Clinical Assessment of Skin Quality and Efficacy of Dermal Line Improvement Following Four Bipolar Radiofrequency Microneedling Treatments

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Clinical Assessment of Skin Quality and Efficacy of Dermal Line Improvement Following Four Bipolar Radiofrequency Microneedling Treatments

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[redacted]	[redacted]
PRINCIPAL INVESTIGATOR	Dr. Jeffrey Kenkel, MD
SUB-INVESTIGATORS	Dr. Abby Culver, MD Jasmine Panton, MBe

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2. Purpose

The primary objective of this study is to evaluate the safety and efficacy of a bipolar fractional radiofrequency treatment via use of the InMode Morpheus8 System to achieve skin texture and quality change and to treat facial fine lines and wrinkles of the lower face.

3. Study Design

This is a single center, unblinded, non-randomized, non-controlled study designed to follow a total of up to thirteen (13) qualified and consenting subjects receiving 4 bipolar fractional radiofrequency microneedling treatment of the lower face, once every 4-6 weeks for a total of 4 treatments, under an IRB approved protocol. Following these treatments, patients will have follow-up visits at 3-months, and 6-months post-treatment. The effects of bipolar fractional radiofrequency treatments via the InMode Morpheus8 System will be determined by subjective and objective analysis through clinician and subject assessments.

Overall assessment of clinical outcome and safety will be based on clinic visits and evaluation of pre- and post-procedural photos. These photos will be identifiable full face photos, and subjects will be adequately informed of such. One unblinded clinician's assessments of satisfaction will be characterized using the Lemperle Wrinkle Assessment Scale, a four-point Allergan skin fine line scale and a four-point Allergan Skin Roughness scale at baseline, 3 month follow up and 6 month follow up visits. The five-point Global Aesthetic Improvement Scale (GAIS) will also be used at 3 month and 6 month follow up visits. Additionally, evaluation of pre- and post-procedural photos will be performed comparing baseline and follow ups by blinded raters. In conjunction with standard and close-up photography, subjects will also have photos taken using the VISIA Imaging system and will undergo high-resolution ultrasonography, transepidermal water loss (TEWL) measurements and/or BTC 2000 measurements for exploratory purposes. High-resolution ultrasound will be utilized for assessment of skin thickness and density. TEWL measurements are taken via the Bio Aquaflux and will be used to evaluate barrier function of the skin epidermal layer to determine progress of epidermal healing after treatment and BTC

2000 will be used to measure skin laxity, viscoelastic deformation, stiffness, energy absorption, elasticity and deformation values of skin. Additionally consenting subjects will undergo skin biopsies at the treatment site to better qualify the measurements and results from the items mentioned above. Micro-biopsies using 0.33mm size punches will be used to extract core tissues pre- and post-treatment for histological evaluation (tissue structure, elastin, collagen and hyaluronic acid expression) and gene expression assessment (elastin, other major ECM molecules and elastin related genes).

From these exploratory procedures the improvement in skin quality and dermal lines of the lower face and jawline can be evaluated in comparison to pre-treatment assessments.

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5. Eligibility Criteria

5.1. Inclusion Criteria

1 Healthy male and female adults between ages 21-70 years of age.
2 Presence of facial dermal lines and skin changes of the lower face associated with age or environmental exposure.
3 Subjects who can read, understand, and sign the Informed Consent Form.
4 Subjects willing and able to comply with all study requirements.
5 Fitzpatrick skin type I-VI.
6 Minimum of 1 on the Lemperle Wrinkle Assessment Scale, Allergan Fine Line Scale and Allergan Skin Roughness Scale
7 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:

1 Active localized or systemic infections, that may alter wound healing.
2 Immunocompromised subjects.
3 Subjects with coagulation disorder.
4 History of skin photosensitivity disorders, or use of photosensitizing drugs (e.g., tetracycline or sulfa drugs).
5 Pregnant and/or lactating (All female volunteers will be advised about using birth control during the period of study).
6 5 on the Lemperle Wrinkle Assessment Scale or 4 on the Allergan Fine Line Scale and/or Allergan Skin Roughness Scales
7 Scarring in areas to be treated.
8 Tattoos in the treatment areas to be treated.
9 Significant open facial wounds or lesions.
10 Severe or cystic acne in treatment areas.
11 Current active smoker.
12 Use of Accutane (Isotretinoin) within the past 6 months.
13 Use of topical retinoids within 48 hours.
14 Use of prescription anticoagulants.
15 Pacemaker or internal defibrillator.
16 History of skin disorders resulting in abnormal wound healing (i.e. keloids, extreme dry and fragile skin).
17 Subjects on current oral corticosteroid therapy or within the past 6 months
18 Metal implants in the treatment area.
19 In the opinion of the investigator, subject is unwilling or unable to adhere to all study requirements, including application and follow-up visits.
20 Subjects with a history of radiation therapy to the treatment area.
21 Subject has a history of allergy to lidocaine or ester-based local anesthetics.
22 Subjects with significant cardiac history or rhythm disturbance who may be unable to tolerate lidocaine with epinephrine.

