

IRB Study Number: 20171006

Version #, Date:

Title: Prospective Comparative Study of Non-ablative Laser with and without Lytera™ 2.0 Pigment Correcting Serum on the Appearance of Skin Tone and Photoaging

NCT: NCT03661697

Last IRB Modification and Approval: 3/25/2019

1) **Protocol Title**

Effect of Combination Laser Treatment and Skin Brightening Topical on the Appearance of Skin tone and Photoaging: A Pilot Study

2) **Objectives***

Our objective is to **determine** the effects of (1) basic skin care regimen + “active” (Lytera 2.0) vs (2) basic skin care regimen only, both groups combined with laser treatment on the **appearance** of skin tone and photoaging on the face

Our hypothesis is that combination laser + brightening cream (active arm) will **improve appearance** of skin tone and photoaging of the face when compared to combination laser + non-brightening cream.

3) **Background***

Photodamaged skin can be characterized by alterations to skin tone, fine wrinkles, and tactile roughness. These changes in skin appearance are usually due to chronic exposure to ultraviolet radiation. It is a common and often distressing skin condition that can also be difficult to treat. A wide variety of treatments are available to treat these alterations in skin such as cosmetic topicals, chemical peels, dermabrasion, cosmetic lasers, neuromodulators, and dermal fillers. Topicals are often the starting point for treatment of photodamage and can be used before, during, and after office procedures to augment outcomes for patients. Laser treatment is indicated for correction of existing mild-severe photodamage/aging skin. After treatment, patients can expect to have more uniform skin tone, improved texture, more radiant skin, minimized pore size appearance, and skin that looks and feels clear and brilliant. Results can be immediate but are also progressive, improving over multiple treatments. Clinicians have now begun to investigate the usefulness of integrating skincare products and cosmetic lasers.

The gold standard for improving the appearance of photoaging and hyperpigmentation (specifically solar lentigines) has been a hydroquinone-containing product. Makino et al compared Lytera 2.0 (a Correcting Serum) to Hydroquinone 4% in a randomized, split-face double blind study in subjects with moderate to severe skin tone. Lytera 2.0 showed statistically significant results at 2 weeks and Hydroquinone 4% showed statistically significant results at 4 weeks. Lytera 2.0 is a cosmetic product that is for brightening the appearance of skin does not contain any hydroquinone or other ingredient classified as a drug. (Please see the Lytera 2.0 patient brochure in the attached documents).The 1927 nm fractional non-ablative

laser has also been found to be effective in treating the pigment in photo-damaged skin.

In our study, only patients with Fitzpatrick skin types I through IV will be recruited as those with a higher level than skin type IV can be prone to overproduction of melanin following certain laser types. Fitzpatrick skin type I is highly sensitive, always burns, and never tans. Type II is very sun sensitive, burns easily, and hardly tans. Type III is sensitive, sometimes burns, and tans to light brown. Type IV is minimally sun sensitive, burns minimally, and tans to moderate brown. Type V is insensitive skin, rarely burns, and tans well. Type VI is insensitive, never burns, and is deeply pigmented.

Although laser treatment and lightening skin care products have been shown to improve skin tone and photo aging, currently, there is no clinical data to support the efficacy and longevity of combination laser treatment + brightening skin care products for photoaging and skin tone. Our study will attempt to observe if combination non-ablative laser (1927 nm also known as Clear and Brilliant) and Lytera 2.0 Correcting Serum will improve the appearance of skin tone and photoaging when compared to laser alone.

4) Inclusion and Exclusion Criteria*

Inclusion criteria:

- Healthy adult male and female patients 18 years and older
- Fitzpatrick skin types I-IV
- Has at least mild mottled skin tone of the face (score of 2 or more on a 5 point skin tone scale)
- Has at least 2 areas of the face with significant roughness, dyspigmentation, or fine lines or has all these characteristics in 1 or more areas
- Willing to refrain from using any other topical products on the face, systemic retinoids, or steroids, facial peels or other facial laser procedures throughout the duration of the study
- Willing to refrain from any cosmetic procedure including but not limited to facial surgery, dermal fillers, and neuromodulators for the duration of the study
- Willing to use only the facial skin care product regimen provided for the study
- Willing to avoid extended periods of sun exposure and the use of tanning beds during the study
- Willing to have photographs taken of the face to be used de-identified in evaluations, publications, and presentations
- For females: proof that they are not pregnant (urine pregnancy test)
- English-speaker

