Official Title: Comparison of Fractional Erbium-Doped 1,550-nm Laser and a Bipolar Fractional Radiofrequency Microneedle Device for the Treatment of Atrophic Acne Scars in Ethnic Skin: A Randomized Split-Face Controlled Pilot Study

NCT number: NCT03380845

Document Date: 1/31/2018

Detailed Protocol
1/31/2018

I. Background and Significance

Acne is a highly prevalent disease and post-acne scaring has shown to have detrimental effects on a person's physical, mental, and social well-being.[1] Acne scars can be divided in general categories of hypertrophic or keloid scars, atrophic scars (icepick, rolling, boxcar), and pigmentation alterations (redness, hypo and hyper-pigmentation). This study will focus on treatment of moderate to severe grades of atrophic acne scarring. Our aim is to compare the efficacy and safety of a erbium-doped 1,550-nm non-ablative fractional laser and a bipolar fractional radiofrequency microneedle device for the treatment of atrophic acne scars in ethnic skin (Fitzpatrick Skin Phototypes III-VI) by performing a split-face randomized controlled trial.

Skin type	Typical Features	Tanning ability
I	Pale white skin, blue/green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Both devices in this study are already FDA approved treatment modalities for acne scarring.

<u>History of erbium-doped 1,550-nm non-ablative fractional laser (Fraxel® Restore Laser System, Solta Medical, Inc., Hayward, CA):</u>

Non-ablative fractional lasers work via the theory of fractional photothermolysis, which creates hundreds to thousands of microscopic thermal zones (MTZs), or columns of thermally injured skin, while sparing the surrounding tissue. The pixilated nature of treatment and the functionally unimpaired stratum corneum allow for rapid tissue healing and allows for safer treatments of our patients.[2] Mechanistically, fractional photothermolysis allows controlled amounts of high energy to be delivered deep within the dermis resulting in collagenolysis and neocollagenesis, which smoothes the textural abnormalities of acne scarring.

Multiple published studies have demonstrated that erbium-doped 1,550-nm non-ablative fractional laser ("**NAFL"**) can be successfully utilized in the treatment of all forms of atrophic acne scarring – ice-pick, boxcar, and rolling scars – with a very favorable safety profile in all skin types, and thus, has been cleared by Food and Drug Administration (FDA) for that particular indication.[3-6] According to the manufacture manual (reference attached in the "Documents and Attachments" section), NAFL is indicated for "use in skin resurfacing procedures as well as treatment of acne scars, surgical scars, lentigos (age spots), solar lentigos (sun spots), actinic keratosis, and melasma."

History of the fractional radiofrequency microneedle device (Fractora; Invasix Ltd./InMode MD Ltd., Israel):

Fractional radiofrequency is not a laser. Instead, these devices use an array of electrodes that allows for zones of thermal wounds to be created between areas of unaffected zones, thus stimulating dermal remodeling and allowing for a supply of reservoir cells to promote healing.[7] Variations of fractional radiofrequency exist that employ microneedles to deliver electrical current to a particular depth within the dermis that decreases damage to the epidermis. These fractional radiofrequency microneedle devices provide an alternative to conventional methods of acne-scar treatment (such as NAFL). Great interest has been culminating over the recent years for the use of such devices in acne scars due to the absence of light scattering and the absence of chromophore-specific targets traditionally needed with laser treatments. As melanin is not a target, it is felt to have a higher safety profile in darker skin phototypes.[8,9]
A recent study investigated the safety and efficacy of a specific bipolar fractional radiofrequency microneedle device (Fractora; Invasix Ltd./InMode MD Ltd., Israel) for acne and acne scarring.[10] In this study, Hellman reported on 8 patients with acne scars and noted that all patients (regardless of their skin phototypes) had improvement in their active acne and acne scars after 4 treatments and a 1 month, on average follow-up period. The treatment was well tolerated without any side-effects. Skin biopsies from this study showed reduction in scar depth and new collagen formation with an increase in elastic fibers and adnexal structures noted. In a follow-up report, Hellman[11] showed that 4 out of 8 patients who were in the original study returned for a long term follow-up from 1 to 2 years, that showed ongoing clinical improvements in these patients. This specific bipolar fractional radiofrequency microneedle ("**FRM")** device has been FDA-approved for acne scars and skin rejuvenation.
To this date the efficacy and safety of 1,550-nm fractionated photothermolysis system has not been compared to a fractional radiofrequency microneedle device for atrophic acne scars in ethnic skin in a randomized split-face controlled trial.[12] A major advantage of a split-face self-controlled design would be to minimize any confounding factors. Laser resurfacing has been well studied and is widely used in individuals with fair skin - Fitzpatrick skin phototypes (SPT) I to II. However, there is a paucity of published studies involving individuals with darker skin types (SPT III–VI)—a population that has a higher risk of laser-associated dyspigmentation.

