Clinical Research Protocol

Protocol Title:	Evaluation of the Lutronic PicoPlus for the treatment of dermatological conditions such as unwanted tattoos and benign pigmented lesions
Protocol Number:	L16004
Version:	5.0
Date:	May 23, 2019
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1 Objective

The objective of this investigation is to evaluate the Lutronic PicoPlus for the treatment of dermatological conditions, such as, but not limited to, unwanted tattoos and benign pigmented lesions. The primary objective is to evaluate the capability of the technology to remove unwanted tattoos and benign pigmented lesion including melasma. In this pilot protocol, the PicoPlus treatment may be compared to other commercially available medical laser devices as part of this study.

2 Non-Significant Risk Determination

In accordance with the definition of "Significant Risk Device" provided in 21 CFR 812.3, each device to be used in this study has been determined to be Non-Significant Risk devices based on the following:

a) It is not an implant
b) It is not purported or represented to be for use in supporting or sustaining human life and do not present a potential for serious risk to the health, safety or welfare of a subject
c) It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health
d) Use of the device poses no risk to the health, safety, or welfare of a subject

3 Study Device

3.1 Device Description

The Lutronic PicoPlus System (Lutronic Corp, Seoul, S. Korea) to be used in this pilot study is an investigational device intended to be used for dermatological conditions including unwanted tattoos and benign pigmented lesions. All PicoPlus devices to be used in the study will bear the following required labeling:

"CAUTION: Investigational Device.
Limited by Federal (or United States)
Law to Investigational Use."

The PicoPlus System is a state-of-the-art Q-switched laser system with multiple handpieces and similar to the Cutera Enlighten laser system (Cutera Inc, Brisbane, CA) which received 510(k) market clearance (K160488, K140727 & K133945) from the Food and Drug Administration (FDA) on Oct. 28, 2016, Nov 6, 2014 and Aug 11, 2014, respectively. The Cutera Enlighten laser system is intended for use in surgical and aesthetic applications in the medical specialties of dermatology and general and plastic surgery.

The 1064 nm wavelength of the enlighten laser system is indicated for:

- treatment of benign pigmented lesions on patients with all skin types (Fitzpatrick I-VI)
- tattoo removal for dark colored tattoo inks and for multicolored tattoos containing dark colored tattoo inks on patients with all skin types (Fitzpatrick I-VI)

The 532 nm wavelength of the enlighten III laser system is indicated for:

- treatment of benign pigmented lesions on patients with Fitzpatrick skin types I-III
- tattoo removal for lighter colored tattoo inks, including red and yellow inks, on patients with Fitzpatrick skin types I-III

The 670 nm wavelength of the enlighten III laser system is indicated for treatment of benign pigmented lesions on patients with Fitzpatrick skin types I-III.

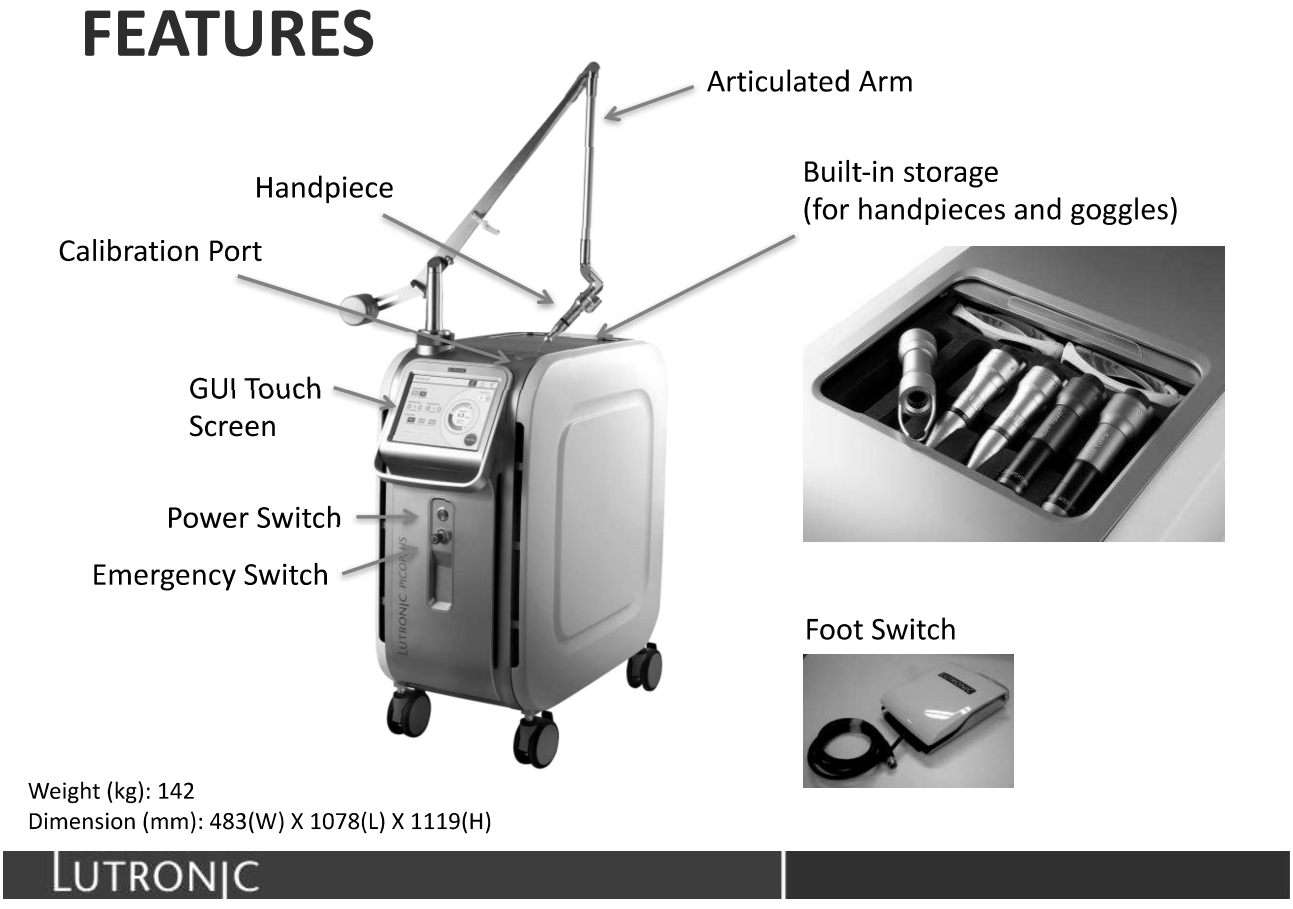
Table 1 provides a summary of PicoPlus system specifications and comparison to the Cutera Enlighten device.

