may be unable to tolerate lidocaine with epinephrine.
w. Subjects with any skin pathology or condition in the treatment area that could interfere with evaluation or with the use of typical ancillary medical treatments or care used before, during or after treatments (e.g. psoriasis, rosacea, eczema, seborrheic dermatitis, vitiligo, hyper or hypo-skin pigmentation conditions such as post inflammatory hyperpigmentation).
x. Subjects who are unwilling to shave excessive hair in the treatment area that might influence or impair evaluation in the opinion of the Investigator.
y. Subjects have undergone skin resurfacing or tightening treatments in the treatment area over the past year.
z. Subjects have undergone dermatological treatments such as fillers and neurotoxins for the past 6 months in the treatment area.
aa. Subjects have undergone laser and light treatments in the treatment area over the past 3 months.
bb. Subjects have undergone superficial peel or microdermabrasion within 4 weeks.

6. Study Endpoints

6.1 Primary Endpoints

6.1.1 Primary Efficacy Endpoint

- Overall volume change of treated tissue in the submental region
    - Percent change from baseline of soft tissue surface area assessments that characterize the degree of stretch, compression, lift and volumization, as measured using the Markerless Tracking feature on Canfield's H2 3D Imaging System

6.1.2 Primary Safety Endpoint

- Incidence, severity, and relatedness of adverse events

6.2 Secondary Endpoints

- Improvement in overall lifting of treated tissue in the submental region via Blinded Evaluation of Baseline (pre-procedure) and Day 180 (post-procedure) photos and video obtained via the H2 3D Imaging System and Standup Vectra
- Blinded Reviewers assessment of improvement via the GAIS (Baseline vs. Day 180).
- Subject Assessment of Pain
    - The subjects' assessment of pain will be completed using an 11-point pain scale, where 0 = no pain, 10 = extreme pain (See Appendix A)
- Improvement in skin texture and laxity
    - Micro-biopsies for histology/gene expression
    - High-resolution ultrasound (HRUS)
    - Transepidermal Water Loss Measurements (TEWL)
    - Optical Coherence Tomography (OCT)
    - BTC 2000

Primary Endpoint Analysis:

Safety Endpoint

Safety will be determined based on adverse event data collected from both the Profound treatment visit and all follow-up evaluations of the treated areas. The Primary Safety Endpoint will be the incidence rate, severity, and relatedness of the adverse events that are observed in the study. All adverse events that arise during the course of the study will be recorded and summarized in the final study report.

7. Study Visit Procedures

7.1 Pre-screening

Prior to start of the study, prospective subjects will be screened for eligibility requirements by telephone. Subjects who are interested will then be scheduled for a screening visit. Additionally, if subjects express an interest in the procedure during a clinic appointment with Dr. Kenkel, he may discuss the study with them and assess the treatment area. If a subject is still interested and deemed a good candidate, the PI will connect the patient with a research coordinator to answer any further questions and provide consent for review.

7.2 Screening Visit (Visit 1)

The purpose of the study and specific inclusion and exclusion criteria and potential risks will be discussed with the potential study subject. All interested subjects will be given the Informed Consent Form with adequate time for review. The Investigator and/or designee will address questions and concerns raised by the subject. Those subjects who elect to participate, will sign the Consent Forms prior to any study procedures.

Subjects will be screened to ensure that they meet all study criteria. The following enrollment and screening activities will be performed:

a. Discuss the bipolar fractional radiofrequency device with each subject presenting for treatment
b. Obtain informed consent and HIPAA authorization
c. Collect any appropriate medical and surgical history including current medications, skin type, recent sun exposure, allergies, major illnesses, etc.
d. Close-Up and standard photography
e. Surface area assessments via the Vectra H2 3D Imaging System and Standup Vectra
f. Images will be obtained using the optical coherence tomography, BTC 2000, Bio Aquaflux, and/or high-resolution ultrasound.
g. Urine pregnancy test for women of childbearing potential
h. Examination of the treatment area by the physician
i. Location and approximate area of treatment area (s) will be mapped
j. Pre-existing skin conditions will be evaluated for potential study impact
k. Other assessments may be conducted per the clinical sites standard practice
l. Weight measurement