Exclusion criteria:

- Has any uncontrolled systemic disease (such as autoimmune disorders and

connective tissue disorders such as lupus erythematosus or Sjogren's syndrome
Has any active infection in face
Has history of any skin conditions that could interfere with treatment
Has used self-tanner recently
Is currently participating in another drug research study
Is NOT willing to refrain from using any other topical products such as skin lightening, retinoids, alpha/beta-hydroxyl acids, salicylic acid, vitamins C or D, steroids, or antibiotics on the face or systemic retinoids, steroids, facial peels, neuromodulators, dermal fillers, facial surgery, or other facial laser procedures throughout the duration of the study
For females: is pregnant
Non English-speaker

Individuals will be screened for eligibility via questionnaires that address each of the inclusion and exclusion criteria. Our final study sample will include the subjects who met the inclusion/exclusion criteria and did not voluntarily drop out of the study or develop adverse effects that prohibited them from safely completing the study. We will exclude adults unable to consent, patients under the age of 18, pregnant women, and prisoners.

5) Number of Subjects*

After recruiting our subjects, 14 patients will be randomized into either arm of the study (7 in each arm).

6) Study-Wide Recruitment Methods*

This is a single center study. We will recruit subjects from a clinical database of the practice of Dr. Lisa Grunebaum. We will use several recruitment methods including invitation via a scripted email providing information describing the study protocol and end-points, scripted invitation telephone calls, and flyers.

7) **Study Timelines***

	Screening/Baseline Visit 1	Washout period	Visit 2 First Laser treatment (4 weeks +/- 5 days after baseline visit)	Visit 3 Second Laser Treatment (3 weeks +/- 5 days after first laser treatment)	Visit 4 Last day of topical treatment (4 weeks +/- 5 days after second laser treatment)
Procedures					
Informed Consent	X				
Inclusion/Exclusion criteria	X				
Demographic History Questionnaire	X				
Medical History Review	X				
Skincare History Review	X				
Evaluate Fitzpatrick skin type	X				
Evaluate baseline hyperpigmentation	X				
Urine dipstick test	X		X	X	X
Self assessment questionnaire	X				X
Standardized Digital photography	X		X	X	X
Adverse effects review	X		X	X	X
MoPASI evaluation	X		X	X	X
GAIS evaluation	X		X	X	X
Anesthetizing topical application			X	X	X
Protective goggles placed			X	X	
Laser treatment performed			X	X	
Exit Questionnaire					X

Potential participants will receive a thorough history and dermatologic physical exam to determine if patients meet the inclusion/exclusion criteria for being in the study. Urine dipstick tests will be performed on female

patients to confirm they are not pregnant. Consent will be obtained from eligible participants and will be enrolled in the study.

The study will be conducted over a 12 week period. There will be a 4 week washout period prior to laser treatments when the subjects will begin two skin care regimens, which are described below. Then there will be 2 laser treatments separated by 3 weeks. The subjects will continue the topical treatment 1 month after the 2nd laser treatment.

There will be 4 study visits: Baseline Visit 1, First laser treatment Visit 2 (4 weeks +/- 5 days after baseline visit), Second laser treatment Visit 3 (3 weeks +/- 5 days after first laser treatment), and Last day of topical treatment Visit 4 (4 weeks +/- 5 days after second laser treatment). During these visits, photographs of the participants' faces will be taken. Patient questionnaires will be given at baseline and at the end of the study.

Investigators will complete the study 4 months after subjects have completed their participation in the study.

8) Study Endpoints*

The study will reach endpoint for each patient either 1) once they have completed their exit survey after the 2 laser treatments and the topical treatments or 2) if they experience any adverse reactions from treatment and must be pulled from the study.

9) Procedures Involved*

One month prior to laser treatments (washout period), 14 male and female subjects with moderate hyper pigmentation and photo damage of the face will be randomized to 2 skincare regimens.