Lutronic's new PicoPlus system delivers picosecond and nanosecond pulse durations at 1064nm and 532nm wavelengths plus 2 wavelengths from solid dye handpiece, the 595nm and 660nm. The touch screen control of the PicoPlus device auto detects the user selected handpiece (5 choices: 1064/532 with Zoom & Pico Toning Collimated, 595nm, 660nm and 1064nm Focused Dots) attached to the articulated arm (Figure 1). The Zoom and Pico Toning Collimated handpieces allow the user to select a range of spot sizes and the touch screen's available parameters automatically adjusts to the selected spot size. A detailed description of the system and its capabilities is provided by Lee et al., (1)

Table 1. PicoPlus™ Specifications

	Lutronic PicoPlus	Predicate Cutera Enlighten
Type	Q-switched Nd:YAG laser	Q-switched Nd:YAG laser
Wavelength	532nm, 595nm, 660nm and 1064nm	532nm, 670nm and 1064nm
Maximum Delivered Energy	300mJ at 532nm 800mJ at 1064nm 110mJ at 595nm 90mJ at 660nm	300mJ at 532nm 600mJ at 1064nm 125mJ at 670nm
Maximum Fluence	1064nm: 100 J/cm2 @ 1mm, to 1 J/cm2 @ 10mm 532nm: 45J/cm2 @0.9mm to 0.45 @9mm	2.5 J/cm2 at 532nm 10 J/cm2 at 1064nm
Pulse Duration	550 ps, 2 ns	532&1064nm 750 ps or 2 ns; 660ps 670nm
Repetition Rate	1, 2, 5 or 10 Hz or single shot	1, 2, 3.3, 5 or 10 Hz or single shot
Handpiece Spot Size	(1) Zoom 1- 6 mm @ 1064 nm 0.9 - 5.3 mm @ 532 nm (2) Pico Toning Collimated 6 - 10mm @1064nm 4.3 - 9mm @ 532nm (3) 2, 5mm @ 595nm (4) 2, 3mm @ 660nm (5) Focused Dots 7.4x7.4mm @1064nm with 81 focused spots of 100um each	2, 3, 4, 5, 6, 7 or 8 mm 532 and 1064nm (2, 3, 4, 5 & 6mm 670nm)
User Interface	LCD color touchscreen	Push-button control or LCD color touchscreen
Delivery System	Articulated arm with laser handpiece	Articulated arm with laser handpiece
System Cooling	Air plus water cooling	Closed cycle water to air heat exchanger
Aiming Beam	Laser diode 655nm <5mW	Laser diode 635nm <1mW
Weight	142 kg	324lbs (147kg)
Dimension	483x1078x1119mm 19x45x30 in	910x510x840mm 36 X 20 X 33 in
Power	100-240VAC max 15A, 50-60Hz	100-120VA, 20A 240VAC 15A, 50-60Hz