Thus, we would like to compare these two devices (NAFL vs FRM) in the treatment of acne scarring in Fitzpatrick skin phototypes III-VI by performing a split faced randomized trial with

three treatments each spaced 4 weeks apart. Photographs will be taken prior to and after each treatment as well as after final follow up. Blinded reviewers will perform photographic review to evaluate for efficacy and safety.

II. Specific Aims

The hypothesis of this study is that both erbium-doped 1,550-nm non-ablative fractional laser and the bipolar fractional radiofrequency microneedle device are equally effective for the treatment of atrophic acne scars in ethnic skin (SPT III-VI). However, the bipolar fractional radiofrequency microneedle device has less adverse effects than erbium-doped 1,550-nm non-ablative fractional laser due to the absence of scattering and the absence of chromophore-specific targets - predominantly melanin - traditionally needed with laser treatments; hence the fractional radiofrequency microneedle device will have a higher safety profile in darker skin types .

Objective: To compare efficacy and safety of a erbium-doped 1,550-nm non-ablative fractional laser and a bipolar fractional radiofrequency microneedle device for the treatment of atrophic acne scars in ethnic skin (SPT III-VI) by performing a split-face randomized controlled trial.

Primary Endpoint: Improvement in acne scarring will be measured by two blinded evaluators both by in-person assessments and by photographic review (digital photography will be used under standardized conditions). A quartile grading scale (1 = 1% to 25%, 2 =26% to 50%, 3 =51% to 75%, 4 = >76% improvement) will be used to measure acne scar improvement.

Exploratory Objective: Comparing side effects of the different lasers.

Exploratory Endpoint: measure side effects by patient reported adverse events and blinded physician assessment of adverse effects on follow up visits 4 weeks after each treatment as well as at final follow up 3 months after last treatment. Wound healing will be graded on a 2-point scale (0=appropriate, 1=non-appropriate). Parameters, including erythema, edema, blistering, crusting, scarring, hypopigmentation, and hyperpigmentation, will be graded on a 4-point scale (0 = absent, 1= mild, 2 = moderate, and 3 = severe). Patients will also be evaluated the intensity of pain during each treatment session using a visual analogue scale (0 = absence of pain, 10 = most-severe pain). Mild discomfort, erythema, and edema lasting 4-7 days is expected and usual side effects for both of these treatment modalities. Unexpected adverse events may include blistering, hypopigmentation, hyperpigmentation, severe discomfort, bleeding, erosions, ulcers, scabbing, scarring.

III. Subject Selection

Inclusion criteria: Men and women with Fitzpatrick skin types III through VI and facial acne scarring of grades III-IV (moderate to severe – see grading chart below) will be enrolled.

Both sides of the participants' face should have similar amount and severity of acne scarring. Participants will be over 18 years old.

Grades of Post Acne Scarring	Level of disease	Clinical features
1	Macular	These scars can be erythematous, hyper- or hypopigmented flat marks. They do not represent a problem of contour like other scar grades but of color.
2	Mild	Mild atrophy or hypertrophy scars that may not be obvious at social distances of 50 cm or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in men or normal body hair if extrafacial.
3	Moderate	Moderate atrophic or hypertrophic scarring that is obvious at social distances of 50 cm or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extrafacial, but is still able to be flattened by manual stretching of the skin (if atrophic).
4	Severe	Severe atrophic or hypertrophic scarring that is evident at social distances greater than 50 cm and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extrafacial and is not able to be flattened by manual stretching of the skin.

Exclusion criteria: Patients have to be overall healthy without a history of keloidal scarring, localized or active infection in the treatment region, immunodeficiency disorders, porphyria or light sensitivity, and connective tissue disorders. Per PI discretion, any serious medical condition that may interfere with the study. In addition, pregnant or nursing women, patients who have been taking isotretinoin for a period of 6 months before treatment, and patients who have received any cosmetic treatment (lasers, dermabrasion, chemical peels, etc) in the previous 6 months will be excluded. Also, patients with renal disease and any allergies to Lidocaine, Tetracaine, or Valtrex will be excluded.

Recruitment/Participant Identification Process: Patients recruited will mostly be current patients of MGH Department of Dermatology. Providers in and outside of our institution regularly send patients to be considered for studies and these patients will be pre-screened by study personnel (coordinators and investigators). We will send out an email to all current dermatologists within the department asking for referrals to this study. If they have patients with acne scarring who are interested in participating in this study, they will refer the patients to the study by providing the PI and sub-investigator with patient's name and DOB. There will also be a flyer about the study available in the MGH Dermatology clinics. The patient's medical record will then be reviewed by the PI or sub-investigator in order to determine if patient meets inclusion criteria. Possible participants will be called by the PI or sub-investigator to invite them to an introductory visit during which they will be given details about the study and their eligibility will be determined by the PI. If the patients are interested in participating in the study at this visit, they will be asked to sign the consent form.

