Combination Topical Cysteamine and Fractional 1927nm Low-Powered Diode Laser

UnionDerm

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Protocol Summary

Study Device: Clear & Brilliant Touch

Protocol Number: XXXXXXX

Projected Study period: Initiation Date: November 2022 Completion Date: November 2023

Study Duration: 12 months

Purpose: To evaluate the efficacy and safety of the combination 1927nm Low-Powered Diode laser and topical cysteamine cream for treatment of melasma on the face.

Procedure:

Visit 1 (Screening and Initial Treatment Visit)

- Verify that subject is qualified to participate in the study.
- Ask subject to give personal information, such as name, date of birth, race and ethnicity.
- Review medical and dermatology (skin) history, including history of previous treatments to area being treated.
- Review past and current medications and skin care products.
- See how tall subject is and how much subject weighs
- If subject is a woman and can have children, urine will be tested to see if subject is pregnant. The study doctor or study staff will tell subject if pregnancy test results are positive. The results of the pregnancy testing must be negative in order for subject to be in the study.
- Supply patient with topical cysteamine cream and review instructions for its use
- Identify and examine the area (i.e, side) of face to which the Diode 1927 nm laser will be used (mapping)
- Take photos of face
- Perform grading of melasma
- Perform treatment according to guidelines stated in protocol
- Schedule the next study visit

Visit 2 and 3 (Week 4 and 8)

- Assess side-effects of the treatment at initial visit
- See how tall subject is and how much subject weighs
- Perform treatment according to guidelines stated in protocol
- Schedule the next study visit
- Take photos of face

Visit 4 (Week 12)

- Assess side-effects of treatment
- See how tall subject is and how much subject weighs
- Take photos of face
- Perform grading of melasma
- Post-treatment questionnaire
- Evaluation of photos comparing visit 1 and 4 to be performed

Risks and Discomforts: Blistering, edema, erythema and local pain are typical reactions to laser treatment. A lesser possibility exists for hyperpigmentation, hypopigmentation scarring, and/or infection. These conditions may or may not resolve over time. As with any method of tissue destruction, there is a risk of infection and of scarring, which is minimized with proper wound care. Eye injury due to the use of the laser is a risk to the subject as well as the operator. The subjects may experience partial or permanent hair reduction. Risks of the topical include temporary irritation, burning or heating up sensation that resolves within 30 minutes

Benefits: The subjects may or may not show improvement of melasma on the treatment sites. There is no guarantee of success.

Background:

Melasma is a commonly acquired hyperpigmentary condition characterized by brown spots on sun exposed areas of the face. Treatment of melasma can be challenging as many patients are refractory to therapy, while others experience a chronic or relapsing course. Melasma also significantly impact patients' quality of life with many reporting feelings of frustration, embarrassment, and depression related to their condition. Mainstay of treatment includes topical skin-lightening and brightening agents such as hydroquinone, tranexamic acid, retinoids, azelaic, kojic and ascorbic acids, as well as various chemical peels, laser and light-based therapies. Current gold standard is a triple combination cream consisting of topical hydroquinone, tretinoin, and fluocinolone, along with broad-spectrum sunscreen. However, use of topical hydroquinone is associated with adverse events including irritation and a paradoxical exogenous ochronosis with prolonged use, making its use challenging. Hence, for this difficult, and often recalcitrant disease, additional therapeutic options are needed.

Topical cysteamine is safe, generally well tolerated, and can be used continuously without treatment holidays. Multiple studies have demonstrated its efficacy in the treatment of melasma, including two double-blind, randomized, and placebo controlled clinical trials. Combination therapy of lasers with lightening agents have been shown to augment melasma treatment. However, data on combination laser and topical cysteamine is sparse, and no controlled or split-faced studies have been published. Thus, we aim to investigate combined topical cysteamine with laser, compared with topical cysteamine alone to assess whether this adjuvant therapy can improve the efficacy of cysteamine in the treatment of melasma.

The primary objective of our study is to determine the efficacy of combined topical cysteamine cream with a 1927 diode non-ablative laser (Clear + Brilliant Permea®; Solta Medical, Inc.), compared to topical cysteamine alone in the treatment of melasma. This efficacy will be assessed using modified Melasma Area and Severity Index (mMASI) scores, a validated physician assessment tool, at baseline and at follow up visits at week 4, 8 and 12 as well as Investigator Global Assessments. Secondary objectives also include an assessment of patient satisfaction which will be evaluated via patient questionnaires distributed to patients at baseline and at week 12. In addition, impact on quality of life will also be assessed utilizing the melasma quality of life scale (MELASQoL) questionnaire which will be administered to patients at baseline and at week 12.

