Investigating the efficacy of a fractionated 1927 nm laser for diffuse dyspigmentation and actinic changes in Fitzpatrick Skin Phototypes V and VI

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Sponsor	University of Texas Southwestern Medical Center Department of Plastic Surgery
Testing and Administrative Facility	University of Texas Southwestern Medical Center 1801 Inwood Road Dallas, TX 75390-9132
Principle Investigators	Jeffrey Kenkel, MD
Sub-Investigators	Vidhya Nadarajan
Study Coordinator	Jennifer Barillas
Additional Study Personnel	Deborah Noble

Background

Hyperpigmentation is a common disorder resulting from increased activity of melanocytes in response to inflammation or injury and is particularly prevalent in patients with skin of color [1]. PIH can result from a wide range of intrinsic insults such as acne or dermatitis, or extrinsic insults such chemical exfoliants or UVA/UVB exposure. As a result, PIH is a common cosmetic concern in patients with Fitzpatrick Skin Phototypes III-VI [2].

It is theorized that the increased presence of melanosomes in darker skin types (Fitzpatrick Skin Phototypes III-VI) increases susceptibility to hyperpigmentation, a hypothesis supported by the increased prevalence of PIH in Hispanic and Black patients, with one study showing it to be the second most common dermatologic diagnosis among this population [3]. Treatment options for hyperpigmentation in skin of color include first-line therapies such as sun-protective behaviors, treatment of underlying disorder, topicals such as hydroquinone and retinoids, and second-line therapies such as superficial chemical peels and low-fluence laser therapy [4-6].

Since their approval by the Food and Drug Administration in 2011, non-ablative, fractional laser treatment has emerged as a viable therapeutic modality for facial rejuvenation in patients with skin of color, using low-energy, low-density settings to reduce the risk of iatrogenic dyspigmentation. Recently, non-ablative fractional lasers of 1927 nanometers have been used successfully in patients with skin of color to treat acne scarring, facial hyperpigmentation and melasma [7-10]. For individuals with skin of color, adjunctive regimens have emerged to minimize the risk of iatrogenic, postprocedural hyperpigmentation. Popular adjuncts include prescribing several weeks of retinol, 2-4% hydroquinone, and/or corticosteroids, up to 1 month preceding the study and following treatment, and epidermal cooling or topical corticosteroid post-treatment to minimize heat exposure and inflammation. The literature suggests routine and varied use of these topical regimens in this population in both clinical research and clinical practice [11].

While some trials have leveraged fractionated, non-ablative 1927nm for the treatment of dyschromia or acne scarring among SPT I-V, to our knowledge, there is a paucity of studies that quantify hyperpigmentation or melasma response among patients with Fitzpatrick Skin Phototype VI. In this study, we sought to quantify efficacy of this laser in a population comprised of patients of Fitzpatrick Skin Phototypes V and VI.

Purpose and Objective

This single-center observational study is being conducted over the course of 7-12 months.

> Part 1 will consist of one Initial Screening Visit (-42 to -28 Days) and use of the topical regimen will be started for at least 30 days before the treatment series are scheduled. Following the subjects consistent use of topical medications three treatments (Day 0, Day 30, Day 60) will be scheduled followed by 1-month and 3-month follow-up visits (Day 90 and Day 150).
>
> Part 2 will consist of a Screening Visit followed by a 30-day washout period of any prescription grade topical regimen on the face. Following the washout period subjects will be scheduled for three 1927 treatments (Day 0, Day 30 and Day 60). After each treatment subjects will be asked to apply Clobetasol twice a day for four days and apply ice to the treated area four times a day. Subjects will return to for follow up visits at 1-month and 3-month (Day 90 and Day 150).

The primary objective of this study is to quantify the hyperpigmentation response after 1927nm non-ablative fractionated laser therapy in subjects with Fitzpatrick Skin Phototypes V and VI and explore an effective, adjunctive pre- and post-procedural topical regimen to prevent iatrogenic dyspigmentation or scarring in this population.

We will explore this question with a non-blinded, observational study at a single center.