The subjects may be enrolled among the PI or sub-investigators own patients. In those instances, we will avoid the possibility of patients feeling obligated to participate by offering patients the opportunity to take home the consent form and call back to speak with Dr. Sandeep Saluja if they want further information about the study or wish to participate.

IV. Subject Enrollment

Informed Consent Procedure:

Location: MGH Dermatology, Laser and Cosmetic Center at 50 Staniford St, Stuire#250, Boston, MA - 02114. This clinic has private patient rooms where consent will be obtained.

Screening visit and Consent Process: For screening, subjects who meet inclusion/exclusion criteria will be asked to read and sign the informed consent document. The consent process is conducted and completed prior to conducting any study procedures. Typically, a summary of the study is presented by the study staff to patients who are interested and appear to be eligible for the study. There is no mandatory waiting period, but sometimes patients are informed of the study during clinic or over the phone, and an appointment is then scheduled in the dermatology clinic to conduct the formal consent process.

During this appointment, which is conducted in the clinic in a private and quiet study clinic room, the study staff will present an overview of the study. They are given the Informed Consent Form (ICF) and asked to read it. We allow them to read it in private and we remain immediately available (outside the door of the clinic room) and ask them to alert us when they are finished. We will step in to monitor their progress periodically. The ICF is then reviewed with the study staff who will ensure that the patients questions are answered. The PI is also available to answer questions. If the patient feels that they have had ample opportunity to review the ICF, understand the study, and want to participate, then the ICF is signed and dated by both parties.

At any point in the process, if the participant wants more time to consider the study, the ICF, or other standard treatment options, that participant is encouraged to take the ICF home to discuss with family and/or friends. Patients who sign the informed consent will be enrolled in the study.

Once the patient has been consented, patient will be randomly assigned (via coin flip by study coordinator) to have one side of their face treated with a non-ablative fractional 1550 nm erbium-doped fiber laser (Fraxel® DUAL Laser System, Solta Medical, Inc., Hayward, CA), while the other side of the face treated with a fractional radiofrequency microneedle device (Fractora; Invasix Ltd./InMode MD Ltd., Israel). All laser treatments were performed by the same dermatologist.

V. Study Procedures

Screening Visit

. Participants will be screened based on inclusion and exclusion criteria, Fitzpatrick skin type will be determined, and full details of study are explained. If participation is desired, patients will sign the consent form at this time. For patients with documented histories of herpes labials (cold sores), antiviral prophylaxis (oral valacyclovir 500 mg twice a day for 5 days, starting the day before each laser treatment) will be prescribed. All patients will be instructed to apply Lidocaine 7%, Tetracaine 7% ointment to the entire face one hour prior to treatment.

Treatment phase

Week 0:

- Baseline full face photographs taken
- Blinded evaluators will assess the patient's photographs. To ensure blinded evaluations, the same unblinded investigator will perform all the laser treatments, whereas efficacy evaluations will be performed by two trained and experienced evaluators who are blinded to the treatment assignment.
- Subjects will apply topical anesthetic (Lidocaine 7%/ Tetracaine 7% Ointment) to the entire face one hour prior to the procedure.
- Treatment #1 to both sides of the face (entire R and L sides of the face are each treated with one of the two study devices based on randomization). The participant will be blinded to which side of face receives which laser or device.
- Review post-laser standard-of-care skin care with participants (sun avoidance, sunscreen use, moisturizer use) and provide patient with post-procedure hand-out.
- Complete VAS pain assessment (see documents attached) ((0 = absence of pain, 10 = most-severe pain)
- Prescription given for oral valacyclovir per protocol

Week 4:

- Full face photographs taken
- Blinded evaluators will assess the patient's photographs for any adverse events.
- Review and evaluation of any adverse events from previous session and complete assessment of adverse events form (see attached documents)
- Subjects will apply topical anesthetic (Lidocaine 7%/ Tetracaine 7% Ointment) to the entire face one hour prior to the procedures.
- Treatment #2 to both sides of the face (entire R and L sides of the face are each treated with one of the two study devices based on randomization). The participant will be blinded to which side of face receives which laser or device.
- Review post-laser standard-of-care skin care with participants (sun avoidance, sunscreen use, moisturizer use) and provide patient with post-procedure hand-out.