This visit will take about 1.5 – 2.5 hours

7.3 Treatment Visit (Visit 2)

The treatment visit activities may be combined with the Screening Visit. Prior to treatment, the treatment area should be cleaned of all debris cosmetics with antiseptic cleanser. Subjects may be given subcutaneous injection with 0.5%-1.0% lidocaine with epinephrine 1:100,000 -200,000 (or carbacaine 3% for those who intolerant of epinephrine) to anesthetize the areas and for hemostasis control. Starting with lower volumes of injectable anesthetic and increased as needed to achieve effective pain and hemostasis control. Total injected volume to treatment area should not exceed 50cc and must be in consideration of safe weight-based dosage limits of medications with systemic and local toxic effects. During administration of local injectable anesthetic, provider prescribed chilled air, topical anesthetic, inhaled analgesia, and/or oral sedative may be prescribed for additional palliative measures.

The following activities will be performed on all subjects:

a. The study treatment (bipolar fractional radiofrequency) per study treatment guidelines provided
b. Review of post treatment expectation and management for the treatment as detailed in the study device instruction for use (IFU)
c. All expected (e.g., edema, erythema) and unexpected (e.g., burn, blister) treatment adverse events will be documented and graded
d. During the treatment, subjects will be asked to rate any pain or discomfort using an eleven-point Numerical Pain Rating Scale (NPRS)

The following activities will also be for exploratory purposes:

a. Collection of two 0.33mm biopsies using WellTech Rapid-Core 0.33mm Biopsy Punch pre-treatment. The biopsy will be taken from the submental skin within the designated area for treatment. One biopsy will be used for histological studies and the other for gene expression studies

This visit will take about 2-3 hours.

Post-treatment care and precautions
Appropriate post-treatment care instructions will be provided as deemed appropriate by the Investigator or study staff.

Post treatment assessment will be performed. Subjects will be instructed that blistering, bleeding, oozing, strong pain, swelling persisting for more than 72 hours, or signs of infection (e.g., pus, drainage, fever) are cause for immediate concern and they should contact the investigator and/or his designee, to be evaluated. Downtime after treatment typically can last approximately 0-2 days.

7.4 Follow-up Visits (Visits 3 and 4)

At a minimum, all subjects will return for follow-up at 3 months (+/- 7 days) and 6 months (+/- 7 days) after treatment.

The following activities will be performed on all subjects during the follow-up visits:

a) The physician or study staff will perform an examination of the skin of the treatment area.
   - All expected (e.g., edema, erythema) and unexpected (e.g., burn, blister) treatment local skin responses will be documented and graded at every visit
b) Adverse Event Review
   - Query the subject regarding any change in health since enrollment into the study.

- Perform a detailed cutaneous exam of the treatment area, review and record any local adverse events related to cutaneous changes.

c) Collect an updated surgical history and record any change in concomitant medications or treatments.
d) Images will be obtained using the optical coherence tomography, BTC 2000, Bio Aquaflux, and/or high-resolution ultrasound, as was done previously.
e) The two small biopsies within the treatment area will be taken at each visit.
f) Take close-up and standard photography
g) Surface area assessments via the Vectra H2 3D Imaging System and Standup Vectra

These visits will take about 45 minutes – 1 hour.

7.5 Additional, Unexpected Follow-Up Visits

If a potential adverse event is reported by the subject or identified during examination, the Investigator or study staff will schedule the subject for an Event Follow-up Visit within 24 hours. At this visit the Investigator or his designee will:

a. Obtain a complete history of the event in question as well as conduct an examination of the subject and determine if the reported event qualifies as an Adverse Event. If the event is determined to be an Adverse Event, an Adverse Event (AE) case report form and Event Follow-up (EF) Visit case report form must be completed. One AE case report form should be used to track the history of an individual AE throughout the period of the study.
b. Collect an updated medical and surgical history along with recording of concomitant medications or treatments.
c. Take photographs of the subject with attention to the area in question.
d. Render treatment for the event, if any, as determined by the medical judgment of the investigator.

Additional follow-up visits may also be required after the last scheduled visit to assess resolution of adverse events.