Multiple studies have demonstrated the efficacy of topical cysteamine in the treatment of melasma. Mansouri et al. conducted a double-blind, randomized, controlled clinical study, which included 50 melasma patients, and demonstrated significant efficacy of topical cysteamine in the treatment of melasma.One comparative trial demonstrated that topical 5% cysteamine, though safe and well-tolerated, was less effective than topical 4% hydroquinone in the treatment of facial melasma ; however, a later published response indicated that the concentration of cysteamine may have been less than the reported 5%. A single-blind, randomized comparative trial of 54 melasma patients found no statistically significant difference in the efficacy of topical cysteamine compared to topical tranexamic acid; however, cysteamine was better tolerated amongst the patients. Finally, Karrabi et al. also found that cysteamine 5% cream showed greater efficacy than the gold standard, modified Kligman's formula, in their randomized, double-blind trial of 50 patients with epidermal melasma.

Non-ablative fractional lasers (NAFL) target water-containing tissues to create microthermal zones (MTZ) in the dermis and induce neocollagenesis and remodeling without damage to the epidermis. These lasers have been shown to be effective in the treatment of melasma with a more durable response compared to other lasers and energy-based devices. The efficacy of combined topical agents with NAFL in the treatment of melasma has also been thoroughly studied. Mohamed et al. investigated the use of fractional Er:YAG laser with topical steroids compared to the laser alone in 22 patients with melasma and found significantly improved outcomes with the use of combined therapy. Tourlaki et al. reported the combination of fractional 1540nm Erbium-glass laser with a triple-combination cream (hydroquinone 4%, retinoic acid 0.03%, hydrocortisone butyrate 0.1%) resulted in marked improvement in 67.1% and moderate improvement in 21.1% of patients who were previously resistant to triple-combination cream alone. Several authors have also shown that laser-assisted delivery with lowenergy, low-density 1927 nm fractional thulium fiber laser combined with topical tranexamic acid results in significant improvement in melasma.[1011] Combination of the same laser with 4% hydroquinone cream demonstrated more than 50% improvement in 60% of melasma patients after one treatment in another retrospective study. In addition, a retrospective review of 11 patients with melasma and subtle or sub-clinical telangiectatic erythema found improvement in 6 out of 11 patients treated with the 595-nm pulsed dye laser (PDL) combined with the 1927-nm fractional low-powered diode laser. Per authors, patients in this study were continued on various topical therapies including hydroquinone 4% cream or gel although compliance was not measured.

Thus far, one case series has been published investigating the combination of topical cysteamine with laser. Johnson et al treated three melasma patients with nightly cysteamine and monthly treatments with a 650-microsecond nd-YAG 1,064-nm laser, resulting in all patients reporting satisfaction and persistent results noted two months later. In summary, while the efficacy of topical cysteamine has been demonstrated and combination laser treatment with multiple topical agents such as tranexamic acid and hydroquinone have been thoroughly studied, there have been no controlled studies investigating combination therapy with topical cysteamine.
We hypothesize that addition of 1927-nm fractional low-powered diode laser therapy to topical 5% cysteamine will result in significantly greater improvement in both the clinical appearance of melasma as well as patient satisfaction, compared to topical cysteamine alone. Specifically, we hypothesize:
1) Patients will experience improvement in their melasma on both treated sides, with greater improvement noted with combined topical and 1927-nm fractional low-powered diode laser treatment noted on their mMASI scores at weeks 4, 8 and 12.
2) Patients will report improvement in satisfaction on patient questionnaires on both treated sides, however there will be greater change in satisfaction noted with combined topical and 1927-nm fractional low-powered diode laser treatment at week 12 compared to baseline (week 0)

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Purpose:
To evaluate the efficacy and safety of the Clear & Brilliant® Permea laser in combination with topical cysteamine for the treatment of melasma of the face.

