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Protocol Title:	Evaluation of the PicoWay® Laser System with 730 nm and Resolve™ Fusion Handpieces for Treatment of Benign Pigmented Lesions and Wrinkles
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1. Study Synopsis

Protocol Number	PWY18010
Protocol Version	v 1.0 28NOV2018
Protocol Title	Evaluation of the PicoWay® Laser System with 730 nm and Resolve™ Fusion Handpieces for Treatment of Benign Pigmented Lesions and Wrinkles
Short Title	PicoWay 730 Resolve Fusion
Device Description	PicoWay® Laser System, Candela Corporation, Wayland, MA
Study Design	Prospective, non-randomized, multi-center, evaluator blinded, safety and efficacy clinical study
Study Objective	Evaluate the safety and efficacy of the PicoWay® Laser System with 730 nm and Resolve™ Fusion handpieces for treatment of benign pigmented lesions including dyschromia, and wrinkles including fine lines
Investigative Sites	Up to two (2) investigational sites located in the United States
Number of Subjects	Up to 160 subjects
Study Duration	The overall duration of this study is not expected to exceed 24 months
Study Overview	Upon enrollment subjects will be assigned to one or possibly both of the following laser treatment groups based on their qualifying indications: Group A: Benign Pigmented Lesions including dyschromia Group B: Wrinkles including fine lines Subjects will receive up to 4 laser treatments at 6 ± 2 week intervals with the PicoWay® Laser System. Handpiece selection and specific treatment parameters will be determined by the clinician. The treatment area will be photographed at every visit. Baseline photographs will be compared to follow-up photographs to determine the effectiveness of the laser treatments. The Study Doctor or staff will contact subjects by telephone 10 days after each treatment visit to assess healing response. Optional skin punch biopsies may be collected prior to or immediately after laser treatment, or at follow-up visits at clinician's discretion. Subjects must provide signed written consent prior to any biopsy procedure. Subjects may still participate in the study if they choose not to undergo biopsies. Subjects will be scheduled for follow-up visits at 4 ± 1 week, 8 ± 2 weeks and 12 ± 2 weeks after the final laser treatment. Additional visits may be requested at the discretion of the clinician.

Study Population	Adults seeking treatment of benign pigmented lesions including dyschromia and/or wrinkles including fine lines, and who satisfy all study inclusion and exclusion criteria, and who provide written informed consent will be considered eligible for this study.
Study Eligibility	Inclusion Criteria Subjects must meet all inclusion criteria to be enrolled in this study: 1. Willing to provide signed informed consent 2. Adults age 21 to 80 3. Fitzpatrick Skin Type (FST) I to VI 4. Presence of benign pigmented Lesions assessed at baseline as Pigment Severity Score (PSS) of “2” or higher and/or wrinkles assessed at baseline as Fitzpatrick Wrinkle Score (FWS) of “2” or higher 5. Willing to allow photographs and/or video to be taken of treated areas for the purposes of this research study 6. Willing to abstain from any other procedures for treatment of benign pigmented lesions or wrinkles in the laser treatment areas for the duration of the study including surgery, light, laser, ultrasound or radiofrequency treatments 7. Willing to abstain from use of prescription cosmetic products for treatment of benign pigmented lesions or wrinkles in the laser treatment areas for the duration of the study including injections of neurotoxins or dermal fillers, skin lightening creams, and wrinkle creams 8. Willingness to adhere to study treatment and follow-up visit schedules Exclusion Criteria Subjects who meet any exclusion criteria cannot be enrolled in the study: 1. Pregnant, planning pregnancy or breast feeding 2. Allergy to topical or injectable lidocaine or similar medications 3. Allergy to topical steroid or similar medications 4. Unprotected sun exposure in the six weeks prior to enrollment, or active tan in the laser treatment area 5. History of melanoma in the intended treatment area 6. History of keloid or hypertrophic scar formation 7. Use of topical or systemic retinoid therapy during the past six (6) months 8. Use of neurotoxins in the intended treatment area within the past three (3) months or throughout the duration of the study 9. Use of dermal fillers in the intended treatment area within the last six (6) months or throughout the duration of the study