The regimens are:

- "Placebo arm" – Basic skin care regimen* (Facial Cleanser, TNS ceramide Treatment Cream (standard post-procedure moisturizer), and Essential Defense Mineral Shield Broad Spectrum SPF35 (all-physical sunscreen))
- "Lytera arm" – Basic skin care regimen + **Lytera 2.0**, which will be added between the Facial Cleanser and TNS Ceramide Treatment Cream

*The basic skin care regimen is a standard regimen used in several skincare product experiments

After cleansing the face, the patients in the Lytera arm will apply one pump of the pigment-correcting serum in a circular motion to the entire face

including the forehead, cheeks, chin, nose, and neck with care to avoid the eyes. The Lytera 2.0 is applied prior to applying moisturizer and sunscreen.

On laser treatment days, patients will come into the office without having applied any topical cream that day. Lidocaine topical may or may not be applied over the face avoiding the eyes (lidocaine use will be at discretion of Principal Investigator), and patients will be given protective goggles to shield the eyes during laser treatment. Next, the laser wand is pressed to the face and passed over the skin in various horizontal and vertical directions. Treatment takes 20 to 30 minutes.

Standardized digital photographs will be taken at baseline and at each subsequent visit using the Canfield VISIA Complexion Analysis (VISIA-CA) camera system at the highest resolution in a consistent position. Pictures will be taken before laser treatments on Visit 2 and Visit 3.

The subjects will complete an exit questionnaire after completion of the study at their last study visit (Visit 4). Through the questionnaire, we will obtain information on subject satisfaction with the study as well as their opinion of how their skin has changed. We hope to use the responses to assess efficacy of our skincare regimen and to improve future related research protocols.

Local tolerability including itching, redness, burning, or pain will be assessed at each visit by the investigator. Subjects will also be asked to assess discomfort during treatment and also to maintain diary at home to record any side effects after each facial laser treatment. To lessen the probability of risks of laser treatment, will use the standard pulse energy and coverage known to produce the minimal amount of side effects, increase subject comfort, and allow for rapid healing.

Once all subjects have completed the study, one independent evaluator will retrospectively analyze the VISIA high definition photography data that was taken at each visit. The independent observer will evaluate the photos of each patient for clinical efficacy and tolerability using two validated grading scales (Modified Pigmentation Area and Severity Index (MoPASI) and Global Aesthetic Improvement Scale (GAIS)) at baseline and at weeks 5, 8, and 12.

The GAIS is used to evaluate change in aesthetics after intervention. 0 = worse, 1 = no change, 2 = improved, 3 = much improved, 4 = very much improved. The MoPASI is a dermatologist-developed modified scale derived from the validated Melasma area and severity index scale. Pigmentation is assessed in 4 sections of the facial skin, and three variables are assessed within each region: percentage of area involved, darkness of pigment in the area, and pattern of involvement in the area. Subjects will complete self-

assessment questionnaires at baseline and at the end of the study.

The Clear and Brilliant 1927nm laser has been used extensively in facial cosmetic surgery for skin resurfacing to improve the skin changes associated with photoaging and skin tone. The laser is FDA approved for this use (see Device attachments for documentation). The Solta Medical Company has proven that it produces safe and effective treatment and even in combination with topicals, has a high safety profile (see supporting documents).

Lytera 2.0 Correcting Serum, a Skin Medica product, is a non-hydroquinone, non-drug advanced Correcting Serum that has been proven to minimize the appearance of skin discoloration and dark spots. Our proposed study is to observe the effect of Lytera 2.0 on skin tone, and will not evaluate any underlying changes to skin structure or function. The assessments in the proposed study are observational and do not include biopsy or other method.

Key ingredients of Lytera 2.0 Pigment Correcting Serum:

Tranexamic Acid

Phenylethyl Resorcinol

Niacinamide and Tetrapeptide 30

Marinen Extract blend

Phytic Acid

Other ingredients: Vitis Vinifera SCE, Plankton Extracts, Hydroxyacetophenone, Artemisia Capillaris, Marine Exopolysaccharides

Data that will be collected about subjects (see attached data collection form):

Age

Gender

Race

Past medical history including current and past illnesses, current medications, allergies, past surgeries, any past adverse effects to facial cosmetics, family history, social history including alcohol, tobacco, or illicit drug use.