Clinical Study Design

Overview of Clinical Study

This is a single-site, prospective observational, non-randomized, non-controlled pilot study being conducted at the University of Texas Southwestern Medical Center at Dallas in the Department of Plastic Surgery. The study is designed to follow changes in hyperpigmentation in approximately 20 qualified and consenting subjects receiving f1927 hyperpigmentation standard care treatment using VISIA and/or VISIA-CR. The Principal Investigators (PIs) have been selected based on their expertise, qualifications, subject access, prior clinical research, facilities, and interest in this field of research. Subjects will be recruited through IRB-approved advertisements or identified by Dr. Jeffrey Kenkel at the University of Texas Southwestern Medical Center. Subjects will be numbered sequentially in the order in which they initially qualify for entry into the study. Subjects who continue the study from Part 1 will retain their subject number through Part 2. Any new subjects recruited for Part 2 will be numbered sequentially in the order they qualify for entry into the study.

Part 1:

Study doctors will explain and prescribe subjects a standard of care topical regimen 4-6 weeks prior to f1927 treatments.

Part 2:

Subjects will be asked to complete a month-long washout period of all topical regimens prior to f1927 treatments. Following each treatment subjects will be asked to apply Clobetasol twice a day for four days and apply ice to the treated areas four times a day.

Clinical Treatment and Assessments

Participating subjects will receive treatment using an FDA-approved f1927 laser, currently considered a standard of care treatment for melasma and hyperpigmentation in Fitzpatrick Skin Phototypes I-VI. Subjects will undergo treatments over the entire face. Subjects' response to effects of the f1927 treatment will be quantified based on evaluation of standard and clinical photography and H2 3D Imaging System images taken pre- and post-procedure. These photos will be identifiable full-face photos, and subjects will be adequately informed and consent of such. In addition to the two standard care photographic assessments, subjects will also have photos taken using the VISIA and/or VISIA-CR (Canfield Scientific, Fairfield, NJ). A quantitative assessment of the effects of treatment will be performed using VISIA and/or VISIA-CR at 1-month and 3-months post-treatments. Additional assessment will be provided by use of the Skin Hyperpigmentation Index (https://shi.skinimageanalysis.com/ - Inselspital, Freiburgstrasse, Switzerland) [12-15] a web-based software used to quantify hyperpigmentation. Changes in the Skin Hyperpigmentation Index over time will be used to objectively report on subjects' treatment response.

From these procedures, the improvement in diffuse pigmentary changes can be evaluated in comparison to pre-treatment assessments.

Primary Endpoints

1. Quantifying Improvement in overall facial hyperpigmentation in response to laser treatment, by measuring pigmentation at baseline and follow-up visits post-treatment using the VISIA and/or VISIA-CR
2. Changes in Skin Hyperpigmentation Index (SHI) Scores from Baseline to post-treatment visits..

Secondary Endpoints

1. Monitoring incidence, severity, and relatedness of adverse events throughout the study
2. Monitoring the efficacy of pre- and post-treatment regimens with tretinoin and hydroquinone
3. Monitor the efficacy of the pre- and post-treatments with Clobetasol and ice.

Standard of Care Treatment Device

Proprietary Name	Device Description	Regulatory Information
Sciton MOXI	Aesthetic device that utilizes a fractionated laser to initiate resurfacing for the treatment of dyspigmentation and healing of photoaged skin.	Class II 510(K) Number: N/A Regulation Number: 878.4810

Study Population, Screening, and Enrollment

Study Population

The study population in question includes patients ages 18-75 with Fitzpatrick Skin Phototypes V and VI.

Subject Enrollment

Healthy subjects within the study population of interest who will be undergoing fractionated 1927nm laser to treat hyperpigmentation will be recruited for the study through IRB-approved recruitment flyers, emails, and social media posts. Potential subjects will be screened to check if they are acceptable candidates by a designated member of the research team. Additionally, if subjects inquire about the study during an unrelated clinic appointment with Dr. Kenkel, or staff aesthetician, he or she may discuss the study with the potential subject and assess the treatment area.

If a subject is deemed an eligible candidate, Dr. Kenkel will connect the patient with a research coordinator, investigator, or designated member of the research team to answer further questions. Subjects meeting all eligibility requirements will be scheduled for an official screening visit. Candidate subjects will have the study explained to them, will be asked about their willingness to participate in the study, and their willingness to sign an informed consent form.

Informed Consent Form

An IRB-approved informed consent form (ICF) explaining the purpose, design, risks, benefits, and timeline of the study will be given to each candidate subject prior to participation in any study procedures. The candidate subject will be given as much time as needed to read the ICF and will have the opportunity to ask study-related questions and have them answered by a member of the research team. Each participating subject's signed ICF will be retained in the study file and each subject will receive their own signed copy. By signing the consent form, subjects indicate and confirm that they are willing to have their full-face photographed 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 as photographs will be used to both qualitatively and quantitatively assess the treatment outcome and are a critical tool for study evaluation. The candidate subject will be ineligible to participate in this study without a signed ICF.