8. Schedule of Events

Procedures	**Pre-Screening**	**Screening: Visit 1[#]**	**Treatment: Visit 2** (Day 0)[#]	**Follow Up: Visit 3** (Month 3)	**Follow Up: Visit 4** (Month 6)
Telephone/Telehealth Screen	X				
Informed Consent		X			
Inclusion/Exclusion Criteria		X			
Demographics		X			

Medical History/Concomitant Medications		X	X	X	X
Physical Exam		X			
Urine Pregnancy		X			
Treatment			X		
Standard Photographs		X		X	X
Surface area assessment using the H2 3D Imaging System and Standup Vectra		X		X	X
Clinician GAIS					X
Non-invasive Skin Tests*		X		X	X
Biopsy			X	X	X
Safety Assessment			X	X	X

The treatment visit activities may be conducted at the Screening Visit

* TEWL measurement, OCT images, BTC-2000, and/or high frequency ultrasound images will be taken

9. Statistical Methods of Analysis:

This initial study will include change from baseline analysis.

The primary outcome measure of effectiveness will be a paired comparison of baseline to all applicable post-baseline time points using data obtained from a trans-epidermal water loss assessments, high resolution ultrasonography, optical coherence tomography, BTC 2000 measurements, biopsies results, and 3D imaging results. Photographs and 3D video of treated skin at follow-up visits will be compared to baseline for blinded scoring evaluations. Mean of the change from baseline (defined as post-baseline value minus baseline value) will be estimated at post-baseline time points for applicable parameters.

The following will be calculated and reported for each evaluation parameter at the applicable post-baseline time point(s):

$$\text{Percent mean change from baseline} = \frac{(\text{visit mean score} - \text{baseline mean score}) \times 100}{\text{baseline mean score}}$$

For clinician's global aesthetic improvement assessment, the null hypothesis that the mean score is equal to 4 (no change) will be tested.

10. Blinded Evaluation

Blinded evaluation will be performed by three physicians (dermatologist and/or plastic surgeons) to determine if the Profound System is effective for treatment to lift lax submental (beneath the chin) tissue.

Three qualified, non-treating clinicians will be trained to independently review Baseline and Follow-up photographsfor each subject. The reviewers will be blinded to subject information and the temporal order of the photographs. No information will be provided to the reviewers that may allow them to determine the Baseline from the Follow-up imaging.

The pair of scans (labeled A and B) for each subject will include the pre-treatment photographs and post-treatment photographs (6 months follow-up).

The three blinded reviewers will individually be asked to review a randomized presentation of each subject's photographs. Each reviewer will be asked to record if he/she observes a difference between the pair (before and after) of the photographs. If the reviewer determines there is a difference, the reviewer will record which pair (A or B) he/she believes correlates to the Follow-up photographs. Improvement will be based on at least two of the three (2/3) blinded reviewers correctly identifying the post-treatment photographs. Secondarily, each reviewer will score the photo pairs in which they observed a difference for improvement via the GAIS.

Assessments of 2/3 blinded reviewers selecting "no change" will be considered as "no improvement, neither worsening". Assessments of 2/3 blinded reviewers selecting "change" and incorrect identification of the pre and post photographs will be considered as "worsened".

The identified reviewers will be instructed that their participation is completely voluntary and has no impact on performance review at their institution. It will be clearly stated that consent is implied with the institution's survey completion. No identifying information about these blinded reviewers will be published but will be maintained in a secure manner to be monitored by the research team. If no incentive is to be provided to the blinded reviewers for their participation, this will be known to them prior to their participation. A waiver of documentation is requested as no subject Personal Health Information (PHI) will be collected, recorded, or shared. Blinded reviewers will be asked to attend one visit for the purposes of evaluating pre procedure photos and post procedure photos via a survey. Prior to the survey, study coordinator will ask for a verbal consent from the reviewers indicating approval to use their responses in the study. Reviewers will assess the images on a local computer.