Figure 1. Lutronic PicoPlus System and accessories



3.2 Background

The nanosecond domain Q-switched Nd:YAG laser (for example Lutronic's Spectra), operates under the theory of selective photothermolysis at the wavelengths of 532 nm and 1064 nm, and has become the treatment of choice for removal of tattoos and pigmented lesions. The Spectra offers highly selective pigment removal with minimal thermal damage to the adjacent tissues. The nanosecond QS lasers are safe and effective in the treatment of tattoos, although treatment sessions are often painful and as many as 6 to 10 treatments are necessary to achieve acceptable clearance. Also the ns-based approach has some limitations due to the mostly thermal nature of the reaction, and in tattoo removal, the increasing variety of colors used often results in incomplete removal of the tattoo. Moving into the picosecond domain removes much of the photothermal nature of the reaction, replacing it with a nonlinear photoacoustic effect. The more complete breakup and smaller resulting particles are more readily removed by natural healing mechanisms through lymphatics, phagocytosis or trans-epidermal elimination. The photoacoustic effect also transfers most of the energy to mechanical forces resulting in a significantly reduced thermal effect on surrounding tissue compared to ns-domain. The lessened thermal effect is thought to account for the reduction in tissue side effects observed using picosecond laser treatment.

Since the introduction of the Picosure 755nm picosecond laser (Cynosure), several other picosecond laser devices have been launched that now include 1064nm, 532nm, 785nm and 670nm wavelengths. Numerous published studies demonstrate the ability of

picosecond lasers (2-15) to achieve better tattoo clearance in fewer treatments with less tissue side effects and similarly remove unwanted pigmented lesions.

For pigmented lesions the target chromophore is the melanin granules located inside the melanosomes generated by melanocytes. Using pulses significantly less than the thermal relaxation time of melanosomes and melanin granules, *i.e.* in the ps domain, should get even better results than the ns-domain, and by photooptical breakdown should induce a nonlinear reaction in the target so that destruction would not be thermal, but mechanical in nature [15].

The purpose of this exploratory investigational study is to evaluate the enhanced capabilities of the Lutronic PicoPlus laser system with its 5 handpieces and the broader range of power output for removal of unwanted tattoos or pigmented lesions as well as to explore other treatment opportunities.

4 Study Population

Adults between 18 and 60 years of age with unwanted tattoos or suitable dermatological condition who provide informed consent, and who meet inclusion/exclusion criteria.

4.1 Inclusion Criteria

- Male or Female
- Adults between age 18 and 60 years old
- Group A: Fitzpatrick skin type I – VI for unwanted tattoos and Group B: Fitzpatrick Skin Types I – IV for benign pigmented lesions and other conditions
- Unwanted tattoo that contains single or multi-color ink, and
    - Wiling to cover tattoos with a bandage or clothing; and/or have very limited sun exposure and use an approved sunscreen of SPF 50 or higher on the treated area starting 2 to 4 weeks before the treatment
- Ability to read, understand, and sign the Informed Consent Form
- Willing to have digital photographs taken of the treatment area and agree to use of photographs for presentation, educational or marketing purposes.
- Understands and accepts the obligation not to undergo any other procedures in the areas to be treated
- Willing and able to comply with all study participation requirements including returning for follow-up visits and abstaining from exclusionary procedures for the duration of the study

4.2 Exclusion Criteria

- If receiving treatment for unwanted tattoo: double tattoos (tattoo over tattoo), history of allergic reactions to pigments following tattooing, local anesthetics or topical antibiotics
- If receiving treatment for benign pigmented lesions including melasma: history of use of a lightening medication (hydroquinone, tranexamic acid), isotretinoid (or retinoid), or light-sensitive medication in the last 6 months

- Known cardiovascular disease or cardiac surgery that in the opinion of the investigator would interfere with study treatments
- Previous interventions or treatment with another device in the target area within 6 months of enrollment or during the study
- Pregnant or lactating or planning pregnancy before end of study
- Presence of an active systemic, local skin disease, medication or condition that may affect wound healing or interfere with participation or treatment to the active area.
  - Active or recurrent cancer of current chemotherapy or radiation therapy
  - History of seizure disorders due to light
  - History of vitiligo, eczema, or psoriasis
  - History of connective tissue disease, such as systemic lupus erythematosus or scleroderma
  - History of pigmentary disorders, particularly tendency for hyper- or hypo-pigmentation
  - History of disease stimulated by heat, such as recurrent herpes simplex and/or herpes zoster (shingles) in the treatment area, unless treatment is conducted following a prophylactic regimen
  - History of keloid scarring, hypertrophic scarring or of abnormal wound healing.
  - History of immunosuppression/immune deficiency disorders or currently using immunosuppressive medications.
  - History of seizure disorders due to light.
  - Suffering from coagulation disorders or taking prescription anticoagulation medications
  - History of keloid scarring, hypertrophic scarring or of abnormal wound healing Any use of medication that is known to increase sensitivity to light according to Investigator's discretion
- Excessive or recent significant tan in areas to be treated or unable/unlikely to refrain from tanning during the study
- Current smoker or history of smoking within 3 months of study participation
- Systemic use of corticosteroid or isotretinoin within 6 months of study participation
- Anytime in life, having have used gold therapy (gold salts) for disorders such as rheumatologic disease or lupus
- Any physical or mental condition including alcohol or drug abuse that in the opinion of the investigator could interfere with subject's suitability for inclusion in study

5 Study Design

5.1 Number of Subjects

Up to 100 subjects will be enrolled in this study. Subjects will be enrolled only after written approval to conduct this study has been received from an Institutional Review Board (IRB); and only after providing signed, informed consent to participate in the study.