	10. Severe immunosuppression resulting from medications and/or a medical condition that could impair healing after treatment. 11. Open wound or infection in the intended treatment area 12. History of light induced seizure disorders 13. Dermatologic and/or cosmetic procedures in the intended treatment area(s) during the past six months 14. The subject is not suitable, in the opinion of the clinician, for participation in the study due to medical or other reasons that could compromise the study integrity or subject safety
Study Visit Outline	NOTE: Screening Visit and Baseline/Treatment Visit #1 may occur on the same day Screening Visit: 1. Informed Consent 2. Inclusion and Exclusion Criteria Review 3. Medical History Review 4. Concomitant Medication Review 5. Fitzpatrick Skin Type (FST) Evaluation 6. Benign Pigmented Lesion and Wrinkle Evaluation Baseline / Treatment Visit #1: 1. Clinical Photography 2. Laser Treatment 3. Local Skin Response Assessment 4. Subject Pain Score Assessment 5. Safety Assessment 6. Skin Biopsy (optional) Telephone Contact 1. 10 days +/- 7 days after each treatment Treatment Visits #2 to #4: 1. Clinical Photography 2. Subject Satisfaction Score 3. Laser Treatment 4. Local Skin Response Assessment 5. Subject Pain Score Assessment 6. Safety Assessment 7. Skin Biopsy (optional) Follow-Up Visits: 4 ± 1 week, 8 ± 2 weeks, 12 ± 4 weeks. 1. Clinical Photography 2. Subject Satisfaction Score 3. Local Skin Response Assessment 4. Safety Assessment 5. Skin Biopsy (optional)
Measurement Instruments	5-Point Pigment Clearance Scale (Appendix A) 9-Point Fitzpatrick Wrinkle Scale (Appendix B)

	11-Point Subject Pain Scale (Appendix C) 5-Point Subject Satisfaction Scale (Appendix D) Local Skin Response (Appendix E)
Primary Efficacy Endpoints	1. Benign Pigmented Lesions Mean difference from Baseline to 12-week follow-up in Pigment Clearance Score (PCS) as determined by blinded evaluators from clinical photography 2. Wrinkles Mean difference from Baseline to 12-week follow-Up in Fitzpatrick Wrinkle Score (FWS) as determined by blinded evaluators from clinical photography
Secondary Efficacy Endpoints	1. Benign Pigmented Lesions Percentage of subjects demonstrating Pigment Clearance Score (PCS) of 3 or 4 (> 50% improvement) comparing Baseline to 12-week follow-up as determined by blinded evaluators from clinical photographs 2. Wrinkles Percentage of subjects demonstrating ≥ 1 score improvement in Fitzpatrick Wrinkle Score (FWS) from Baseline to 12-week follow-up visit as determined by agreement of 2 out of 3 blinded evaluators from clinical photographs 3. Subject Satisfaction Mean and distribution of Subject Satisfaction Scores at all visits beyond Treatment Visit #1 4. Subject Pain Mean and distribution of Subject Pain Scores following each treatment
Primary Safety Endpoint	Incidence, severity and relatedness of adverse device effects based on total number of laser treatments performed
Exploratory Endpoint	Analysis of laser-tissue effects and/or healing response from pre- and post-treatment skin biopsies using light microscopy and/or scanning electron microscopy

2. Abbreviations

ADE	Adverse Device Effect
cm, cm^2	Centimeter, Square Centimeters
CFR	Code of Federal Regulations
Ø	Diameter
FDA	Food and Drug Administration
FST	Fitzpatrick Skin Type
FWS	Fitzpatrick Wrinkle Score
GCP	Good Clinical Practice
Hz	Hertz
IEC	Independent Ethics Committee
IRB	Institutional Review Board
J	Joule
µbeam	Microbeam
µm	Micron
µs	Microsecond
mJ	Millijoule
mm	Millimeter
ms	Millisecond
nm	Nanometer
Nd:YAG	Neodymium: Yttrium Aluminum Garnet (YAG)
NSR	Non-Significant Risk
PCS	Pigment Clearance Score
PSS	Pigment Severity Score
ps	Picosecond
SE	Side Effect
SOP	Standard Operating Procedure
Tx	Treatment
UADE	Unanticipated Adverse Device Effect

3. Study Objective

The purpose of this study is to evaluate the PicoWay® Laser System with 730 nm handpiece and Resolve™ Fusion 1064 nm and 532 nm fractional handpieces for the treatment for benign pigmented lesions including dyschromia, and wrinkles including fine lines.