Subject Identification

Subjects will be assigned a 2-digit Subject Number, which, when used in conjunction with the Clinical Study ID, will uniquely identify each subject participating in the study. The Subject Number will remain unchanged throughout the study and should be used in all references to the individual in this study. No number will be reassigned once the study begins.

Eligibility Criteria

Inclusion Criteria: Part 1 & Part 2

1. Healthy male, female, and non-binary adults between 18 and 75 years of age
2. Fitzpatrick Skin Phototype V and VI
3. Individuals undergoing fractionated 1927nm laser to treat hyperpigmentation in the past 3 months.
4. Individuals willing to withhold aesthetic therapies (excluding those explicitly prescribed by the Investigator as pre-treatment) for the duration of the study
5. Women of childbearing potential who agree to take a urine pregnancy test at the Screening visit or when deemed by Investigator. Women of childbearing potential must have a negative urine pregnancy test and must not be lactating at Screening. Women must be willing and able to use an acceptable method of birth control (see below) during the study. Women will not be considered of childbearing potential if one or more of the following is documented:
    - Postmenopausal for $\geq$ 12 months prior to initiation of the study
    - Without a uterus +/- both ovaries prior to initiation of the study
    - Bilateral tubal ligation $\geq$ 6 months prior to initiation of the study
6. Individuals of childbearing potential who use an acceptable method of contraception for the duration of the study. Acceptable modes of birth control include the following:
    - Established use of hormonal contraception (oral, injectable, implanted, patch or vaginal ring)
    - Barrier methods with spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
    - Intrauterine device (IUD) or intrauterine system (IUS)
    - Surgical sterilization (e.g., vasectomy confirmed to be effective by sperm count check, tubal occlusion, hysterectomy, bilateral salpingectomy/oophorectomy)
    - Abstinence from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal methods are not acceptable forms of contraception.
7. Individuals who can read, speak, write, and understand English and who are willing to provide written informed consent.
8. Individuals willing to sign a photography release.
9. Individuals willing and able to cooperate with all study requirements for the duration of the study

Exclusion Criteria

1. Ages < 18 or > 75 years old
2. Fitzpatrick Skin Phototypes I-IV
3. Known history of allergies or irritant contact dermatitis in response to general skin care products, including Hydroquinone and Retinol
4. Known allergies or irritant contact dermatitis in response to common ingredients of physical sunscreen, including but not limited to Zinc Oxide
5. Known allergies or irritant contact dermatitis to topical anesthetics, including Benzocaine and Tetracaine.
6. Active local or systemic disorders that may affect wound healing or integrity of the integumentary system
7. History of active or inactive systemic granulomatous disease, (e.g., Sarcoidosis, Tuberculosis, Granulomatosis with Polyangiitis, etc.), or connective tissue disorders (e.g., Systemic Lupus Erythematosus, Dermatomyositis, Scleroderma, etc.)
8. Recent history of surgery or significant trauma to the area(s) to be treated
9. Significant scarring (excluding acne scars) in the area(s) to be treated
10. Current or history of hypertrophic scarring or keloid scars
11. Severe or cystic and clinically active acne on the area(s) to be treated
12. Tattoos in the area(s) to be treated

13. Individuals who currently have cancerous or pre-cancerous lesions in the area(s) to be treated and/or have a history of skin cancer
14. Individuals with skin pathology and/or pre-existing dermatologic condition in the treatment area (i.e., psoriasis, rosacea, eczema, seborrheic dermatitis, vitiligo, hyper or hypo-skin pigmentation conditions such as post inflammatory hyperpigmentation) that the Investigator deems inappropriate for participation or could interfere with outcomes of the study.
15. History of chronic drug or alcohol use.
16. Microdermabrasion or glycolic acid treatment to the treatment area(s) within 4 weeks of study participation or who plan on having this treatment during the study.
17. Individuals undergoing concurrent therapy that, in the Investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study devices:
    - Antiplatelet agents/anticoagulants (Coumadin, Heparin, Plavix, chronic NSAID use), and/or
18. Psychiatric drugs that, in the Investigator's opinion, would impair the subject from understanding protocol requirements or understanding and signing consent.
19. Individuals who are pregnant or nursing or those planning on becoming pregnant during the study according to self-report.
20. Immunocompromised individuals or those currently using immunosuppressive medications and/or radiation.
21. Individuals with uncontrolled disease such as asthma, diabetes, hyperthyroidism, medically significant hypertension, or hypothyroidism. Those with multiple health conditions may still be excluded from participation even if conditions are controlled.
22. Individuals with any planned surgeries, overnight hospitalization, and/or invasive medical procedures planned during the study.
23. Individuals who, in the Investigator's opinion, have a history of poor cooperation, unreliability or noncompliance with medical treatment.
24. Individuals who are unable to understand instructions or give informed consent
25. Individuals who have physical or psychological conditions which, in the opinion of the Investigator, makes them unable to complete the study per protocol (e.g., not likely to avoid other cosmetic treatments to area; not likely to stay in study for entire duration due to other commitments; or those with concomitant conditions that may develop symptoms that might confuse or confound study treatments or assessments).
26. Individual who are using hydroquinone and tretinoin (4 wk wash out period necessary before treatment).