5.2 Study Design

The study design is a multicenter exploratory, open-label, clinical trial comparing each subject's condition before to after treatment. Subjects will be selected and assigned to Group A for treatment of unwanted tattoos and Group B for treatment of unwanted benign pigmented lesions, melasma or other skin conditions such as skin rejuvenation.

5.2.1 Group A Treatment Plan

Subjects receiving treatment for unwanted tattoos (Group A) will receive 1 - 8 treatments (typically 3 – 5) at 2 - 12 week intervals (typically 6- 8 week) with an optional follow-up visit 1-2 weeks after the first treatment for safety evaluation and a final follow-up 1-3 months after the last treatment for safety and efficacy evaluation. At the discretion of the Investigators, additional follow-up visits may take place to observe the time course of reactions after treatment and/or to assess efficacy (i.e. 6 month follow-up). Table 2 summarizes the visit schedule and Table 3 summarizes the study event schedule. The screening/pre-treatment visit and first treatment visit may occur on same day.

5.2.2 Group B Treatment Plan

Subjects receiving treatment for unwanted benign pigmented lesions or other dermatological condition such as skin rejuvenation (Group B) will receive 1 - 8 treatments (typically 2 – 4) at 1 – 12 week intervals. For facial treatments the typical interval is 3 – 5 weeks and for off-face the interval is typically a little longer. Subjects may have an optional follow-up visit 1-2 weeks after the first treatment for safety evaluation and at least one final follow-up visit 1-3 months after the last treatment for safety and efficacy evaluation. At the discretion of the Investigators, additional follow-up visits may take place to observe the time course of reactions after treatment and/or to assess efficacy. Table 2 summarizes the visit schedule and Table 3 summarizes the study event schedule. The screening/pre-treatment visit and first treatment visit may occur on same day.

Table 2. Study Visit Schedule

Visit	Group A Tattoo	Group B Pigment and other conditions
Evaluation	1	1
Treatment	1 to 8 treatments Typically 3-5	1 to 8 treatments Typically 2-4
	Typically at 6 -8 week interval, but PI could schedule at 2 to 12 weeks interval	Typically at 3 - 5 week interval, but PI could schedule at 1 to 12 weeks interval
Follow-up	1 at least 3 months after last treatment 2nd follow-up 6mo	1 - 3 months after last treatment

Table 3. Study Event Schedule

Procedures	Site Initiation	Screen / PreTx Evaluation	1st Tx Visit	Optional 1 – 2 wk safety evaluation	2nd Tx Visit	3rd Tx Visit, etc.	1 - 3 month follow-up visits (s)
Review protocol & study requirements	x						

Inclusion / Exclusion		x					
Med History Review		x	x	x	x	x	x
ICF		x					
Pre-Treatment Skin Evaluation		x	x	x	x	x	x
Laser Treatment			x		x	x	
Immediate Post-Tx Skin Evaluation			x		x	x	
Pre-Tx Clinical Photos			x	x	x	x	x
Post-tx Photos			x	x	x	x	
Patient Satisfaction Questionnaire							x

5.3 Investigational Sites

Up to seven (7) investigational sites may participate in this study. The following sites have been identified to date.

Site #1: PI: Girish S. Munavalli, MD
Dermatology Laser & Vein Specialists of the Carolinas
1918 Randolph Road Suite 550
Charlotte, NC 28207
Phone: 704.375.6766

Site #2 PI: Emmy M. Graber, M.D., M.B.A.
The Dermatology Institute of Boston, PC
441 Stuart Street, Suite 404
Boston, MA 02116
Work Phone: 857.317.2057

Site #3 PI: Arisa Ortiz, MD
UC San Diego, Department of Dermatology
8899 University Center Lane
San Diego, CA 92122
Phone: 818.744.3322

Site #4 PI: Hyun-Soo Lee, MD
Metro Dermatolog8
40-12 80th Street
Elmhurst, NY 11373
Phone: 718.395.5125

Site #5 PI: Kelly Stankiewicz, MD
DMG Aesthetics
2155 City Gate Lane,
Suite 225
Naperville, IL 60563

Phone: 630-547-5040

Site #6 PI: Omar Ibrahimi, MD, PhD
Connecticut Skin Institute Skin Cancer, Laser & Cosmetic Surgery
999 Summer Street, Suite 205
Stamford, CT 06905
Phone: 203.428.4440

Site #7 PI: William E. LoVerme, MD
19 Fortune Drive
Billerica, MA 01821
Phone: 339-234-3008

5.4 Study Duration

This study is not expected to exceed 36 months in duration.