23 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).

24 Subjects who are unwilling to shave excessive hair in the treatment area that might influence or impair evaluation in the opinion of the Investigator.

25 Subjects have undergone skin resurfacing or tightening treatments in the treatment area over the past year.

26 Subjects have undergone dermatological treatments such as fillers and neurotoxins for the past 6 months in the treatment area.

27 Subjects have undergone laser and light treatments in the treatment area over the past 3 months.

28 Subjects who have undergone surgery in the proposed treatment area within the past 3 months.

29 Subjects have undergone superficial peel or microdermabrasion within 4 weeks.

6. Study Endpoints

6.1. *Primary Endpoints*

1 Improvement of fine lines and wrinkle severity using a modified Lemperle Wrinkle Assessment Scale, the Allergan Scale for Fine Lines and the Allergan Skin Roughness Scale Assessment at baseline, 3-months, and 6-months post-treatment

2 Clinician's Global Aesthetic Improvement Scale (CGAIS) at 3-months and 6-months post-treatment

6.2. *Secondary Endpoints*

1 Monitoring of adverse events throughout the course of the study.

2 Subject Global Aesthetic Improvement Scale (SGAIS) at 3-months and 6-months post-treatment

3 Patient Satisfaction Questionnaire at 3-months and 6-months post-treatment

4 Exploratory skin measurements using high resolution ultrasound, TEWL measurements (Bio Aquaflux) and BCT 2000 to assess skin thickness, density, firmness as well as the integrity of the stratum corneum

5 Micro-biopsies for histological evaluation (tissue structure, elastin, collagen and hyaluronic acid expression) and gene expression assessment (elastin, other major ECM molecules and elastin related genes)

7. Safety Endpoint

Safety will be determined based on adverse event data collected from both the Morpheus8 treatment visits and all follow-up evaluations of the treated areas. The Primary Safety Endpoint will be the incidence rate, severity, and relatedness of adverse events 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.