Past skin care history including any surgical cosmetic procedures, fillers, injectables, lasers, or topical treatments.

Fitzpatrick skin type (I-IV)

Evaluation of baseline skin tone

Adverse effects experienced throughout the study

MoPASI scores

GAIS scores

Representative photographs of subjects at baseline and at subsequent visits

10) **Data and Specimen Banking***

Data will be stored on Box, a secure file sharing, storage, and collaboration system using a password-protected, encrypted laptop. Data will be stored for 1 year after the completion of the study. Only Dr. Lisa Grunebaum, principal investigator and Dr. Ope Fawole and Caitlin Covielo, co-investigators and study coordinator will have access to the data. Data will only be released by Drs. Grunebaum or Fawole for publication of study results.

Stored data will include:

Age

Gender

Race

Past medical history including current and past illnesses, current medications, allergies, past surgeries, any past adverse effects to facial cosmetics, family history, social history including alcohol, tobacco, or illicit drug use.

Past skin care history including any surgical cosmetic procedures, fillers, injectables, lasers, or topical treatments.

Fitzpatrick skin type (I-IV)

Evaluation of baseline skin tone

Adverse effects experienced throughout the study

MoPASI scores

GAIS scores

Representative photographs of subjects at baseline and at subsequent visits

11) **Data Management***

Statistical analysis will be conducted to determine the effect size necessary to power a study. All statistical tests will be two-sided and interpreted at a 5% significance level. The primary analyses will be based on the MoPASI and GAIS scores. Scores after each laser treatment will be compared to baseline scores using the appropriate statistical test.

Data will be secured and stored on Box, a secure file sharing, storage, and collaboration system using a password-protected, encrypted laptop.

Information that will be included in data include demographic information, skin type, baseline hyper pigmentation, adverse effects, validated scale scores, photographs, past medical and skin care history as listed above.

Data will be stored in Excel sheet on the encrypted system, Box, which will

give us access to the data via an encrypted stream of traffic. No actual copy of the data will be stored on a machine. Data will be stored for a short-term retention period of 5 years or less at the location 1150 NW 14th St Suite 150 Miami, FL 33136. The principal and co investigators will have access to the data. Drs. Grunebaum and Fawole will be responsible for transmission of data. Data will be transported via laptop. Aforementioned laptop will be completely shut down after all browser data has been cleared before being transported or left unattended. In addition to the data encryption, a passcode into the device will be required.

12) Provisions to Monitor the Data to Ensure the Safety of Subjects*

The physician investigators and the subjects themselves will monitor the type, severity, duration, and frequency of adverse effects during treatment. Adverse effects will be evaluated by investigator at each visit. Subjects will fill out diary while at home to record any adverse effects. Investigator will be accessible to subjects via email and phone to answer questions about any adverse effects. Safety data and efficacy data (based off of validated scale scores) will be reviewed after each visit. Safety information will be collected at study visits and by email communication with participants. Safety data collection will begin on day 1 of the washout period when subjects begin the skin care regimen. The investigators will review the data at each visit and as needed. Safety information that will be collected includes pain, visual disturbance, rash, fever, infection, photosensitivity, scarring, and changes in skin color.

If a patient becomes pregnant, develops severe post-inflammatory skin tone, or experiences an anaphylactic or other severe allergic reaction, they will be pulled from the study. If they exhibit any of the "exclusion criteria" after initial evaluation of eligibility for participation in study, they will also be removed from the study.

13) Withdrawal of Subjects*

If a patient becomes pregnant, develops severe post-inflammatory skin tone, excessive scarring, burning, or experiences an anaphylactic or other

severe allergic reaction or infection requiring antibiotic treatment, they will be pulled from the study.

If they exhibit any of the “exclusion criteria” after initial evaluation of eligibility for participation in study, they will also be removed from the study.