6 Study Treatment

6.1 Pre-Treatment

Prior to the first treatment, the Investigator or his/her designee will obtain a medical history for each subject and determine study eligibility in accordance with the Inclusion and Exclusion Criteria specific to this protocol. Subjects will be directed to not use self-tanners within the target treatment area for at least 4 weeks prior to treatment and to avoid using harsh skin treatments such as depilatories, abrasive cleansers, etc. for 1-2 weeks prior to treatment. If the patient is a female capable of pregnancy, a urinary pregnancy test will be performed prior to study participation to determine if she is pregnant. If the result of the test is positive or if the female is breast feeding, she is not eligible to participate in study. The treatment area can be on the face, chest arms, legs or body. High-resolution digital photographs will be taken before and after each treatment. The pre-treatment photo will serve as the baseline for comparison to follow-up photos to assess safety and efficacy. Skin instrumental measures may be taken with standard devices such as DSM II colorimeter (Cortex Technology, Hadsund, Denmark). Other instruments may measure skin properties or visualize the skin using an ultrasound device. Prior to each subsequent treatment, the investigator or his/her designee will review and update the medical condition and compliance with inclusion and exclusion criteria. The clinician will evaluate and grade the skin condition before each treatment and insure that the area has recovered suitably from the prior treatment(s) before proceeding to further treatments. In the event that treatment is delayed the investigator will record the specific skin condition and have subjects return after an additional 1 to 4 weeks for reassessment and subsequent treatments.

6.2 Anesthesia

Adjunctive cooling either by moist air, cool gel packs, or cool saline wipes may be used during and/or after treatment to enhance comfort. If subjects require additional means of reducing treatment or post-treatment discomfort, optional pre-treatment application of

topical anesthesia, such as BLT (20% benzocaine, 6% lidocaine, 4% tetracaine - Sobanko Derm Surg 2012), EMLA®, ElaMax® or Pliaglis® will be applied using an occlusive technique for up to 60 minutes prior to treatment. At the discretion of the Investigator. subjects may be given anesthesia with a local intradermal or nerve block injection of lidocaine with or without epinephrine, or equivalent, for areas treated at more aggressive settings. However, subjects will NOT be given sedation to the extent that all sensation is blunted and the subject is not able to verbally participate during the treatment process. If the pain becomes too uncomfortable, the treatment will be discontinued, or the settings on the laser can be lowered to a more comfortable level.

6.3 Analgesic and anxiolytic oral medications

At the discretion of the PI subjects may be offered oral analgesic and/or anxiolytic medication to further manage discomfort during treatment. Due to the side effects caused by these types of medications, subjects will be required to have a driver provide transportation for the procedure. These subjects must be willing to comply with pre-treatment medication instructions and sign the “Analgesic & Anxiolytic Medication Consent”.

6.4 Biopsies

In some subjects biopsies may be taken to evaluate the effect of treatment on the skin and to evaluate the safety and time course of healing. Biopsies are *optional* and may be taken immediately after treatment or at various days, weeks and monthly intervals post treatment. Biopsies will typically be of the punch type and range in diameter from 2- 6 mm, depending on the device setting and anatomic location. The areas of the skin to be biopsied will be numbed with an injection of local anesthetic. Biopsies will be retained for histological analysis. Subjects will return after an appropriate interval (5-7 days face, 10 – 14 days, trunk and limbs) depending on location of the biopsy on the body to have the sutures removed, or sutures may be removed during subsequent biopsy visit or another scheduled follow-up visit.

6.5 Study Treatment

Selection of settings will be based upon the practitioner’s judgement and in accordance with treatment guidelines, publications and experience with similar ultrashort pulse laser devices. A series of test spots may be performed within the treatment area or on a less noticeable area with similar skin color and texture. After application of test spots, skin reactions will develop and can be evaluated for selection of setting parameters usually in 15 minutes for Skin Types I – III, but will take from 24 – 72hrs or longer to develop for darker skin types. For darker skin type subjects, if test spots are used to establish treatment settings, the treatment will take place on a separately scheduled session. To help evaluate performance the investigator may compare effects of the PicoPlus laser system to other FDA approved commercially available nanosecond or picosecond laser systems. Commercially available products will be used according to the manufacturer’s recommendations and investigator’s experience.

In preparation for treatment, the test spot or skin treatment area will be cleansed with mild soap and water and dried. If hair is present, the area should be shaved. Topical anesthetic cream such as BLT will be applied using an occlusive dressing technique for sufficient time (typically 45-60 min) to the point where adequate anesthesia is achieved. If topical anesthetic is used, the anesthetic will be thoroughly removed, the skin wiped clean and then sanitized with an antiseptic scrub such as Hibiclens®. If discomfort is experienced during treatment, subjects may be offered adjunctive cooling such as cold air, cool gel packs, or cold moist cloths. Subject discomfort during study treatment will be documented using a 0 (None) to 10 (Severe) pain rating scale. Mild discomfort is typical during the treatment of benign pigmented lesions. For tattoo removal treatments, because settings are typically higher, moderate to significant discomfort is frequently reported. Most patients describe the discomfort as less than when the tattoo was applied. Some areas are more sensitive than others. Subjects may request that treatment be discontinued at any time for any reason.