11. Non-significant Risk Determination

In accordance with the definition of "Significant Risk Device" provided in the U.S. Code of Federal Regulations 21 CFR 812.3, the study device to be used in this research study has been determined to be a Non-Significant Risk (NSR) device based on the following:

a) It is not an implant
b) It is not purported or represented to be for use in supporting or sustaining human life
and do not present a potential for serious risk to the health, safety or welfare of a subject
c) It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health
d) Use of the device poses no risk to the health, safety, or welfare of a subject

12. Device Description

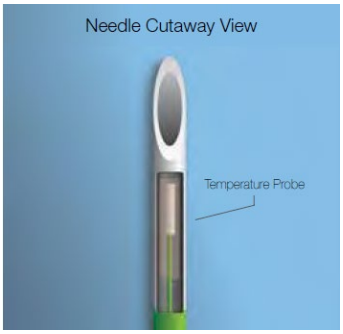
The device to be used in this study is an FDA cleared device [510(k), K161043] for percutaneous treatment of facial wrinkles and improvement in appearance of cellulite in subjects with Fitzpatrick skin types I-III. The Profound System (Image 1) consists of a reusable console which contains a radiofrequency (RF) generator and graphical user interface, two re-usable treatment handpieces, and two disposable, single use, sterile electrode cartridges.

Image 1: Profound System

The Profound system has a powered console with a graphical user interface for adjustment of treatment parameters. The RF frequency of the Profound System is 460 +/- 5kHz. Bipolar RF travels from the RF generator, through the electrodes, into the dermal layers beneath the surface of the skin. The dimensions of the treatment area vary depending on the handpiece (Image 2). The 25° handpiece has 5 independent channels and covers a treatment area of 14mm. The 75° handpiece consists of 7 independent channels and covers a treatment area of 20mm. Specifically, the 25° Dermal handpiece and cartridge are used for the percutaneous treatment of facial wrinkles, while the 75° SubQ handpiece is used to improve the appearance of cellulite (Image 3). Additionally, the Profound System provides real-time temperature feedback through temperature sensors. For this study, only the 25° handpiece will be utilized.

Image 2: Dermal Handpiece

- Treats the Dermal layer, between 1 – 2 mm
- Single-use cartridge with 5 pairs of micro-needles
- Cold plate for epidermal protection



13. Potential Risks

Blistering, burning, and infection: **(Rare)**
A crust, blister or superficial wound can occur at the treatment area. The risk of infection will be minimized by proper wound care.

Bruising: **(Rare)**
A mild bruising may occur at the treatment area as a result of radiofrequency exposure. This is usually transient and resolves in a few hours to few days.

Transient edema and/or erythema**: (Occasionally)**
May develop within the irradiated areas but are usually temporary and fade within 24-72 hours.

Pigmentary changes: **(Rare)**
Radiofrequency exposure can cause pigmentary changes such as hyper- (and hypopigmentation. Although this is usually temporary, it may be permanent on rare occasions. Sun avoidance and/or the use of a total sun block (SPF 30 or higher) will help minimize the intensity and duration of any pigmentary changes.

Scarring: **(Rare)**

As with any form of energy exposure, there is a small risk of scarring. However, this is minimized by proper technique and wound care.

Allergic Reaction: **(Rare)**
There is a possibility of an allergic or toxic reaction to anesthesia used to numb the areas. Subjects will be questioned with regard to any history of allergies and carefully monitored for signs of allergic reaction.

Biopsy
Risks associated with biopsy include: 1) scarring - a small risk of scarring, which can be mitigated by proper technique and wound care; 2) allergic reaction - there is a possibility of an allergic or toxic reaction to anesthesia used to numb the areas. Subjects will be questioned with regard to any history of allergies and carefully monitored for signs of allergic reaction.

Photography
The subject may be uncomfortable with sitting still for an extended period of time or from turning his/her body in various positions. Subjects may be sensitive to the bright and repeating flashes from the camera, which can sometimes cause headaches, irritation of the eyes, discomfort, after effects such as seeing spots, and in rare cases, could stimulate a migraine headache or epileptic seizure.

Photographs include a risk of identification, as these will be full face photos. Privacy will be protected to the greatest extent possible. Photos will only be identified by a unique subject identification number that contains no personal identifying information. All photos will be stored on a password secure drive, with only access by research personnel. For research purposes, photos may be used in scientific publications.