- Complete VAS pain assessment (see documents attached) ((0 = absence of pain, 10 = most-severe pain)
- Prescription given for oral valacyclovir per protocol

Week 8:

- Full face photographs taken
- Blinded evaluators will assess the patient's photographs for any adverse events.
- Review and evaluation of any adverse events from previous session and complete assessment of adverse events form (see attached documents)
- Subjects will apply topical anesthetic (Lidocaine 7%/ Tetracaine 7% Ointment) to the entire face one hour prior to the procedures.
- Treatment #3 to both sides of the face (entire R and L sides of the face are each treated with one of the two study devices based on randomization). The participant will be blinded to which side of face receives which laser or device.
- Review post-laser standard-of-care skin care with participants (sun avoidance, sunscreen use, moisturizer use) and provide patient with post-procedure hand-out.
- Complete VAS pain assessment (see documents attached) ((0 = absence of pain, 10 = most-severe pain)
- Prescription given for oral valacyclovir per protocol

Week 20:

- Full face photographs taken
- Blinded evaluators will assess the patient's photographs for any adverse events
- Complete physician assessment of improvement of acne scarring (see documents attached) by two blinded evaluators.
- Participants fill out final satisfaction survey (see documents attached)

End of Study

Post Study: There is a chance that acne scarring on one side of your face would significantly improve more than the other side (meaning that one laser was much more effective than the other). If this happens, the principal investigator (Dr. Sandy Tsao) will talk with you about using the laser that you feel worked the best on the other side after the study is over. If you did choose to do additional treatments after the study for balancing out the treatments, you will have to pay for these additional treatments ($500 per laser treatment), since this is a cosmetic treatment and insurance will not pay for it.

VI. Biostatistical Analysis

Statistical Methods

The two devices will be randomized to the left and right side of the same patient. To compare the devices, a paired sample t-test will be used.

Sample Size Determination

It would be important to know if one device is a whole category better than the other device, as a one category difference would be noticeable to the patient, but a smaller difference might not be noticeable. The acne scar improvement scale has 4 categories (0 = <25% improvement, 1= 25 to 50%, 2 = 51 to 75%, 3 = >75%). Assuming the standard deviation is one-half of the mean, with means of 1 and 2, to have **90% power** to a detect a pairwise difference (left and right side of the face) of mean±SD, 1±0.5 vs 2±1, with a correlation of r=0.5 between the two sides of face, using an alpha 0.05 two-sided comparison, a sample size of **n=20 patients** is required.

VII. Risks and Discomforts

Risks of the both types of devices used are similar and include redness, swelling, hyperpigmentation (temporary darkening of the skin), hypopigmentation (temporary lightening of the skin), scarring, crusting, bacterial skin infection, cold sore reactivation, and blistering of the skin. Even though topical numbing cream will be applied for one hour prior to treatment, participants will likely feel some discomfort or pain during the procedure.

Valtrex (anti-viral medication for patient with history of herpes labialis/cold sores) taken one day prior to procedure for a total of 5 days has the following possible side effects: nausea, headache, vomiting, dizziness, abdominal pain, rash.

There is a chance that acne scarring on one side of the face would show greater improvement than the other side (meaning that one laser was more effective than the other).

We will offer patient care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill patient's insurance company or other third parties, if appropriate, for the care the patient get for the injury. We will try to have these costs paid for, but the patient may be responsible for some of them. For example, if the care is billed to patient's insurer, the patient will be responsible for payment of any deductibles and co-payments required by the patient's insurer.

VIII. **Potential Benefits**

Acne scarring can be disfiguring and can greatly impact one's social interactions and psychological wellbeing. This study helps improve our understanding of efficacy and safety of two lasers in treatment of acne scarring in darker skin phototypes. Patients will receive these FDA approved, treatments at no cost for their acne scarring that is likely to be very effective based on current data supporting efficacy of the two devices used in this study. Laser and energy-based treatments are the most effective way of minimizing acne scarring, however, such treatments are very expensive, this study would provide treatment at no cost to participants.

Patients who enroll may also feel a sense of contributing to the benefit of others by participating in medical research.

IX. **Monitoring and Quality Assurance**

Immediate side effects from treatments will be monitored and recorded, such as redness, edema, blistering, hyperpigmentation, hypopigmentation, pain. Risks of the both types of lasers/devices used are similar and include redness, swelling, hyperpigmentation (temporary darkening of skin), hypopigmentation (temporary lightening of skin), scarring, crusting, bacterial skin infection, cold sore reactivation, and blistering of the skin.

Safety of devices used will be monitored with attention to above side effects. Study progress for each patient will be recorded at each visit.

There may be other unforeseeable risks to participants from the laser treatments that are currently unknown. Should these risks become known, patients will be informed about such risks, and would be given the option to decide whether they want to continue with the study or they would like to withdraw.

Study could be stopped or modified if there are severe or irreversible unforseeable side effects of the two laser treatments used.
The PI will review events and data for each participant on monthly basis during their monthly visits.
The photographs taken during the study may be used in the future for presentations or publications by the study doctor. The photos will not be identifiable in presentations or publications as we will be masking the eyes in the photographs.

X. **References**

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