4. Background

The use of lasers to selectively target chromophores in the skin was first described by Anderson and Parrish in 1983[1] which led directly to the development of the first pulsed dye laser to be used in dermatology to treat vascular lesions. As laser technology advanced shorter pulse duration lasers, such as nanosecond pulse duration domain Q-switched Ruby and Nd:YAG lasers among others, were developed to safely and effectively remove tattoos and pigmented lesions using the same principles of selective photothermolysis.[3-5] Further advances led to the introduction of lasers with pulse durations in the picosecond domain including the Nd:YAG at wavelengths of 532 nm,1064 nm; and the alexandrite at 755 nm which have both been demonstrated as safe and effective for treatment of benign pigmented lesions, wrinkles, tattoo removal, and other indications.[6-13]

5. Study Design

This is a prospective, non-randomized, multi-center, evaluator blinded, safety and efficacy clinical study. Subjects will serve as their own control as the appearance of their benign pigmented lesions and/or wrinkles at baseline is compared to the appearance following laser treatment.

6. Study Overview

Subjects will participate in a Screening Visit to evaluate the presence of benign pigmented lesions including dyschromia, or wrinkles including fine lines. After evaluating all inclusion and exclusion criteria, and providing signed informed consent, subjects will be considered enrolled in the study and assigned a unique identification number that will appear on all records for that subject as the Subject ID.

Subjects will then either be scheduled for the Baseline / Treatment Visit #1 at a later date, or the Screening and Baseline / Treatment #1 Visits may be combined into the same visit.

Subjects will receive up to four (4) study laser treatments at 6 ± 2 week treatment intervals.

NOTE: Fewer than four (4) Treatment Visits may be required to reach maximum expected clinical results in some subjects. Treatments may therefore be stopped, and subject placed into the Follow-Up phase at the discretion of the Investigator.

The Study Doctor or staff will make up to three (3) attempts to contact subjects by telephone 10 days after each treatment to assess healing response.

After the final study laser treatment, subjects will be schedule for three (3) follow-up visits at 4 ± 2 week intervals, or approximately 1, 2 and 3 months.

After successful completion of the 12 week follow-up visit, subjects will be exited from the study.

7. Study Population

Up to 160 subjects will be enrolled in this study at up to two (2) investigational sites in the United States.

The Study Population will be enrolled at the discretion of the Investigator after determining that eligible subjects have unwanted benign pigmented lesions including dyschromia on the face, scalp, neck, chest, back, arms, hands, legs or feet; or wrinkles including fine lines on the face.

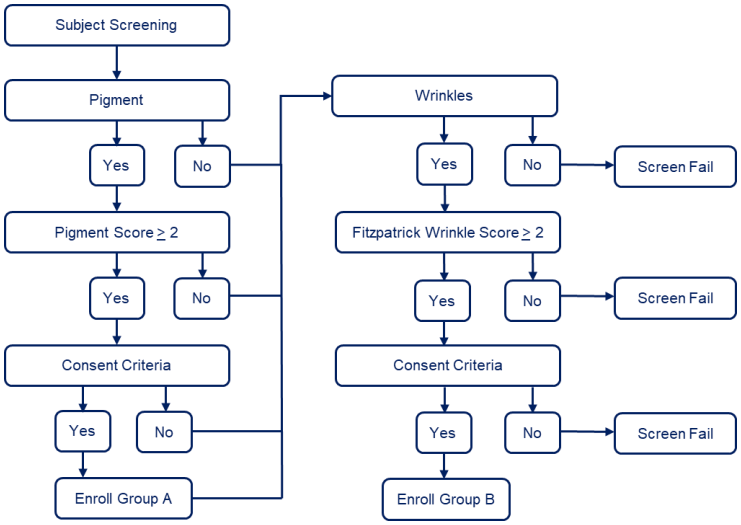
Subjects will be assessed at the Screening Visit and allocated to one ***or both*** study sub-groups if eligible:

Group A: Benign Pigmented Lesions including dyschromia

Group B: Wrinkles including fine lines

The logic scheme used for group allocation is provided below in Figure 1.