Objectives:

A. To evaluate the efficacy of the Clear & Brilliant Permea laser system in combination with topical cysteamine
    a. To assess for improvement of melasma after completion of three treatments as determined by the treating clinician and objective measures
    b. To evaluate subject's satisfaction with melasma treatment and assessment of improvement after three treatments
    c. To evaluate the length of treatment.
B. To evaluate the safety of melasma treatment in all skin types using the Clear & Brilliant Permea laser in combination with topical cysteamine
    a. To evaluate the immediate response to treatment
    b. To evaluate the subject's assessment of comfort associated with treatments
    c. To determine the rate of adverse events for the treatment group as a whole

Study Design: Single Center, Prospective, With Before-After Analysis

Study population: Twenty healthy male or female patients, 18-74 years of age, of all skin types with melasma on the face that wish to be treated. Each subject will receive topical cysteamine cream which they will be instructed to use once a day at home. In addition, one side of the face will be randomly selected for treatment with laser. Patients will receive three monthly treatments, at 4-6 week intervals**,** on the selected side of the face with the Clear & Brilliant Permea laser. The treatment duration including pre and post treatment procedures is estimated to be 90 minutes per subject. Subjects will return for a follow-up visit 3 months after the initial treatment for a total of four visits. The treatment plan will be the same regardless of the subject's skin type. Four passes, at high setting will be performed.

During the first and fourth visit, the areas of treatment will be photographed with a digital camera under controlled conditions. Subject improvement will be assessed via investigator and subject grading at visit 1 and 4. Improvement in melasma will be assessed by blinded evaluators who will review pre and post treatment photographs taken with VISIA® Skin Analysis System for facial imaging (Canfield Scientific Inc) from visit 1 and 4. Side effects (including pain, redness, dryness, and hyperpigmentation) will be assessed and recorded at visits 2, 3, 4.

Research Coordinators and Investigators who are all listed in the IRB-approved research protocol will obtain informed consent. Both a research assistant and an M.D. Investigator will be available to discuss the consent. Criteria for study inclusion will include subjects with melasma on the face. They will be followed through to completion at the one month follow up.

The study device is not subject to IDE regulations because devices used are not diagnostic devices and are not undergoing consumer preference testing. The study is exempt from IDE regulations.

They will be recruited by offering participation to existing subjects at Union Square Laser Dermatology, by referrals, and by online advertisements.

Sample size justification:

Statistical Hypothesis:

Null hypothesis: Treatment of melasma on face with Clear & Brilliant laser and topical cysteamine will not lead to significant improvement

Sample Size Calculation:

A sample size is calculated to test the null hypothesis with a one-sided paired t-test for simplicity, although the final analysis may employ a statistically more powerful model.

We calculate that for a two-sided alpha level of 5%, a sample size of 20 subjects will enable us to test the null hypothesis with 80% power. In order to enable the analysis and take into account the potential for dropout we may include up to 25 patients.

Selection Criteria:

Inclusion Criteria:

Healthy subjects of Skin Type I-VI females.
Subjects must be between 18 and 74 years of age, and must have visible melasma on the face.
Subjects must read, understand, and sign the Informed Consent.
Subjects must be willing and able to comply with all follow-up requirements.

Exclusion Criteria:

Subjects must not have active or localized or systemic infections.
Subjects must not be immunocompromised.
Subjects must not have a coagulation disorder, and must not be using anticoagulation medications.
Subjects must not have history of surgical or cosmetic treatment, including prior skin lightening agents, microneedling or microdermabrasion, or laser or light-based therapies, to the planned treatment areas in the prior six weeks.
Subjects must not have photosensitivity or allergy.
Subjects must not be mentally incompetent.
Subjects must not be pregnant or breastfeeding.
History of skin cancer or pre-cancerous lesions in the treatment area
Subjects must not be currently using aspirin or antioxidants.
Subjects must not refuse to sign the Informed Consent document and/or refuse to comply with all follow-up requirements.
Subjects must never have had gold therapy.
Subjects must never have had radiation therapy to the face. Recent or current suntan or sunburn within 2 weeks.
Clinically dysplastic nevi in the treatment area.
Subjects must not have had collagen, other methods of tissue augmentation, botox, chemical peels, dermabrasion, or resurfacing within the last year.
Oral retinoid (Accutane or Soriatane) or photosensitizing drugs, e.g. Declomycin®, a tetracycline with light absorption in the range of 400 to 450 nm use within 24 months of study entry.
Topical retinoid therapy on neck and/or chest within one month of study entry.
History of keloids or hypertrophic scars
A history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, or photodermatosis.

Mapping and Pretreatment evaluation:

Photographs of the treatment areas will be taken so as not to reveal the subject's identity and identifying information will be coded.

Wrinkle Classification:

Each subject will be classified into mild, moderate and severe according to the severity of pre-treatment melasma.