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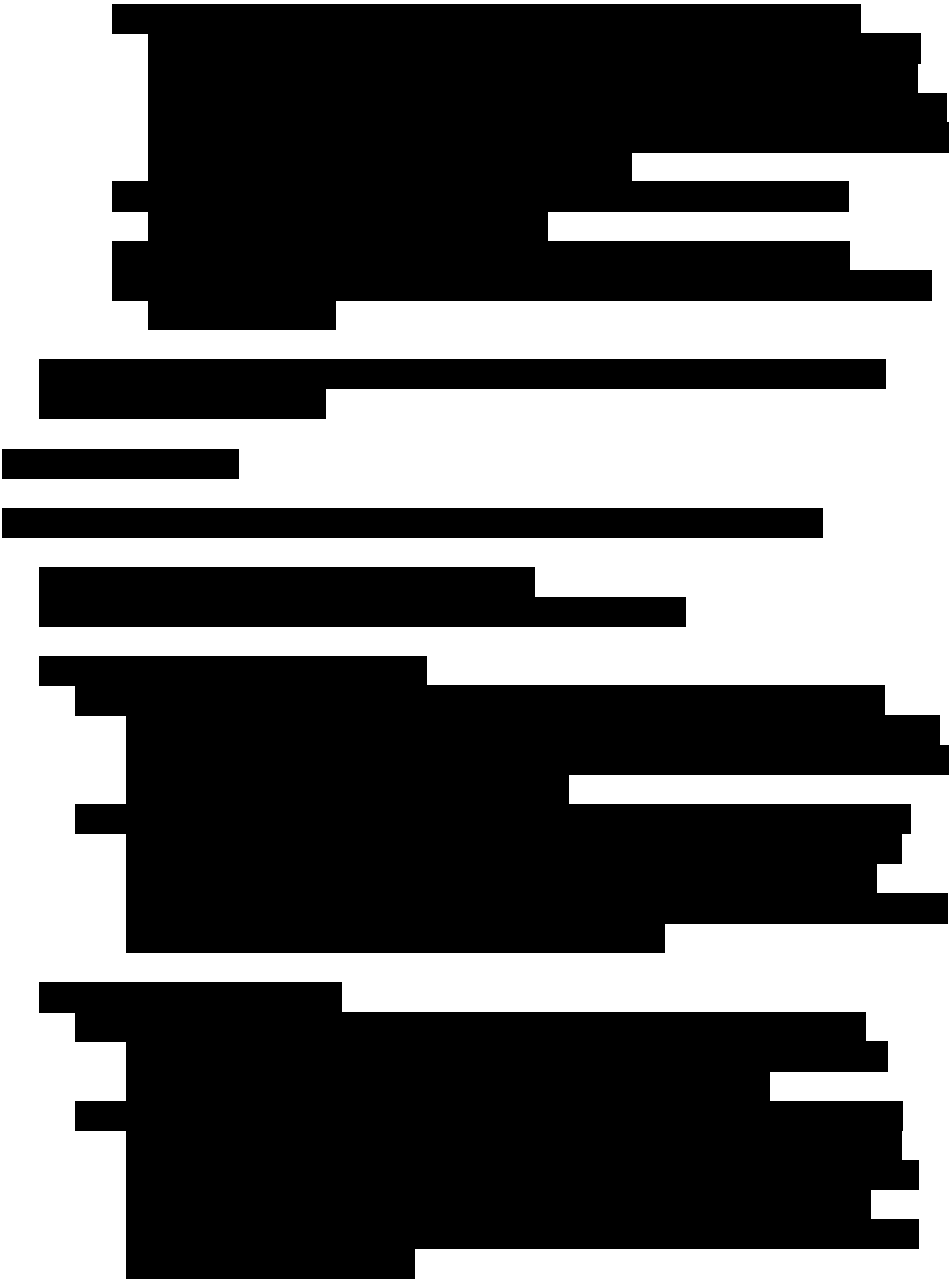

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10. Schedule of Events

	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6* (Month 3)	*Visit 7* (Month 6)
Procedures	**Screening#**	**Treatment 1#**	**Treatment 2**	**Treatment 3**	**Treatment 4**	**Follow Up 1**	**Follow Up 2**
Informed Consent	X						
Eligibility Criteria	X						
Demographics	X						
Medical History/ Concomitant Medications	X	X	X	X	X	X	X
Physical Exam	X						
Urine Pregnancy	X						
InMode Treatment		X	X	X	X		
Standard Photographs		X				X	X
Surface area assessment using H2 3D Imaging and Standup Vectra		X				X	X
CGAIS/SGAIS						X	X
Patient Satisfaction Questionnaire						X	X
*Objective Assessments^*		X				X	X
*Non-invasive Skin Tests**		X				X	X
Biopsy		X				X	X
Safety Assessment		X	X	X	X	X	X
Blinded Evaluations							X

Treatment visit activities may be conducted at the Screening Visit
^ Lemperle Wrinkle Assessment Scale, Allergan Fine Line Scale, Allergan Skin Roughness Scale
* TEWL measurement, BTC-2000, and/or high frequency ultrasound images will be taken

11. Assessments

Note that the order of the assessments listed below may be altered from the order indicated in the study visits in order to help study flow, or at the recommendations of the Sponsor or Investigator. Any change in the order of procedures will not compromise study data.

11.1. Assessment of Facial Wrinkling

Assessment of facial wrinkling will be performed at baseline and at 3-months and 6-months post-treatment. Facial wrinkling will be assessed using the Lemperle Wrinkle Assessment Scale[9]. Wrinkling in the following regions- forehead, glabellar folds, periorbital, preauricular areas, cheek, nasolabial folds, upper lip, marionette lines, corners of mouth, chin, and neck- can be assessed according to scale's definitions (See Appendix I).

11.2. Assessment of Fine Lines

Assessment of fine lines will be performed at baseline and at 3-months and 6-months post-treatment. Fine lines will be assessed using the Allergan Fine Line Scales for Facial Fine Lines [11]. Fine lines on the midface/cheeks will be assessed according to the scale's definitions (See Appendix IIa and IIb).