Subject Instructions

Part 1:

At subject's initial Screening visits, subjects will discuss the adjunctive topical regimen with their provider and have these prescriptions sent to a pharmacy of their choice. The adjunctive regimen is standard care and is outlined below:

Pre-treatment

1. 4-6weeks of 4% Hydroquinone cream applied twice daily to entire face
2. 4-weeks of Tretinoin 0.1% cream applied nightly to entire face
3. Judicious application of physical sunscreen of ≥SPF 30 at least 15 minutes before sun exposure with reapplication after water exposure.

Post-treatment

Patient should resume use of topical hydroquinone and retinol regimen the same evening as their last laser treatment, as enumerated below:

1. 4 weeks of 4% Hydroquinone cream applied twice daily to entire face
2. 4 weeks of Tretinoin 0.1% cream applied nightly to entire face
3. Judicious application of physical sunscreen of ≥SPF 30 at least 15 minutes before sun exposure with reapplication after water exposure.

Following the final treatment, patients should continue to take their 4% Hydroquinone and Tretinoin 0.1% cream as prescribed through the remainder of the study.

Part 2:

Subjects will be asked to refrain from using any topical prescription medications on their face for at least 4 weeks prior to treatments commencing. Subjects who participated in Part 1 will be eligible for Part 2 if they agree to complete the topical regimen washout period and agree to refrain from any other treatments for the remainder of their trial participation.

Pre-Treatment Instructions:

Subjects will be asked to wash off all skincare products at least 30 minutes prior to each scheduled clinic visit using a cleanser of your choice. If a subject arrives having not removed skincare products, she or he will be required to remove the residual product at the clinic and wait at least 20 minutes prior to procedures.

Post-treatment Instructions:

Immediately post-treatment Clobetasol Propionate 0.05% and ice will be applied to the treated areas for 15-20 minutes. The subject will be instructed to re-apply Clobetasol Propionate 0.05% twice a day and ice the treated area for 15 minutes up to four times a day for four days.

Blistering, bleeding, oozing, strong pain, swelling persisting for more than 24 hours, or signs of infection (e.g., pus, drainage, fever) are cause for immediate concern and you should contact the investigator and/or his designee to be evaluated and potentially treated at no cost to the subject.

Subjects will be asked to avoid extended periods of sun exposure and all use of tanning beds for the duration of the study. Extra care should be taken to wear protective clothing and avoid sun exposure from 10 AM to 4 PM.

Subjects will be encouraged to consistently use face wash, moisturizer, and sunscreen of their choosing. Subjects will be asked to refrain from using any new anti-aging, acne, and acne scar products or devices and beginning the use of any new skincare products or devices other than the assigned test material for the duration of the study.

Study Design

Study Timeline and Procedures

	Study Procedure	Part 1							Part 2					
		Screening	Treatments			Follow Up			Screening	Treatments			Follow Up	
		Visit 1 **Visit 1** Day -42 to -28	**Visit 2** Day 0	Visit 3 **Visit 3** Day 30 (± 3 days)	**Visit 4** Day 60 (± 3 days)	**Visit 5** Day 90 (± 7 days)	**Visit 6ay** 150 Day 150 (± 7 days)	Wash out Period (4-6 weeks)	**Visit 7** Day -30 to -1	**Visit 8** Day 0	**Visit 9** Day 30 (± 3 days)	**Visit 10** Day 60 (± 3 days)	**Visit 11** Day 90 (± 7 days)	**Visit 12** Day 150 (± 7 days)
R	Eligibility Criteria & Informed Consent	•							•					
R	Enrollment Paperwork	•							•					
R S	Medical History & Concomitant Medications	•	•	•	•	•	•		•	•	•	•	•	•
S	Pregnancy Test	•							•					
S	Tretinoin/ 4% Hydroquinone	•	•			•	•							
S	MOXI Treatment		•	•	•					•	•	•		
S	Clobetasol /Ice									•	•	•		
S	Standard Photography	•				•	•		•				•	•
R	Vectra H2 3D Photography	•				•	•		•				•	•
R	VISIA-CR Photography & Skin Imaging Analysis	•				•	•		•				•	•
R	Safety Assessment	•	•	•	•	•	•		•	•	•	•	•	•