Photographs:

Photographs will be taken at each visit prior to treatment and at follow-up visit 4, to evaluate healing time, clinical improvement of melasma, as well as any side effects. Photographs will be taken using the VISIA® Skin Analysis System for facial imaging (Canfield Scientific Inc). This device ensures face position, lighting, photographer, and camera settings are standardized.

Subjects will be asked to remove all skincare products applied to the facial area prior to treatment with a gentle cleanser and clean towel. Participants will be instructed to sit down & place their face in the holder of the VISIA®. This camera will take 3 pictures of the face, including the left, right, and front facial areas. Study staff may need to adjust the height of the chair and or face holding piece inside the VISIA® for subject comfort.

Laser Parameters:
Following 15 minutes of topical 30% lidocaine application, patient's side of face that will be treated with Clear & Brilliant 1927nm at treatment level high, with total of 4 passes.

The investigator, the subject, and anyone else in the laser treatment room will wear the appropriate protective eyewear.

Post-Exposure Skin Care:
Subjects will be given verbal and written post treatment instructions to clean test sites with warm water and mild soap (Dove™ -- All subjects will be instructed to avoid sun exposure by applying a total block screen with an SPF of 30 or higher and to avoid light exposure to the face for 48 hours after treatment.

Study Oversight:
The study will be made available for monitoring, auditing, IRB review and regulatory inspection by providing direct access to study related source data by Ste IRB. The study may be prematurely terminated if the safety of subjects is compromised. Safety evaluations will be determined by the Principal Investigator who may choose to prematurely terminate the study.

Treatment may be discontinued at any time if deemed inappropriate by a physician evaluation. All AEs and SAEs will be monitored by a physician

Data Management:
All study data will be stored on a password protected hard drive.

Intended Use of the Data:
The expected end use of the data collected will be for the purpose of best practices in treating melasma on the face. As the purpose of the study is to evaluate the safety and efficacy of low energy diode 1927nm, follow-up photos will be examined for melasma improvement by both the investigator(s) and blinded dermatologist reviewers. A satisfaction questionnaire will be given to patients one month after the final laser treatment. Photos and the satisfaction questionnaire will be examined by the principal investigator and sponsor to determine best practices for use of low energy diode 1927nm in treating melasma in face.

Clinical Evaluations:
The following clinical evaluations will be performed throughout the study as detailed in the visit procedure summary. In the event a treatment is to be administered at a visit the scoring should be done before any laser therapy or drug application. The same investigator should complete the evaluations for a given subject throughout the study. If this becomes impossible a sub investigator with overlapping experience with the subject and the study should complete the evaluations.

Wrinkle evaluation:
Evaluation of fine wrinkling only in the facial area.

0- None
1- Minimal
2- Mild
3- Moderate
4- Severe

Tactile Roughness:
Texture of the overall face skin assessed by lightly palpitating by stroking gently with the index finger.

Skin is very smooth
Skin is smooth with very occasional roughness
Mild roughness
Moderate roughness
Severe roughness

Mottled Hyperpigmentation
Evenly Pigmented Skin
Light Hyperpigmentation involving small areas
Moderate hyperpigmentation involving moderate sized areas; Light hyperpigmentation involving moderate areas
Moderate hyperpigmentation involving moderate sized areas: light hyperpigmentation involving large areas; small areas of heavy pigmentation
Heavy hyperpigmentation

All subjects who drop out before the final examination will be maintained in the study for accountability reasons. Any adverse effects that occur, irrespective of subject compliance with the complete follow-up examination schedule, will be reported in the study results.

Criteria of Evaluation (Study Endpoints):

In person assessment by treating physician and photographic assessment in which blinded dermatologists compared photographs of the individual's face areas at baseline and visit 4 from all patients in the study.

Clinical Endpoints:

- In person assessment by treating physicians will measure change in mMASI of the subjects face at between baseline (visit 1) and week 4.
- The Global Aesthetic Improvement Scale (GAIS), a 5-point scale rating global aesthetic improvement in appearance, compared to pretreatment, as judged by the investigator and the subject will also be assessed. The rating categories used on this scale will be "worse" "no change" "improved" "much improved" and "very much improved". The percent ranking improvements in the Investigator and Subject GAIS scale from baseline (visit 1) to visit 4 will be compared.
- Photographic assessment by two blinded dermatologists will measure changes will assess improvement in melasma by mMASI score. In addition, an investigator quartile improvement score from baseline to week 12 (0 – 0%, no improvement; 76%-100% - very significant improvement) will be assessed.