11.3. Allergan Skin Roughness Scale

Assessment of skin roughness will be performed at baseline and at 3-months and 6-months post-treatment. Skin roughness will be assessed using the Allergan Skin Roughness Scale[13]. Skin roughness will be assessed according to the scale's definitions based on descriptions of severity of skin coarseness, crosshatching and elastosis in the midface area (See Appendix IIIa and IIIb).

11.4. Clinician's Global Aesthetic Improvement Scale (CGAIS)

Subjective assessment of aesthetic improvement will be performed at 3-months and 6-months post-treatment (See Appendix IV).

The scale should be completed in two steps:

1 Based on a live assessment of the subject while referring to the subject's pre-treatment photographs of the face and neck, and

2 Based on a comparison of the subject's pre-treatment photographs to the current post-treatment photographs of the face and neck.

11.5. *Subject's Global Aesthetic Improvement Scale (SGAIS)*

Subjective assessment of aesthetic improvement will be performed at 3-months and 6-months post-treatment (See Appendix IV).

11.6. *Patient Satisfaction Questionnaire*

Subjective assessment of patient satisfaction will be performed at 3-months and 6-months post-treatment (See Appendix V).

11.7. Imaging Procedures

Prior to photography procedures, clinic personnel will ensure that subjects have a clean face and neck with no makeup as described in the study procedures. Subjects will remove any jewelry from the area(s) to be photographed and equilibrate for at least 15 minutes to ambient conditions within the clinic before any photographs are taken. Subjects will be provided with a headband or hair tie to keep hair away from the face.

Subjects will be instructed to adopt neutral, non-smiling expressions with their eyes gently closed for VISIA. Subjects will be carefully positioned for each photograph, directly facing the camera for the center view and turned at a 45° angle for the right and left side views.

1 *VISIA Complexion Analysis*
Digital images will be taken of each applicable subject with fine lines and wrinkles on the face using the VISIA Complexion Analysis System at baseline, 3-months post-treatment, and 6-months post-treatment. Each subject will have a total of 3 full-face images taken (right side, left side, and center view) using the following lighting conditions:
Standard lighting 1: visible (bright)
Standard lighting 2: visible (flat)
Cross-polarized:
UV-NF

2 *NIKON D7100*
Standard, close-up and cross-polarized photography of the face and neck will be utilized for evaluation of fine lines and wrinkles. These photographs will be taken utilizing the Nikon D7100 at baseline, 3-months post-treatment, and 6-months post-treatment.

11.8. Noninvasive Procedures

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 BTC 2000 will be used to measure skin laxity, viscoelastic deformation, stiffness, energy absorption, elasticity, and deformation values of skin. All procedures will be performed on the submental area.

11.9. Skin Biopsies

Two 0.33 mm punch biopsies will be taken from the cheek adjacent to the lateral upper lip at Visit 2, Visit 6 and Visit 7. Prior to biopsy the area will be cleaned with alcohol and a local numbing agent, 0.5%-1% Lidocaine with epinephrine, will be used to anesthetize the area being biopsied. If bleeding is present, pressure will be held on the biopsy site until bleeding stops. Immediately after collection, biopsies for histology and gene expression will be put in 4% PFA and RNA-Later solution, respectively. Biopsies will be stored in a cooler for transfer to the Plastic Surgery Research Lab at UTSW for molecular analysis.

11.10. Blinded Evaluation

Blinded evaluation will be performed by three qualified, non-treating clinicians to determine if the InMode Morpheus8 System is effective in improving the appearance of facial and neck skin quality and dermal lines.

At study conclusion, the Principal Investigator will select three blinded, physician evaluators to assess photos of subjects taken pre- and post-treatment. The evaluators will be trained

by the PI or research team member on the grading scales in order to independently review photographs for each subject. The evaluators will be blinded to subject information and will only know that the study consisted of multiple treatment visits and follow up visits at 3 months and 6 months. They will be provided a set of photos taken at three different visits – pre-treatment, 3 month post-treatment and 6 month post-treatment – in a randomized and unidentifiable order. No information will be provided that may allow them to determine the baseline from follow up imaging. Evaluators will be asked to assess the sets of pictures using the Lemperle Wrinkle, Allergan Fine Lines and Allergan Skin Roughness scales. After completion of the scales, the raters will be unblinded and asked to complete the Clinical Global Aesthetics Improved Scale (CGAIS).