R= Research procedure; S=Standard of Care procedure and/or VISIA-CR

Pre-Study Procedures

Prior to the start of the study, potential subjects will be screened for eligibility requirements via chart review on EPIC. Prospective subjects will be informed of study details and study visit instructions as detailed in section 6. An appointment to visit the clinic for an official screening visit will be scheduled if interest is demonstrated. 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 deemed a good candidate, they will be connected to a research coordinator to answer any further questions and provide consent.

Part 1

Visit 1: Screening Visit

Day -42 to -28 Days

The purpose of the study, eligibility criteria, and potential risks will be discussed with the potential subject. All interested candidates will be given an IRB-approved Informed Consent Form (ICF) as detailed in this protocol, with adequate time for review. The Investigator and/or designee will address questions and/or concerns raised by the subject. Those subjects who elect to participate will sign the consent form prior to any study procedures. The subject will receive a signed copy of their ICF and the original will be kept in the study file. Subjects will then be screened to ensure they meet all study criteria.

The following is a complete list of the screening and enrollment activities to be performed:

1. Obtain informed consent and HIPAA authorization.
2. Assign a screening number to candidate subjects that sign the initial paperwork.
3. Collect a brief medical history including current medications, skin type, allergies, major conditions, or illnesses, etc. and assess if subjects meet eligibility criteria.
4. For those that pass eligibility requirements and are females of childbearing potential, perform a urine pregnancy test. If the test is negative or candidate is male, the subject will be enrolled in the study and assigned a subject number.
5. Obtain close-range standard photography as described in section entitled, Assessments. This is standard of care.
6. Obtain photographs and measurements using the Vectra H2 3D Imaging System and VISIA and/or VISIA-CR System as described in section entitled, “Assessment”, for research purposes.
7. Study doctors will call in prescriptions to the subjects preferred pharmacy. This is standard of care.

This visit will take 30-45 minutes.

Visit 2, Visit 3, and Visit 4: Treatment Visits 1-3

Day 0, Day 30, Day 60

A member of the study team will record concomitant medications and will ask subjects if they have experienced any changes in their health since the previous visit. If an adverse event (AE) is reported than the Investigator will be informed, and an AE log will be completed/updated for PI review.

The following activities will be completed before the treatment:

1. The physician or study staff will ask subjects if they have experienced any changes in their health since the previous visit. Changes will be recorded accordingly. If an adverse event (AE) is reported than the Investigator will be informed, and an AE form will be completed.
2. Subjects will acclimate to ambient temperature and humidity conditions for 15 minutes prior to any procedures being done.
3. Obtain close-range standard photography as described in section entitled, “Assessments”. This is standard of care. This will only be completed before their first treatment.

4. Obtain photographs and measurements using the Vectra H2 3D Imaging System and VISIA and/or VISIA-CR as described in section entitled, “Assessment”, for research purposes. This will only be completed before their first treatment.

The procedure will then be performed in our Plastic Surgery clinic following standard of care procedures. A trained staff member will apply a topical triple anesthetic (benzocaine, lidocaine, tetracaine) to anesthetize the areas being treated. After allowing 10 minutes for the anesthetic to take effect, the skin will be cleansed and prepped with antiseptic. A trained staff member will treat the subject’s face with f1927. Treatment settings and parameters will be determined by the provider and will be chosen according to Fitzpatrick skin type and location of the body for which it will be used. Ultimately, 4-6 passes will be performed at the discretion of the treating provider. Post-treatment cooling will be offered at the discretion of the treating provider, depending on clinical need.

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. Expected downtime is minimal after treatment, typically lasting 0-3 days.

These visits will take approximately 1 hour.

Visit 5 and Visit 6: Follow-Up Visits 1 and 2

Day 90, Day 150

At a minimum, all subjects will return for follow-up visits at 1 month (± 7 days) and 3 months (± 7 days) after treatment.