Figure 1: Study Group Allocation Logic



All subjects must satisfy the inclusion and exclusion criteria and provide signed informed consent to be eligible for participation in the study. Subjects enrolled in the study can discontinue their participation at any time for any reason without prejudice or reduction in the quality of their medical care. The Investigator or Sponsor can terminate a subject's participation in this study at any time to protect the subject's health or if a subject fails to

follow directions that result in noncompliance with study procedures. Subjects who withdraw or are terminated from the study prior to completion may be replaced.

8. Inclusion / Exclusion Criteria

8.1. Inclusion Criteria

Subjects must meet all inclusion criteria to be enrolled in this study:

1. Willing to provide signed informed consent
2. Adults age 21 to 80
3. Fitzpatrick Skin Type (FST) I to VI
4. Presence of benign pigmented Lesions assessed at baseline as Pigment Severity Score (PSS) of “2” or higher and/or wrinkles assessed at baseline as Fitzpatrick Wrinkle Score (FWS) of “2” or higher
5. Willing to allow photographs and/or video to be taken of treated areas for the purposes of this research study
6. Willing to abstain from any other procedures for treatment of benign pigmented lesions or wrinkles in the laser treatment areas for the duration of the study including surgery, light, laser, ultrasound or radiofrequency treatments
7. Willing to abstain from use of prescription cosmetic products for treatment of benign pigmented lesions or wrinkles in the laser treatment areas for the duration of the study including injections of neurotoxins or dermal fillers, skin lightening creams, and wrinkle creams
8. Willingness to adhere to study treatment and follow-up visit schedules

8.2. Exclusion Criteria

Subjects who meet any exclusion criteria cannot be enrolled in the study:

1. Pregnant, planning pregnancy or breast feeding
2. Allergy to topical or injectable lidocaine or similar medications
3. Allergy to topical steroid or similar medications
4. Unprotected sun exposure in the six weeks prior to enrollment, or active tan in the laser treatment area
5. History of melanoma in the intended treatment area
6. History of keloid or hypertrophic scar formation
7. Use of topical or systemic retinoid therapy during the past six (6) months
8. Use of neurotoxins in the intended treatment area within the past three (3) months or throughout the duration of the study
9. Use of dermal fillers in the intended treatment area within the last six (6) months or throughout the duration of the study
10. Severe immunosuppression resulting from medications and/or a medical condition that could impair healing after treatment.
11. Open wound or infection in the intended treatment area
12. History of light induced seizure disorders

13. Dermatologic and/or cosmetic procedures in the intended treatment areas during the past six months that would compromise study integrity
14. The subject is not suitable, in the opinion of the clinician, for participation in the study due to medical or other reasons that could compromise the study integrity or subject safety

9. Measurement Instruments

9.1. Pigment Clearance Score (PCS)

Clearance of pigment following study treatment will be measured using a validated 5-point Pigment Clearance Scale (PCS) that categorizes improvement in the appearance of pigmented lesions from 0=0% or No Improvement to 4=75-100% or Excellent Improvement.[14] The PCS scoring scale is provided in Appendix A.

9.2. Fitzpatrick Wrinkle Scale (FWS)

Improvement in the appearance of facial wrinkles following study treatment will be measured using the validated 9-point Fitzpatrick Wrinkle Scale (FWS) that categorized wrinkle severity from 1=Fine Wrinkles to 9=Deep Wrinkles.[15] The FWS scoring scale is provided in Appendix B.

9.3. Subject Pain Scale

Immediately after each treatment subjects will be asked to rate the amount of pain experienced during treatment using an 11-point Subject Pain Scale ranging from 0=No Pain to 10=Extreme Pain. The Subject Pain Scale is provided in Appendix C.

9.4. Subject Satisfaction Survey

At each study visit beyond Treatment Visit #1 the subjects will be asked to rate their level of satisfaction with the treatment results so far using a 5-point Subject Satisfaction Survey ranging from -2=Extremely Dissatisfied to 2=Extremely Satisfied. The Satisfaction Survey is provided in Appendix D.