6.6 Post-Treatment

Cold compresses or chilled gel pack may be applied to the treatment area immediately after treatment to reduce swelling and discomfort. If a blister or greying of skin develops, the area will be treated using standard wound care methods. Subjects will be directed to avoid heat (hot tubs, saunas, etc.) and skin irritant products (products containing tretinoin, retinol, benzoyl peroxide, glycolic/salicylic acids, astringents, etc.) for 1 – 2 days after treatment. At the discretion of the Investigator, subjects may be asked to apply post-treatment products to help minimize skin reactions such as a topical steroid (such as Hydrocortisone Cream) or a skin care lightening agents (such as Tri-Luma® or Hydroquinone Cream) during the course of treatment and post-treatment follow-up period. In the event that any of the skin reactions is excessive or prolonged or unanticipated adverse events occur, additional follow-up visits may be scheduled as deemed appropriate by the investigator. Any additional visits will be recorded and skin condition assessed.

6.7 Follow-Up Visits

Subjects may be scheduled to return for a follow-up visit 1-2 weeks after the first treatment to assess skin safety and skin reactions to treatment. An additional treatment may be performed as well at this visit. To complete the study subjects must return for a follow-up visit 1-3 months after their last treatment to assess safety and efficacy. Clinician grading, patient satisfaction, and standardized photographic methods will be used at the 1-3 month follow-up visit. At the Investigator's discretion, the subject may be asked to return for a later follow-up visit to reassess safety and efficacy.

7 Institutional Review Board Review

All investigational sites in this study will receive approval by local or independent Institutional Review Board (IRB) prior to starting the study.

Sites allowed to use an independent IRB will be reviewed by:

Allendale Investigational Review Board

30 Neck Road
Old Lyme, CT 06371
Phone: 860.434.5872
Chairperson: Robert J. Staab, PhD

8 Informed Consent

Signed informed consent will be obtained from all subjects by the Investigator or his/her designee prior to participation in this study.

9 Study Outcomes

9.1 Standardized methods

Standardized photographs and clinician grading scales will be obtained at baseline and follow-up visits. Camera angle, distance and lighting conditions will be controlled to insure consistency for before and after photographs.

Primary Outcome Measures:

The primary outcome measures that will be analyzed include qualitative clinician grading assessment of improvement as well as patient self-assessed satisfaction. Secondary measures may include colorimeter measurements of changes in skin color and/or other instruments to measure skin properties or visualize the skin using an ultrasound device.

10 Risks and Benefits

10.1 Potential Risks

There is a risk of adverse events, skin reactions or side effects. Expected side effects include:

- Discomfort. Mild discomfort is typical during the treatment of benign pigmented lesions. For tattoo removal treatments, where higher settings are typically used, moderate to significant discomfort is frequently reported. Most patients describe the discomfort as less than when the tattoo was applied. Some areas are more sensitive than others.
- Edema and erythema. Swelling and redness often occur, but will subside in 2-5 days and can be reduced with regular ice application.
- Purpura. The area may appear to be bruised after treatment. The bruising will typically fade in 5-7 days.
- Texture changes. Transient texture changes are often noted, but usually resolve with time. Blisters/scabs/crusting. These may occur and usually take 4-10 days to heal and up to 2 weeks for off-face treatments.
- Petechia or pinpoint bleeding. For tattoo removal treatments, pinpoint bleeding or

oozing may develop and can continue up to 2 days post-treatment. Pinpoint bleeding is less common during treatment of benign pigmented lesions but may develop and will typically resolve within a few hours post-treatment.

- Hyper/hypopigmentation. Skin can develop temporary lightening or darkening after laser treatment. Hyperpigmentation can be worsened with sun exposure. Hypopigmentation usually occurs after multiple treatments. Pigmentary issues typically resolve with time, but can be permanent.
- Allergic reaction. Patients who have had a prior allergic reaction to ink during tattoo application may have a similar reaction after laser treatment. This reaction can be controlled by a pre-treatment and/or post-treatment regimen of steroids and antihistamines.
- Infection. Despite good wound care, pain, swelling, oozing, and fever can indicate the development of an infection. Topical and/or oral antibiotics may be necessary.
- Scarring. Scarring is a rare occurrence, but it is a possibility if the skin's surface is disrupted. To minimize the chances of scarring, it is important that patients follow all post-treatment instructions provided by their healthcare provider. Good post-treatment care can help reduce the possibility of scarring.
- Darkening of lesions. Lesions will darken post-treatment and will slough 5-21 days post- treatment.
- Paradoxical darkening or color change. Some tattoo inks, including many lighter and skin- tone inks, may darken or change color in response to treatment.
- “Bleeding” of ink into surrounding skin. May result in smudging or loss of definition of a tattoo rather than removal.