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

1. The physician or study staff will ask subjects if they have experienced any changes in their health since the previous visit. Changes will be recorded accordingly. If an adverse event (AE) is reported than the Investigator will be informed, and an AE form will be completed. This is standard of care.
2. Subjects will acclimate to ambient temperature and humidity conditions for 15 minutes prior to any procedures being done. This is standard of care.
3. The physician or study staff will perform an examination of the skin in the treatment area. This is standard of care.
4. Obtain post-treatment close-range clinical photography as described in section entitled, “Assessments”, for research purposes.
5. Obtain post-treatment photographs using the Vectra H2 3D Imaging System, as described in section entitled, “Assessments”, for research purposes
6. Obtain post-treatment photographs VISIA and/or VISIA-CR as described in section entitled, “Assessments”, for research purposes.

These visits will take about 30 minutes.

Part 2

Visit 1: Screening Visit

Day -42 to -28 Days

The purpose of the study, eligibility criteria, and potential risks will be discussed with the potential subject. All interested candidates will be given an IRB-approved Informed Consent Form (ICF) as detailed in this protocol, with adequate time for review. The Investigator and/or designee will address questions and/or concerns raised by the subject. Those subjects who elect to participate will sign the consent form prior to any study procedures. The subject will receive a

signed copy of their ICF and the original will be kept in the study file. Subjects will then be screened to ensure they meet all study criteria.

The following is a complete list of the screening and enrollment activities to be performed:

8. Obtain informed consent and HIPAA authorization.
9. Assign a screening number to candidate subjects that sign the initial paperwork. If subject is continuing the study from Part 1 they will use the same screening number assigned.
10. If not already collected, collect a brief medical history including current medications, skin type, allergies, major conditions, or illnesses, etc. and assess if subjects meet eligibility criteria.
11. For those that pass eligibility requirements and are females of childbearing potential, perform a urine pregnancy test. If the test is negative or candidate is male, the subject will be enrolled in the study.
12. Obtain close-range standard photography as described in section entitled, Assessments. This is standard of care.
13. Obtain photographs and measurements using the Vectra H2 3D Imaging System and VISIA and/or VISIA-CR as described in section entitled, "Assessment", for research purposes.
14. Study doctors will call in prescriptions to the subjects preferred pharmacy. This is standard of care.

This visit will take 30-45 minutes.

Visit 2, Visit 3, Visit 4: Treatment Visits 1-3

Day 0, Day 30, Day 60

A member of the study team will record concomitant medications and will ask subjects if they have experienced any changes in their health since the previous visit. If an adverse event (AE) is reported than the Investigator will be informed, and an AE log will be completed/updated for PI review.

The following activities will be completed before the treatment:

5. The physician or study staff will ask subjects if they have experienced any changes in their health since the previous visit. Changes will be recorded accordingly. If an adverse event (AE) is reported than the Investigator will be informed, and an AE form will be completed.
6. Subjects will acclimate to ambient temperature and humidity conditions for 15 minutes prior to any procedures being done.
7. Obtain close-range standard photography as described in section entitled, "Assessments". This is standard of care. This will only be completed before their first treatment.
8. Obtain photographs and measurements using the Vectra H2 3D Imaging System and VISIA and/or VISIA-CR as described in section entitled, "Assessment", for research purposes. This will only be completed before their first treatment.

The procedure will then be performed in our Plastic Surgery clinic following standard of care procedures. A trained staff member will apply a topical triple anesthetic (benzocaine, lidocaine, tetracaine) to anesthetize the areas being treated. After allowing 10 minutes for the anesthetic to take effect, the skin will be cleansed and prepped with antiseptic. A trained staff member will treat the subject's face with f1927. Treatment settings and parameters will be determined by the provider and will be chosen according to Fitzpatrick skin type and location of the body for which it will be used. Ultimately, 4-6 passes will be performed at the discretion of the treating provider. Post-treatment cooling will be offered at the discretion of the treating provider, depending on clinical need.

Immediately post-treatment Clobetasol Propionate 0.05% and ice will be applied to the treated areas for 15-20 minutes. The subject will be instructed to re-apply Clobetasol Propionate 0.05% twice a day and ice the treated area for 15 minutes up to four times a day for four days.

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. Expected downtime is minimal after treatment, typically lasting 0-3 days.

These visits will take approximately 1 hour.

Visit 4 and Visit 5: Follow-Up Visits 1 and 2

Day 90, Day 150

At a minimum, all subjects will return for follow-up visits at 1 month (± 7 days) and 3 months (± 7 days) after treatment.