Noninvasive procedures (exploratory)

- Biox Aquaflux will be used to measure transepidermal water loss (TEWL) measurements which evaluate barrier function of the skin epidermal layer to determine progress of epidermal healing after treatment. The standard time for TEWL measurements should take approximately 5 minutes.

- Vivosight, an Optical coherence tomography (OCT) device, will be used to noninvasively gather topographical and histologic images of pre- and post-treated skin. The standard time for OCT should take approximately 5-10 minutes.

- The BTC 2000 will be used to measure skin laxity, viscoelastic deformation, stiffness, energy absorption, elasticity, and deformation

values of skin. The standard time for BTC 2000 should take approximately 5 minutes.

All these test are considered noninvasive and no risks are anticipated with these tests.

14. Potential Benefits

Subjects may benefit by having an overall improvement in submental skin laxity or an overall improvement in skin tone or texture in the treated areas, but this is not guaranteed. There may be a benefit to the medical community by demonstrating the safety and effectiveness of a new technology in the management of skin laxity of the submentum. This technology may have advantages over existing technologies currently in use (lasers, ultrasound, etc.) because of its combination of bipolar fractional radiofrequency and microneedling technology. This technology may lead to better clinical outcomes for an understudied area.

15. Adverse Events

15.1 Definitions

Adverse Event

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect (defined below) on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

A serious adverse event (SAE) is any adverse event that:

a) led to death,
b) resulted in life-threatening illness or injury
c) resulted in permanent impairment of a body structure or body function
d) resulted in in hospitalization or prolongation of existing hospitalization,
e) resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function, or
f) led to fetal distress, fetal death, congenital abnormality or birth defect

15.2 Reporting

Adverse events, and unanticipated adverse device effects (UADE) are collected from the time of subject consent until the subject exits the study. A description of the adverse event or device event, date of onset, severity, action taken, relationship to study treatment and outcome are documented in the case report form.

The Investigator will submit to the reviewing IRB a report of any unanticipated adverse device effect (UADE)) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (CFR 812.150(a)(1)).

16. Subject Safety and Data Monitoring

For this protocol, which involves the use of a non-significant risk device, the Investigator will be responsible for the conduct of the study including accrual, subject experience, attrition, patterns of expected adverse events and/or unexpected adverse events, any protocol deviations or violations, and any changes in the risk/benefit analysis.

Subjects will be asked about any adverse events throughout the study by the study staff. Subjects will be asked to contact the study staff if adverse events develop between visits. An unscheduled visit will be arranged so that the Investigator can clinically evaluate and photograph these findings. All subjects will be discontinued from the study if their problem remains unchanged/becomes worse. The Investigator can decide to stop the study if he/she believes that the participants' participation is no longer safe or if another treatment may be more helpful. The IRB or FDA may stop the research for the safety of the participants. These adverse events will be documented and reported as required for compliance with applicable regulations.

All study records and information will be identified by the subject number. All subject identifiers will be removed from all documents. The link between subject name and study ID number will be kept in separate password-protected files at the study site. Documents containing identifying information will be kept in locked files in the research staff's locked office. All electronic study data will be password protected with access limited to members of the research team. No direct identifying information will be shared with any outside entities, unless required by regulatory agencies (FDA and IRB). Electronic data (electronic data entry - Case Report Forms) if used will be password protected.

Photographs of the subject's face will be taken at Enrollment/Treatment and Follow-Up visits. These photographs will be identified by subject numbers. Subject confidentiality will be protected to the greatest extent possible. Quantitative surface area assessments will be done on lateral 3D images taken at baseline and compared with 3D images obtained at all follow-up visits.

This study will be performed in accordance with Health Insurance Portability and Accountability Act. These guidelines will be followed specifically with regards to the privacy and confidentiality of subject care and study records. Personnel associated with Investigator's office and the governing Institutional Review Board, have the right to review the data, including photographs, collected during this study.

Personnel associated with Investigator's office and the governing Institutional Review Board have the right to review the data, including photographs, collected during this study.