10. Study Visit Procedures

10.1. Screening Visit

The following activities typically take place during the Screening Visit.

<u>Informed Consent</u>

The site will provide detailed information about the study, including study procedures, visit schedule, potential risks and benefits and alternative treatment options. The subject will be given time to review the informed consent form (ICF). If the subject wishes to participate, he/she will complete the ICF with a signature and date. The original will be retained with subject's study records and a copy will be provided to the subject.

Medical History

Subject's medical history, including dermatological treatment history and assessment of medication use will be documented.

Pregnancy Test

Women of childbearing potential will undergo a urine pregnancy test. Subjects with a positive pregnancy test are ineligible for study participation.

A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose partners have been vasectomized or whose partners are utilizing mechanical contraceptive devices.

Treatment Area Examination and Lesion Identification

Wrinkle evaluation will be performed using the Fitzpatrick Wrinkle Score. Benign pigmented lesions, a description of lesion type anatomical location, and size will be documented.

Inclusion/Exclusion Criteria Review

Study inclusion and exclusion criteria will be reviewed to verify study eligibility.

10.2. Baseline and Treatment Visits

The following activities typically take place during each Treatment Visit.

Pregnancy Test

Women of childbearing potential will undergo a urine pregnancy test. Subjects with a positive pregnancy test will be discontinued from the study. The subject will be followed until the outcome of pregnancy is determined.

Photography

Prior to each laser treatment the treatment areas will be photographed using a high-resolution digital camera. Camera settings and other parameters such as distance, lighting, background and polarization will be recorded and reproduced at subsequent photography sessions.

Subject Satisfaction

At each treatment visit beyond Treatment #1, subjects will be asked to rate their level of satisfaction with the study treatments thus far using the Subject Satisfaction Scale provided in Appendix D.

Eye Safety

The correct eye protection must be worn during all laser treatments by the subject, the treating Investigator, and all other study personnel or observers in the room during laser operation.

Treatment Area Preparation

The intended treatment area will be cleansed with isopropyl alcohol or similar prior to treatment to ensure the treatment area is free of any makeup, creams or lotions.

Skin Biopsy (Optional)

Subjects may be asked if they will allow one or more skin punch biopsies to be performed at or near the treatment area prior to and/or immediately after treatment. Biopsies are optional and will only be performed after written consent is obtained from the subject. The Investigator will determine if biopsies are needed based on the condition being treated, location, or other factors. Performance of the biopsy typically follows these steps:

a) Skin biopsies will be collected at or near the treatment area.
b) Biopsy site will be cleansed with isopropanol alcohol or similar.
c) Local anesthetic injection (lidocaine or similar medication) will be administered intradermally to the biopsy site prior to collection.
d) Biopsy will be collected using sterile, single use disposable 2 mm to 4 mm punch biopsy.
e) Sutures may be used to close the biopsy site as needed.
f) Biopsies will be placed in a container labeled with Subject's ID number and date of collection.
g) Biopsies will be fixed and processed for hematoxylin and eosin staining and/or scanning electron microscopy according to laboratory guidelines.

Anesthesia

To reduce pain and discomfort during laser treatment, the Investigator may recommend use of a topical anesthetic product, such as EMLA or LMX-4 cream, which is applied to the intended treatment area for approximately 60 minutes prior to treatment. The Investigator may also recommend use of a local intradermal injection of anesthesia, such as lidocaine or similar medication. Nonmedicinal methods may also be offered such as simple ice packs, or devices that provide cold air , such as a Zimmer cooling device (Cryo 6, Zimmer Medizin Systems, Irvine, CA). Subjects may also elect to be treated without anesthesia.

Test Spots

Test spots may be performed prior to treatment to help the Investigator establish appropriate treatment parameters to achieve the desired clinical endpoint such as erythema or whitening. Test spot parameters will be guided by subject skin type, lesion type, color or location among other factors. The procedure for test spots involves delivering a laser pulse to the skin at or near the treatment area using a low energy, fluence or other setting, and then increasing the relevant parameters until the desired clinical endpoint is achieved. For the PicoWay® laser system the clinical endpoint is most commonly erythema or whitening of the skin.