Exclusion criteria:

Has any uncontrolled systemic disease (such as autoimmune disorders and connective tissue disorders such as lupus erythematosus or Sjogren's syndrome

Has any active infection in face

Has history of any skin conditions that could interfere with treatment

Has used self-tanner recently

Is currently participating in another drug research study

For females: is pregnant

Non English-speaker

Participants that develop criteria for withdrawal from the study or any potential side effect will be examined in the office. Participants that meet criteria for withdrawal from treatment will be informed during office visit. Safety information will still be collected until week 12 of the study.

14) Risks to Subjects*

Side effects of Lytera topical include stinging or tingling on application, redness, and general irritation in those with sensitive skin.

There are some expected side effects of the Clear and Brilliant facial laser procedure. These may include discomfort, redness, swelling, heat sensation, dark spots, flaking, itching, acne formation, herpes simplex reactivation, blistering, and dryness. Patients can expect facial redness immediately after treatment that commonly resolves within a few hours but may last until the next day in some patients. Possible risks or complications associated with this facial laser procedure include bleeding or crusting, burns, scarring, pigment changes, infection, and eye injury. It has been shown that adverse effects typically resolve without discontinuation of the products. There may be psychological risks associated with treatments as patients may feel self-conscious about erythematous face for a couple days

after the laser treatments. If subjects experience any of the aforementioned side effects, this may also be distressing.

Potential risks of combination Clear and Brilliant laser and Lytera treatment include all of the side effects listed above.

Lytera 2.0 Pigment Correcting Serum does not contain any known teratogenic ingredients, however, the safety of the product has not been established in women who are pregnant, planning to be pregnant, or breastfeeding. While laser treatment is not recommended during pregnancy, it has not been shown to harbor any risks to the embryo. Patients will need to discuss risks vs benefits with their obstetricians. Subjects who become pregnant during study will not continue participation and will also be instructed to notify their obstetrician about their study participation.

15) Potential Benefits to Subjects*

Benefits to subjects are myriad, as combination topical and laser treatment is intended to moderately improve photo damaged and poor skin tone which can be distressing for patients. Facial cosmetic laser helps prevent and address early signs of aging skin, maintain younger-looking skin, and improve tone, texture and radiance. After even two treatments, patients can expect to have more uniform skin tone, improved texture, more radiant skin, minimized pore size appearance, and skin that looks and feels clear. The skin will continue to improve for several months following treatment.

16) Vulnerable Populations*

We will not be investigating any vulnerable populations. Once again, we will not include pregnant females in the study as skin changes that may be seen in pregnancy may influence the results of the study.

17) Sharing of Results with Subjects*

Results of study will be shared with subjects if they are interested in knowing results. This will be shared over the phone after the data has been analyzed.

18) Setting

Research will be conducted in the Facial Plastic and Reconstructive Surgery Department at the Professional Arts Center at the University of Miami Health System.

19) Resources Available

The principal investigator is a double board certified physician by the American Academy of Otolaryngology and the American Academy of Facial Plastic and Reconstructive Surgery. She has been in practice in Miami for over a decade and is thus very familiar with the population seeking skin care options for photo damage. One of her areas of expertise includes laser treatments for scars and facial rejuvenation. She already uses the laser specific to our study in her practice and is thus quite familiar with it. The secondary investigator is a third year Otolaryngology resident with

a 4 month dedicated research period in which she plans on recruiting subjects, performing treatments, taking standardized photos, and analyzing results with the Biostatistician.

Our facilities include a dedicated Plastic surgery and reconstructive state-of-the-art treatment center with spacious, inviting rooms. There is a dedicated area for taking standardized photos.

We will provide pamphlets on medical and psychological resources that subjects may need throughout duration of treatment

We will have several meetings with all members of the team prior to the start of the study in order to make sure everyone is informed about the protocol and their duties.

Recruiting 14 participants for this study is feasible as Dr. Grunebaum's clinical database contains over 100 interested patients.

20) Prior Approvals

We are applying for an Allergan Research Grant for Investigator Initiated Trials.

21) Recruitment Methods

We will recruit subjects from a clinical database of the practice of Dr. Lisa Grunebaum. We will contact these patients with invitation via several methods: a scripted email, a telephone script, and study flyers providing information describing the study protocol and end-points.

22) Local Number of Subjects

We need 14 subjects. Seven patients will be randomized to one of two treatment arms. We expect to screen several patients and identify 14 participants that meet inclusion/exclusion criteria.