17. Protocol Deviations

Emergency deviations (deviation necessary to avoid immediate apparent harm or protect life or physical well-being of subjects or others) and major deviations as defined by the reviewing IRB will be reported to the IRB within 5 working days of occurrence. All deviations will be tracked and summarized in the progress report for the next continuing IRB review.

18. Sources of Research Material

Demographics and medical history will include age, gender, weight, height, BMI, skin type, recent sun exposure, allergies, current medications, major illnesses, photographs, adverse events and treatment. Additionally, OCT images, ultrasound images, TEWL measurements, BTC 2000 measurements, and biopsies will be obtained.

High resolution ultrasound will be used to assess skin thickness and density. The standard time for use of high-resolution ultrasound should take approximately 5 minutes.

Transepidermal water loss (TEWL) measurements will be used to evaluate barrier function of the skin epidermal layer to determine progress of epidermal healing after treatment. The standard time for TEWL measurements should take approximately 5 minutes. Optical coherence tomography (OCT) will be used to noninvasively gather topographical and histologic images of pre- and post-treated skin. The standard time for OCT should take approximately 5-10 minutes. The BTC 2000 will be used to measure skin laxity, viscoelastic deformation, stiffness, energy absorption, elasticity, and deformation values of skin. The standard time for BTC 2000 should take approximately 5 minutes.

Biopsies will be taken using 0.33mm biopsy punches of the submental area. Biopsies will allow investigators to correlate changes seen in skin measurements with histology and gene expression. Time for two biopsies will take approximately five minutes. Biopsies for histology will be fixed immediately after collection in 4% PFA followed by paraffin embedding. Biopsies for gene expression will be put in RNA-Later solution and transferred to the Plastic Surgery Research Lab for gene expression analysis. Whole genome sequencing will not be performed, we will only be analyzing proteins and RNA expression related to collagen, elastin, and the extracellular matrix production.

19. References

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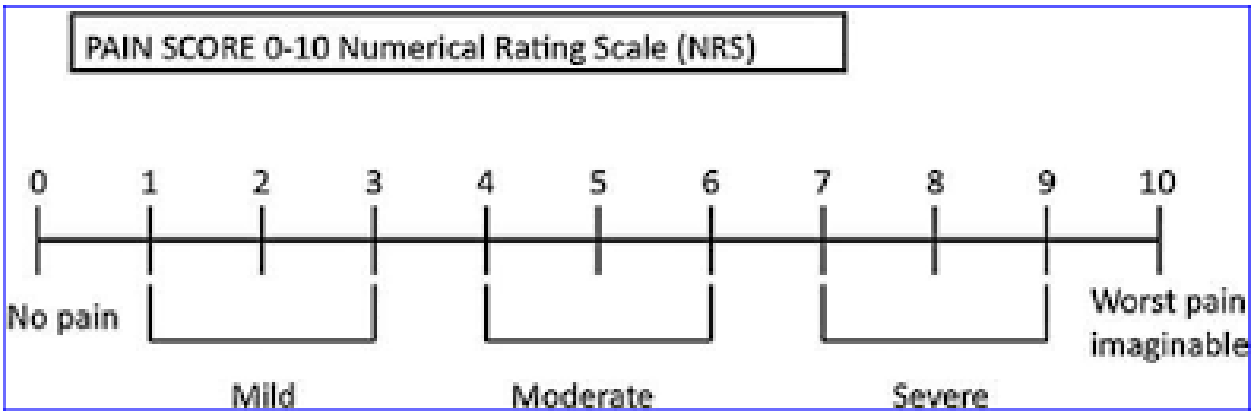
20. Appendix