The source documents will be prepared and distributed to the blinded evaluators by a member of the study staff. A decreased score for each assessment will indicate an improvement for the indicated parameters.

12. 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 transepidermal water loss assessments, high resolution ultrasonography, BTC 2000 measurements, biopsy 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.

13. 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

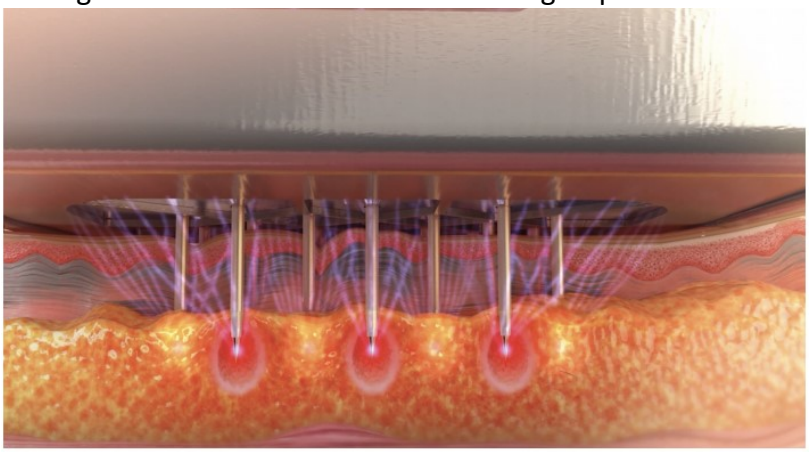
14. Device Description

The InMode Morpheus8 System is a minimally invasive bipolar radiofrequency (RF) microneedling device FDA-cleared for full-body adipose tissue remodeling. The fractional RF device, with adjustable penetration depth and energy delivery, contains 12-24 coated needles. During treatment, these needles penetrate and deliver thermal energy into the subdermal tissue, leading to coagulation of fat and contraction of the reticular dermis and surrounding connective tissue. Additionally, it is theorized that the thermal injury caused by the RF energy initiates the wound healing process, stimulating neocollagenesis, elastogenesis, and angiogenesis.

Image 1. InMode Morpheus8 System

Image 2. Morpheus8 Radiofrequency Microneedling Device

Image 3. Illustration of RF Microneedling Depth and Effect



15. 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, aftereffects 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)

1. 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.

2. 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.

3. The DUB Skin Scanner, a high-resolution ultrasound, will be used to assess skin thickness, epidermal thickness, and skin density. The standard time for DUB should take approximately 5 minutes.

All these tests are considered noninvasive, and no risks are anticipated.

16. Potential Benefits

Subjects may benefit by having an overall improvement in quality and texture of the skin as well as the presence of dermal lines of the lower face. There may be a benefit to the medical community by demonstrating the safety and effectiveness of a new technology in the management of skin quality of the lower face and jawline as well in the treatment of dermal lines. 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.

17. Adverse Events

17.1. 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

17.2. 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)).

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22. Appendix

I. Lemperle Wrinkle Assessment Scale[9]

Classification of Facial Wrinkles

Facial Wrinkle	Class	Description
Horizontal forehead lines Glabellar frown lines Periorbital lines Preauricular lines Cheek lines Nasolabial folds Radial upper lip lines Radial lower lip lines Corner of the mouth lines Marionette lines Labiomental crease Horizontal neck folds	0 1 2 3 4 5	No wrinkles Just perceptible wrinkle Shallow wrinkles Moderately deep wrinkle Deep wrinkle, well-defined edges Very deep wrinkle, redundant fold

II. Allergan Fine Lines Scale[11]

a.

TABLE 1. Descriptors for the Allergan Fine Lines Scale

Grade	*Term*	*Descriptor*
0	None	No fine lines
1	Minimal	1–2 superficial lines
2	Moderate	3–5 superficial lines
3	Severe	Greater than 5 superficial lines; no crosshatching
4	Diffuse	Diffuse superficial lines; crosshatching