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

7. The physician or study staff will ask subjects if they have experienced any changes in their health since the previous visit. Changes will be recorded accordingly. If an adverse event (AE) is reported than the Investigator will be informed, and an AE form will be completed. This is standard of care.
8. Subjects will acclimate to ambient temperature and humidity conditions for 15 minutes prior to any procedures being done. This is standard of care.
9. The physician or study staff will perform an examination of the skin in the treatment area. This is standard of care.
10. Obtain post-treatment close-range clinical photography as described in section entitled, “Assessments”, for research purposes.
11. Obtain post-treatment photographs using the Vectra H2 3D Imaging System, as described in section entitled, “Assessments”, for research purposes
12. Obtain post-treatment photographs VISIA and/or VISIA-CR as described in section entitled, “Assessments”, for research purposes.

These visits will take about 30 minutes.

Assessments

Photography Procedures

Nikon D7200 (Standard of Care)

Standard and close-range of the face will be utilized for evaluation of pigmentation. These photographs will be taken utilizing the Nikon D7200 at Baseline (Screening Visit), 1-month post-treatment and 3-months post-treatment.

Vectra H2 3D Imaging System (Standard of Care)

Subjects will be instructed to adopt neutral, non-smiling expressions for each photograph. Images will be taken of each applicable subject with diffuse pigmentation of the face using the Vectra H2 3D Imaging System at Baseline, 1-month post-treatment and 3-months post-treatment. Each subject will have a total of 3 photos taken (right side, left side and center view).

VISIA and/or VISIA-CR (Research Purposes)

Subjects will be instructed to adopt neutral, non-smiling expressions with their eyes gently closed for each photograph. Images will be taken of each applicable subject using the VISIA and/or VISIA-CR at Baseline, 1-month post-treatment and 3-months post-treatment. Subjects will be carefully positioned for each photograph, directly facing the camera for the center view, and turned at a 45° angle for right and left side views. The scan is objectively able to quantify brown spots for assessment and comparison.

Hyperpigmentation Assessment

Skin Hyperpigmentation Index (SHI) (Research Purposes)

The SHI will be calculated using de-identified, cropped images from patient's unaffected skin and patient's hyperpigmented lesions. Images uploaded will be selected from the clinical or lab-based photography the patient has taken at their screening/baseline visit and their 1-month and 3-month follow-up visits. Care will be taken to compare lesions using the same lighting and angles to reduce confounders. The software is able to calculate the relative contributions of pigmentation of each pixel to create a score, and a coefficient is then derived from comparing Pigmentation Scores of the Area with hyperpigmentation versus the Reference Point. This will be used to quantify the change in pigmentation between treatments.

Statistical Methods of Analysis

The per-protocol (PP) population will be the primary population for all statistical analyses. The PP population will include all subjects who received treatment and completed the study in general accordance with the protocol. Only the data of completing subjects will be analyzed.

This study will include descriptive statistics and change from baseline analysis.

The primary outcome of effectiveness will be a paired comparison of baseline to all applicable post-baseline time points for hyperpigmentation and melasma severity using data obtained from VISIA and/or VISIA-CR and the Skin Hyperpigmentation Index results.

A descriptive statistical summary will be provided via the VISIA and/or VISIA-CR. The descriptive statistical summary includes the number of observations (*n*), mean, median, and standard deviation (SD), minimum (MIN) and maximum (MAX) values at all applicable time points.

A Skin Hyperpigmentation Index is derived automatically using the SHI plug-in. The SHI ranges from 1 (no hyperpigmentation) to 4 (maximum hyperpigmentation) and is a ratio between the Pigmentation Scores of Areas with Hyperpigmentation versus Pigmentation Score of the Reference Point.

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 each new measurement set we will conduct a repeated measures of analysis of variance (ANOVA) to detect difference between sample distributions. If differences are detected, we will subsequently evaluate specific pairwise comparisons among the post-treatment visit times using a paired T-test or Wilcoxon signed-rank tests. All statistical tests will have a significance level α=0.05 (i.e., p<0.05). P-values will be reported to 3 decimal places (0.000).

Potential Risks

Standard of Care Risks

Pre-Treatment: Hydroquinone (Rare)

Hydroquinone is a known and effective treatment for hyperpigmentation disorders and is particularly considered to be the standard of care for dermatologic treatment of unwanted hyperpigmentation. Reported adverse effects of hydroquinone administration are uncommon and include short-term cutaneous side effects like irritant contact dermatitis or, with excessive or long-term use or misuse, exogenous ochronosis. Additionally reported side effects include abnormal skin re-pigmentation in continually sun-exposed areas, or trimethylaminuria with chronic use.