Table. Determination of the Modified MASI (mMASI) Score

Location of Melasma	Scoring[a]	Calculation for Total Score[b]
Forehead	(0.3) (A) (D)	Forehead mMASI Score + Left Malar mMASI Score + Right Malar mMASI Score + Chin mMASI Score = Total mMASI Score
Left malar	(0.3) (A) (D)	
Right malar	(0.3) (A) (D)	
Chin	(0.1) (A) (D)	

Abbreviation: MASI, Melasma Area and Severity Index.

[a] Scoring system: A, Area of involvement rated 0 to 6: 0 indicates absent; 1, <10%; 2, 10% to 29%; 3, 30% to 49%; 4, 50% to 69%; 5, 70% to 89%; 6, 90% to 100%. D, Darkness rated 0 to 4: 0 indicates absent; 1, slight; 2, mild; 3, marked; 4, severe.

[b] Total mMASI score range is 0 to 24 and calculated by adding scores for 4 areas of the face.

Safety Endpoints:

- Incidence of adverse safety events during the treatment and follow up period
- Subject assessment of pain and discomfort associated with treatments using an 11-point visual assessment scale (VAS) pain score

Subject Risks:
Risks to the subjects who participate in this study are the same as those subjects undergoing any dermatological laser treatment, such as for the removal of pigmented or vascular lesions, and permanent hair reduction to the upper lip area. Eye injury, due to the use of the laser, is a risk to the subject and the operator. Blistering, edema, erythema, and mild to moderate local pain are typical reactions to topical laser treatments. A lesser possibility exists for hyperpigmentation, hypopigmentation scarring, and/or infection. These conditions may or may not resolve over time.

Risk Management:
Subjects will be followed closely during the course of the trial and will have access to the investigators at all times via provision of after-hours telephone and/or pager numbers.

Any investigators, subjects or others present in the room while the laser treatment is rendered will wear suitable eye protection. A local anesthetic may be given before treatment to minimize pain and/or discomfort resulting from laser treatment. All other known risks will be disclosed to the subject via the informed consent process. Since this is an elective procedure and the subjects are volunteers, it can be assumed that their signature on the Informed Consent document indicates that the subject acknowledges and accepts the risks involved in the treatment of neck and chest rhytides.

Safety Analysis:
The potential events that are anticipated post treatment include prolonged erythema, discomfort, and herpes simplex reactivation. Other, less frequent transient potential events associated with any dermatological laser treatment include bleeding, crusting, numbness, itching, blistering and dryness. The occurrence of these events will be considered a treatment response and not an adverse device effect. Anticipated adverse device effects associated with any dermatological laser treatment include scarring, undesirable textural changes and depigmentation.

Grading of these clinical observations will be captured on the case report form under the following scale at each treatment visit and follow up visit:

0=none
1=trace
2=mild
3=moderate
4=severe

Complications:
If an unanticipated adverse event occurs at any time during or after the use of the laser within the study period, the Investigator must report it to the sponsor. The sponsor and the Institutional Review Board are to be notified within five days.

Any serious adverse event or complication directly attributable to the use of the laser system will be reported to Union Square Laser Dermatology, as soon as possible within twenty-four (24) hours or sooner and to the Institutional Review Board within five (5) days.

Any deaths, whether or not related to the use of the laser, will also be reported to Union Square Laser Dermatology, within twenty-four (24) hours or sooner and to the Institutional Review Board within five (5) days.

IRB Review/Ethics/Informed Consent
The protocol, informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB prior to use. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56, applicable laws and the IRB requirements.

The sponsor must submit any change to the protocol to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the FDA and the reviewing IRB are notified within 5 working days.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information, before inclusion in the study, using the IRB approved informed consent document, including the objective and procedures of the study and the possible risks involved. Informed consent must be obtained prior to performing any study-related procedures, including screening and changes in medications including any washout of medications. A copy of the signed informed consent document must be given to the study subject. Written, witnessed Informed Consent will be obtained from each subject prior to participation in this study.

Confidentiality:
This study will be performed in accordance with the Declaration of the World Assembly, 1975 Toyko, Japan (Fed. Reg. 40, 16056, April 9, 1975) and the "Good Clinical practices for Drug and Medical Devices". These guidelines will be followed specifically with regard to the privacy and confidentiality of subjects' care and study records. Records of participation in the study will be held confidential except when sharing the information is required by law or as described in this protocol. The study doctor, the sponsor or persons working on behalf of the sponsor and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify subjects by name. This means that absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, subjects will not be identified.

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