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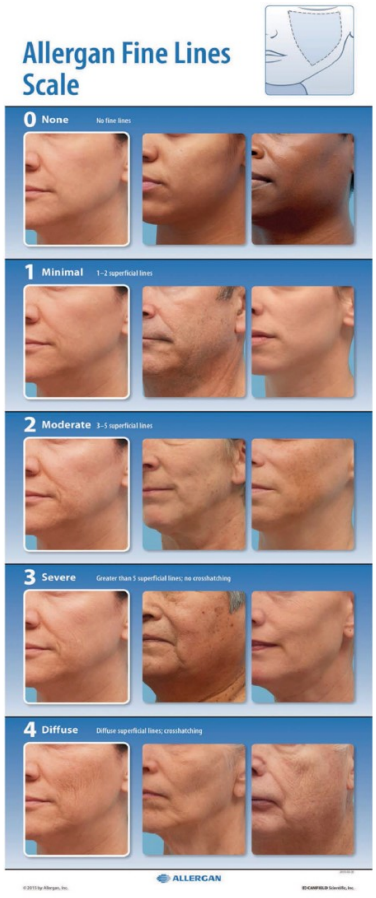


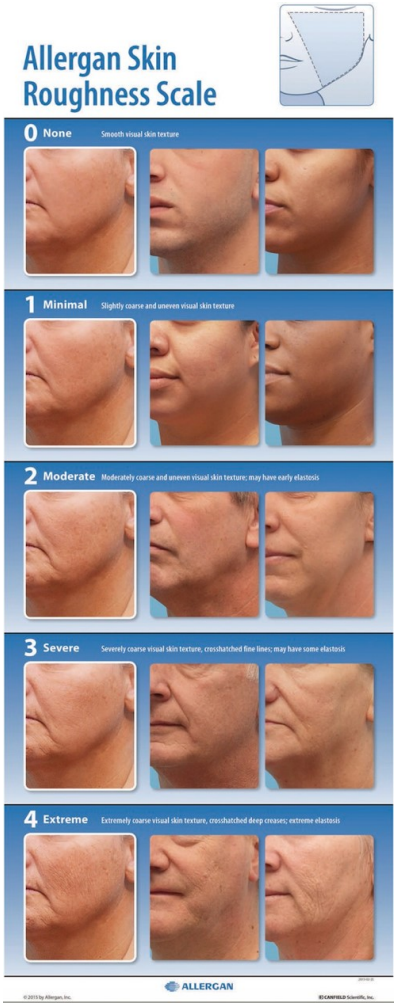
III. Allergan Skin Roughness Scale for Evaluation of Facial Skin Texture[13]

a.

TABLE 1. Descriptors for the Allergan Skin Roughness Scale

Grade	*Term*	*Descriptor*
0	None	Smooth visual skin texture
1	Minimal	Slightly coarse and uneven visual skin texture
2	Moderate	Moderately coarse and uneven visual skin texture; may have early elastosis
3	Severe	Severely coarse visual skin texture, crosshatched fine lines; may have some elastosis
4	Extreme	Extremely coarse visual skin texture, crosshatched deep creases; extreme elastosis

b.



IV. Global Aesthetic Improvement Scale (GAIS)

Rating	Description
1	**Very Much Improved:** Optimal cosmetic result in this subject.
2	**Much Improved:** Marked improvement in appearance from 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.

V. Patient Satisfaction Questionnaire

PATIENT SATISFACTION QUESTIONNAIRE

PLEASE HAVE THE SUBJECT COMPLETE THIS ASSESSMENT WHILE REFERRING TO BASELINE PHOTOS.

COMPARE HOW YOUR FACE CURRENTLY LOOKS WITH YOUR PRE-TREATMENT PHOTOS

Please indicate what you think about how the treated areas of your fine lines and wrinkles look today. Look in the mirror at the treated area on both sides of your face and compare to the photos taken of both sides of your face prior to your study treatment.

1. Do you notice any improvement in how your fine lines and wrinkles look in the treated area?

YES

- ☐ Reduction in the number of fine lines and wrinkles
- ☐ Reduction in the size of fine lines and wrinkles
- ☐ Reduction in pore size
- ☐ Clearer skin
- ☐ Smoother skin texture
- ☐ More even skin tone (color)

Other:

- ☐ NO

2. How would you characterize your satisfaction with the treatment?

- ☐ Extremely Satisfied
- ☐ Satisfied
- ☐ Slightly Satisfied
- ☐ Neither Satisfied or Dissatisfied
- ☐ Slightly Dissatisfied
- ☐ Dissatisfied
- ☐ Very Dissatisfied

3. Would you recommend this treatment to your friends and family members *(check one)*?

YES NO

Thank you for completing this questionnaire.

Subject Initials: _____ Date: _____ (MM/DD/YYYY)