23) Provisions to Protect the Privacy Interests of Subjects

Subject's demographic and safety and efficacy data will be stored in password-protected, encrypted laptop. Only the investigators and biostatisticians will have access to these files. Patients will be de-identified and will be assigned a number that will go along with the data.

Subjects will be reassured that this is a clinical trial and that they can be guaranteed the same confidentiality that they would be afforded in a Doctor's office information. Only personal questions pertinent to patient's history of skin care will be asked. Procedures

are noninvasive and there will be a second party (nurse or assistant) in the exam room during treatments as a witness.

24) Compensation for Research-Related Injury

Participants will not be compensated for this study or for research-related injury. Participants will be treated for their injuries, however, patient or insurance may incur costs related to injury.

25) Economic Burden to Subjects

Topical facial treatments and laser treatments will be provided to the subjects at no cost. Participants will not be compensated for this study or for research-related injury. Participants will be treated for their injuries, however, patient or insurance may incur costs related to injury.

26) Consent Process

After the potential subject receives information/invitational email about the study and endorses interest in participation, the potential subject will be contacted via telephone to schedule a face-to-face interview, history, and physical exam, and to answer any outstanding questions and counsel on what to expect. If potential subject agrees to participate after conversation and meets inclusion/exclusion criteria, we will obtain informed consent. During each visit, subject will confirm ongoing consent to participate in study. We will follow the "SOP: Informed Consent Process for Research (HRP-090)." Our study will NOT include Non-English speaking subjects, minors, cognitively-impaired adults, pregnant women, prisoners, or adults unable to consent. Our rationale for excluding non-English speakers is that the department has no provision for readily available interpreters; thus, it would not be possible to obtain a valid consent due to the inability to fully understand the research and the risks and benefits of participation making this non-English speaking population vulnerable. Given that the study does not target serious or life threatening conditions, the investigators did not find it imperative to include eligible, non-English speaking subjects.

27) Non-English Speaking Subjects

Not applicable

28) Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

A chart review from the Investigator clinical database will be required to identify prospective subjects who will then be contacted and asked to participate in the study. Investigators request a partial HIPAA waiver to review the charts to identify subjects. Only the minimum information will be collected in order to make contact with the subject. Informed consent/HIPAA authorization will be obtained from the subjects prior to any additional data collection.

29) Subjects who are not yet adults (infants, children, teenagers)

Not Applicable

30) Cognitively Impaired Adults

Adults who do not meet minimum criteria on the MME will be excluded.

31) Adults Unable to Consent

Not. Applicable

32) Adults Unable to Consent

Not applicable.

33) Process to Document Consent in Writing

Our study will have a written consent documenting the goals of the study, possible risks and benefits. Consent will be documented on standard informed consent form. (HRP-091 – see attached).

34) Drugs or Devices

The Clear and Brilliant 1927 nm laser handpiece will be kept in the Plastic Surgery clinic and only handled during laser treatments. The topical creams will be applied by subjects at home and held on the day of laser treatment. None of the devices or topicals are investigational.

References:

1. www.skinmedica.com
2. www.clearandbrilliant.com
3. Pandya et al. "Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring

method". Journal American Academy of Dermatology. Apr 16, 2010: 78-83.

4. Fabi, S. Goldman, M. "Comparative Study of Hydroquinone-Free and Hydroquinone-Based Hyperpigmentation Regimens in Treating Facial Hyperpigmentation and Photoaging". Journal of Drugs in Dermatology. Mar 2013: 32-37.
5. Fabi et al. "A Randomized, Split-Face Clinical Trial of Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (1064 nm) Laser Versus Low-Fluence Q-Switched Alexandrite Laser (755 nm) for the Treatment of Facial Melasma". Journal of Cosmetic and Laser Therapy. Sept 2014.
6. Marini, Leonardo. "Advanced film-forming gel formula vs spring thermal water and white petrolatum as primary dressings after full face ablative fractional CO₂ laser resurfacing: A comparative split-face pilot study".
7. Makino et al. "Efficacy of Lytera 2.0 in multiple ethnicities compared to 4% HQ; ingredients, preclinical data." JDD Dec 2016.