10.2 Potential Benefits

Subjects who participate in this study may benefit from an aesthetic improvement in the reduction of the appearance of their tattoo or benign pigmented lesions. There are, however, no guarantees of these or any other benefits from participation. Multiple treatments for removal of pigmented lesions are common, and complete clearing is not always possible. Multiple treatments are required for tattoo removal, and complete clearing is not always possible. Not all ink colors and compositions will respond to tattoo removal treatment.

11 Adverse Events

Adverse events (AE) and/or Unanticipated Adverse Device Effects (UADE) that occur during the course of the study will be documented in the subject’s study records and reported to the Sponsor and IRB as required.

Serious Adverse Events (SAE) will be reported by the Investigator to the Sponsor and IRB immediately upon learning of the event.

Unanticipated Adverse Device Effect (UADE) will be reported as soon as possible to the Sponsor and IRB, but no later than 10 working days after first learning of the effect. The Sponsor requests, however, notification within 48 hours after learning of any UADE.

Severity

Severity of adverse events will be scored by the Investigator or his/her designee using the following scale:

0=None No adverse event observed

1=Trace Slightly observable sign or symptom of adverse event

2=Mild Minimal sign or symptom, usually transient which resolves in a week, which requires no special medical intervention

3=Moderate Sign or symptom sometimes lasting more than a week, which may require simple medical intervention

4=Severe Sign or symptom that is intense or debilitating, sometimes lasting several weeks or longer; requires medical intervention

Relationship to Treatment

The relationship between an adverse event (AE) and treatment is defined as follows:

Related An adverse event that appears in the treatment area and has a direct relationship to the study treatment administered, and such that another etiology is highly unlikely

Probably Related An adverse event that appears in the treatment area that has a strong temporal relationship to the study treatment, and such that another etiology is unlikely or significantly less likely

Possibly Related An adverse event that appears in the treatment area that has a strong temporal relationship to the treatment, and such that another etiology is equally possible

Probably Not Related An adverse event that appears in the treatment area that has little to no temporal relationship to the study treatment, and such that another etiology is likely to exist

Not Related An adverse event that appears in the treatment area that has no temporal relationship to the study treatment, and such that another etiology is nearly certain

12 Subject Accountability

Study participation is voluntary and subjects may withdraw from the study at any time for any reason. In case of subject withdrawal, additional subjects may be enrolled into the study as replacements with prior approval from Sponsor and IRB.

13 Records and Reporting

It is the responsibility of each Investigator to report all AE, SAE and UADE to the Sponsor and IRB. SAE will be reported to the Sponsor and IRB immediately. All UADE will be reported to the IRB and FDA as soon as possible, but no later than 10 working days after learning of the effect. The Investigator will include a listing and description of all adverse events as part of the annual progress report.

14 Confidentiality

Subject confidentiality will be met in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and 21CFR Part 50, Protection of Human Rights. These regulations will be followed specifically with regard to the privacy and confidentiality of subject care and study records.

Personnel associated with Investigator's office, along with the Sponsor of this study, Lutronic, Inc., the FDA and the reviewing IRB, have the right to review all of the data, including photographs, collected during this study. These entities are also required to maintain confidentiality.

15 Subject Payment

Subjects will receive $50 for follow-up visits that occur between treatments and $100 for the follow-up observations after the last treatment visit. Study treatments and post-treatment care visits will be provided at no cost to the subjects. If subjects have any biopsies done, they will be paid an additional $150 for participating in the study.

16 References

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17 Appendix A. Patient Satisfaction Questionnaire

Please evaluate the outcome of you PicoPlus treatments. Before and after photos of your treatment area are available to help you make your assessment.

1. What condition did you have treated:

   ☐ Tattoo ☐ Pigmented Lesions ☐ Melasma ☐ Skin rejuvenation or ☐ Other

2. Have you noticed any improvement in your treated condition?

   ☐ Better ☐ About the Same ☐ Worse

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

   ☐ Very Satisfied ☐ Satisfied ☐ Somewhat Satisfied ☐ Neutral ☐ Disatisfied

4. How much improvement would you say the PicoPlus treatments gave?

   ☐ 75 -100% ☐ 50 -74% ☐ 25- 49% ☐ 10- 24% ☐ 0-10% Barely or not at all

5. Would you recommend treatments to family or friends?

   ☐ Yes ☐ No ☐ Neutral

6. Have others noticed an improvement?

   ☐ Yes ☐ No

7. If you could start over, would you be treated with PicoPlus again?

   ☐ Very Likely ☐ Likely ☐ Neutral ☐ Unlikely ☐ Very Unlikely

8. Would you recommend PicoPlus treatments to family or friends?

   ☐ Definitely Would ☐ Probably Would ☐ Not Sure ☐ Probably Would Not

   ☐ Definitely Would Not

18 Appendix B: Clinician Grading Scales

18.1 Investigator's Global Assessment of Improvement

At 6 to 12 weeks (24 weeks optional for tattoo removal) post-final treatment as applicable, the Investigator will be asked to rate the degree of tattoo clearing or reduction in benign pigmentation observed in the subject's treated area using the Physician's Global Assessment of Improvement Scale:

3 = Very Significant or Complete Clearing (75 – 100%)
2 = Significant Clearing (50 – 74%)
1 = Moderate Clearing (25 – 49%)
0 = Mild or No Clearing (0 – 24%)

18.2 Subject's Global Assessment of Improvement

Subjects will be asked to rate the degree of tattoo clearing or reduction in benign pigmentation at 6 weeks to 12 weeks (24 weeks optional for tattoo removal) post-final treatment as applicable, as compared to baseline, using the Subject's Global Assessment of Improvement Scale:

3 = Very Significant or Complete Clearing (75 – 100%)
2 = Significant Clearing (50 – 74%)
1 = Moderate Clearing (25 – 49%)
0 = Mild or No Clearing (0 – 24%)

18.3 Subject Satisfaction Assessment

At 6 weeks to 12 weeks (24 weeks optional for tattoo removal) post-final treatment as applicable, subjects will be asked to rate their level of satisfaction with the laser treatment outcome and the overall laser treatment procedure, using the Subject Satisfaction Assessment Scale:

2 = Extremely Satisfied
1 = Satisfied
0 = Neutral
-1 = Unsatisfied
-2 = Extremely Unsatisfied

18.4 Blinded Reviewer's Global Assessment of Improvement

At 6 weeks to 12 weeks (24 weeks optional for tattoo removal) post-final treatment, the blinded reviewers may be asked to perform an assessment of subject photographs. Each reviewer will be asked to first determine the temporal order (before and after) of each photograph pair, and then rate the degree of tattoo clearing or reduction in benign pigmentation observed in the post-treatment photograph using the Global Assessment of Improvement Scale:

3 = Very Significant or Complete Clearing (75 – 100%)
2 = Significant Clearing (50 – 74%)
1 = Moderate Clearing (25 – 49%)
0 = Mild or No Clearing (0 – 24%)

18.5 Melasma Area Severity Index (MASI)

At 6 – 12 weeks (24 weeks optional) post-final treatment for melasma, blinded graders will use the melasma area severity index (16) to grade the baseline and after photos. The severity of the melasma in each of the four regions (forehead, right malar region, left malar region and chin) is assessed based on three variables: percentage of the total area involved (A), darkness (D), and homogeneity (H).

A numerical value assigned for the corresponding percentage area involved is as follows: 0=no involvement; 1=<10% involvement; 2=10-29% involvement; 3=30-49% involvement; 4=50-69% involvement; 5=70-89% involvement; and 6=90-100% involvement. The darkness of the melasma (D) is compared to the normal skin and graded on a scale of 0 to 4 as follows: 0=normal skin color without evidence of hyperpigmentation; 1=barely visible hyperpigmentation; 2=mild hyperpigmentation; 3=moderate hyperpigmentation; 4=severe hyperpigmentation. Homogeneity of the hyperpigmentation (H) is also graded on a scale of 0 to 4 as follows: 0=normal skin color without evidence of hyperpigmentation; 1=specks of involvement; 2=small patchy areas of involvement <1.5 cm diameter; 3=patches of involvement >2 cm diameter; 4=uniform skin involvement without any clear areas).

To calculate the MASI score, the sum of the severity grade for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas (10-30%).

Total MASI score: Forehead 0.3 (D+H)A + right malar 0.3 (D+H)A + left malar 0.3 (D+H)A + chin 0.1 (D+H)A

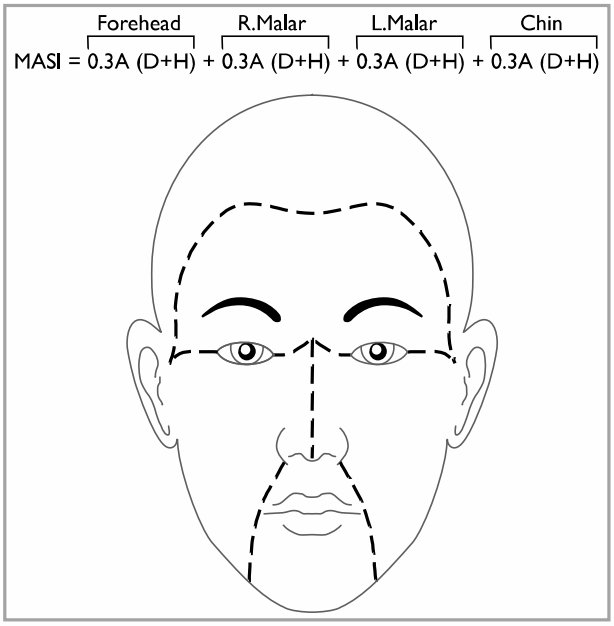

Fig 1. The Melasma Area and Severity Index (MASI).[8] Published with permission. Topical retinoic acid (tretinoin) for melasma in black patients. *Arch Dermatol* © 1994; 130: 727–33. American Medical Association. All rights reserved.