Pre-Treatment: Topical Tretinoin (Rare)

Side effects of topical tretinoin are rare and include stinging of the skin, local dryness, hypopigmentation, application site reactions like erythema, irritation, or exfoliation, or, most rare, contact dermatitis or long-term skin changes.

Treatment: Non-Ablative Laser Facial Resurfacing (Rare)

Blistering, burning, scaling and infection (Rare)

A crust, blister or superficial wound can occur in 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. This is usually transient and resolves in a few hours to few days.

Transient edema and/or erythema (Common)

Edema and erythema typically develop within the irradiated areas but are usually temporary and fade within 24-72 hours. There is a 90% chance of transient edema and 99% chance of erythema to occur after treatment.

Skin roughness and/or peeling (Common)

Patients can expect their treated skin to feel rough like sandpaper for a few days while the skin heals. This is transient and should resolve in a few days. This is specific to the f1927 treatment.

Pigmentary changes (Rare)

This treatment can cause undesired pigmentary changes such as hyper or hypopigmentation. Although this is usually temporary, it may be permanent on rare occasions. Sun avoidance and/or the use of total sun block (SPF 30 or higher) will help to minimize the intensity and duration of pigmentary changes.

Eye injury (Rare)

There is a risk of eye injury associated with the use of this device. This risk will be minimized by wearing protective eyewear designated for use with this device. All subjects and other personnel must use proper protective eyewear during the use of this device

Scarring (Rare)

There is a small risk of scarring. However, this is minimized by proper technique and wound care.

Post-Treatment: Clobetasol (Rare)

Clobetasol is a corticosteroid that helps reduce inflammation, redness and itching on the body. Side effects of topical Clobetasol are rare and include burning, itching, swelling, irritation, dry skin, redness, rash, acne or temporary hair loss.

Assessment: Photography

Photographs will be taken using standard close-range photography, standard 3D photography using the Vectra H2, and the VISIA and/or VISIA-CR. 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 bright and repeating flashes from the camera, which can sometimes cause headaches, eye irritation, discomfort, aftereffects such as seeing spots, and in rare cases, could stimulate a migraine headache or epileptic seizure.

The risks of photography and imaging are the same for all three imaging modalities used: close-range clinical photography (Nikon D7200), 3D Photography (Vectra H2), and the VISIA and/or VISIA-CR. 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 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.

Adverse Events

At each visit, a member of the research team will question the subject about adverse events using an open-ended question. If a potential adverse event is reported by the subject or identified during examination, directed questioning and examination will be performed when appropriate. At this time, the following will be performed:

1. 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 (AE). If the event is determined to be an AE, an 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.
2. Collect an updated medical and surgical history along with recording of concomitant medications or treatments.
3. Take photographs of the subject with attention to the area in question.
4. Render treatment for the event, if any, as determined by the medical judgement of the Investigator.

Photographs will be taken to document any AEs if possible.

For the duration of the study, medical assistance will be provided to the subject for study-related problems at no expense, if in the opinion of the Investigator, the reaction was caused by MOXI treatments. Should a subject choose to seek their own medical treatment, no reimbursement will be offered.

When an AE persists at the end of the study, the Investigator will ensure a follow-up of the subject until the Investigator believes that the event is satisfactorily resolved.

Subject Safety and Data Monitoring

Research Standards and Good Clinical Practice

The conduct of this study will follow all applicable guidelines for the protection of human subjects for research as outlined in 21 CFR 50, in accordance with the accepted standards for Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and the standard practices of UT Southwestern.

Data Monitoring

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

Subjects will be asked about any adverse events throughout the study. Subjects will be asked to contact the Investigator if adverse events develop between visits. If necessary, an unscheduled visit will be arranged so that the Investigator can clinically evaluate and photograph these findings.

Procedures to Maintain Confidentiality

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. Documents containing identifying information will be kept in locked files in the research staffs' 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. Electronic data (electronic data entry - Case Report Forms) will be password protected.

Photographs of subject's faces 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

This study will be performed in accordance with Health Insurance Portability and Accountability Act. These guidelines will be followed specifically with regard to the privacy and confidentiality of patient care and study records. Personnel associated with Investigator's office, the U.S. Food and Drug Administration (FDA) and the governing Institutional Review Board, have the right to review the data, including photographs, collected during this study.

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