A. Numerical Pain Rating Scale

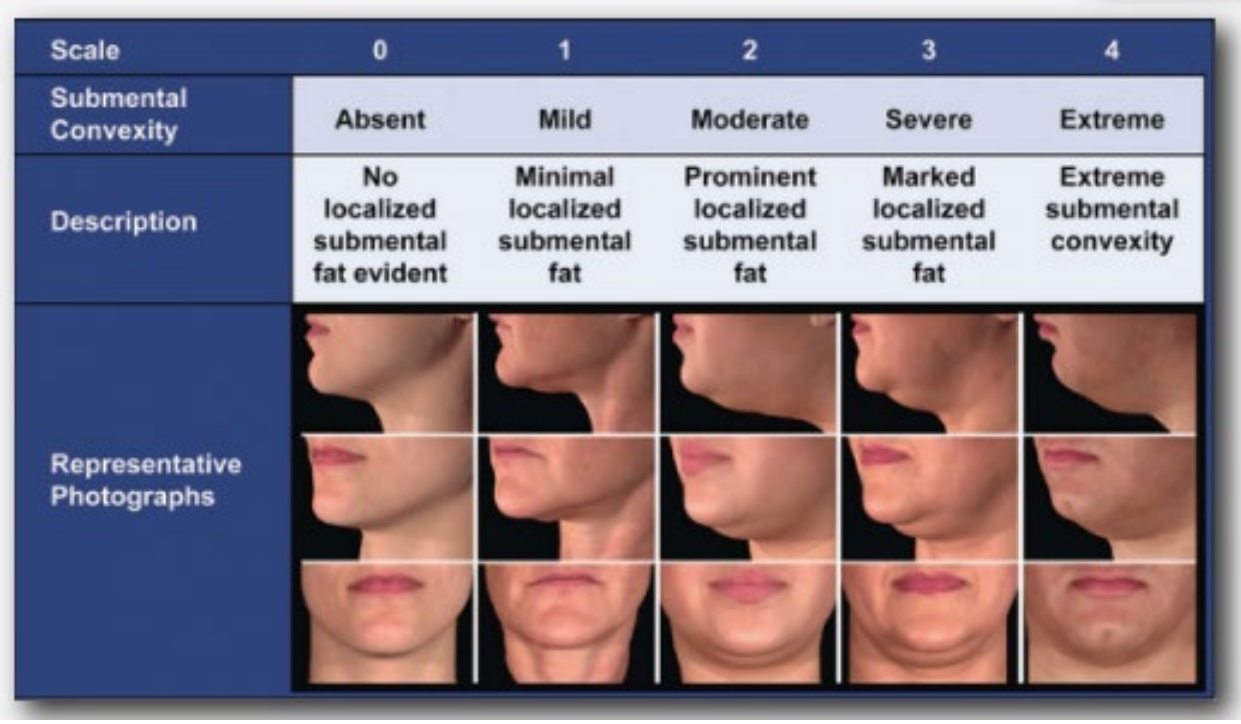


B. Global Aesthetic Improvement Scale (GAIS)

GAIS	Rating	Description
❑ **1**	**Very Much Improved**	Optimal cosmetic result in this subject
❑ **2**	**Much Improved**	Marked improvement in appearance form the initial condition, but not completely optimal for this subject
❑ **3**	**Improved**	Obvious improvement in appearance from initial condition, but a re-treatment is indicated
❑ **4**	**No Change**	The appearance is essentially the same as the original condition
❑ **5**	**Worse**	The appearance is worse than the original condition

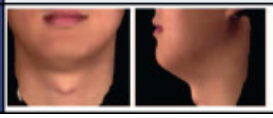
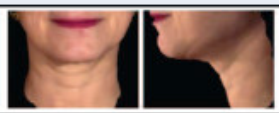
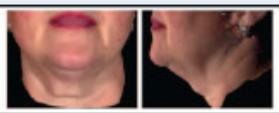
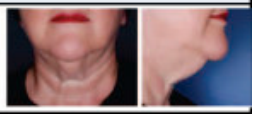
D. Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)[1]

Scale	Description
0	Absent
1	Mild
2	Moderate
3	Severe
4	Extreme



[1]*Dermatologic Surgery: November 2016 - Volume 42 - Issue - p S263–S270*

E. Submental Skin Laxity Grade (SMSLG)[2]

Scale	1	2	3	4
Skin Laxity	None	Mild	Moderate	Severe
Description	None or minimal superficial wrinkles	Mild superficial wrinkles	Moderate superficial wrinkles	Superficial wrinkling present, may be marked
Representative Photographs				

[2]*Dermatologic Surgery: January 2016 - Volume 42 – Issue 1 - p S38–S49*