Laser Treatment

Study laser treatments will be administered using treatment parameters recommended by the manufacturer and study Sponsor, Candela Corporation. The treatment location, wavelength, handpiece, pulse energy, number of passes, and number of pulses will be documented in the case report form.

Benign pigmented lesions including dyschromia will typically be treated with either the 532 nm or 1064 nm Resolve™ Fusion, or 730 nm handpiece.

Wrinkles including fine lines will typically be treated with the 1064 nm Resolve™ Fusion handpiece.

The investigator will determine the treatment specific parameters including wavelength, energy, fluence, spot size and repetition rate for each subject based on the type, color and location of the lesion among other factors. For darker skin types FST V and FST VI the 1064 nm wavelength is most commonly used.

Pain Assessment

Immediately after each treatment subjects will be asked to rate the amount of pain experienced during treatment using an 11-point Subject Pain Scale ranging from 0 (No Pain) to 10 (Extreme Pain). The Subject Pain Scale is provided in Appendix C.

Local Skin Response Assessment

Local skin responses will be assessed and recorded following each laser treatment, normally within the first 30 minutes. The Local Skin Response Form is provided in Appendix E and includes the following most commonly observed skin responses which are both anticipated and in some instances desired clinical endpoints:

- Erythema
- Edema
- Whitening
- Petechiae
- Pinpoint Bleeding
- Purpura
- Crusting
- Blistering
- Burning

Safety Assessment

Local skin responses occurring from prior laser treatments that are deemed more serious due will be recorded as Adverse Device Effects (ADE) on the appropriate study case report form. Examples of anticipated ADE that can be observed following treatment with the PicoWay™ laser include:

- Hyperpigmentation
- Hypopigmentation
- Scarring
- Infection
- Herpes Simplex Activation

Although highly uncommon in conjunction with PicoWay® laser treatments, any Unanticipated Adverse Device Effects (UADE) will also be recorded on case report forms and reported to the Sponsor and IRB as required.

Post-Treatment Care Instruction

Subjects will receive instructions on post-treatment care of their treated areas. These may include the application of a petrolatum gel (such as Aquaphor® or Vaseline®); use of a topical corticosterioid (such as Cortizone®); avoiding sun exposure or use of tanning equipment; and use of a sunscreen with sun protection factor (SPF) 30 or greater for the duration of study.

Telephone Contacts

The Study Doctor or staff will make up to three (3) attempts to contact subjects by telephone 10 days after each treatment (+/- 7 Days) to assess healing response.

10.3. Follow-Up Visits

Subjects will be scheduled for follow-up visits at 4 ± 1 weeks, 8 ± 2 weeks, and 12 ± 2 weeks after their final study treatment visit, or approximately 1, 2 and 3 months. Additional visits may be scheduled by the Investigator as needed.

Photography

Treatment areas will be photographed at all follow-up visits using the same camera settings used previously at Baseline and Treatment Visits.

Subject Satisfaction

Subjects will be asked to rate their level of satisfaction with the study treatments thus far at each follow-up visit using the Subject Satisfaction Scale provided in Appendix C.

Skin Biopsy (optional)

Subjects who have provided prior written consent may have one or more skin biopsy taken from the treated area at the discretion of the Investigator. Biopsy procedure details are provided in the Treatment Visit section above.

11. Schedule of Events

The Study Schedule of Events is provided in Table 1.

NOTE: The Screening and Baseline / Treatment #1 Visits may be combined in the same visit.

NOTE: Fewer than four (4) Treatment Visits may be required to reach maximum expected clinical results in some subjects. Treatments may therefore be stopped, and subject placed into the Follow-Up phase at the discretion of the Investigator.

Table 1: Study Visits and Schedule of Events

Activity	Screening	Baseline Tx 1	Tx 2	Tx 3	Tx 4	1 Month Follow-Up	2 Month Follow-Up	3 Month Follow-Up
	0 to -2 Weeks	Day 0	Week 6 ± 2 Weeks	Week 12 ± 2 Weeks	Week 18 ± 2 Weeks	Week 22 ± 2 Weeks	Week 26 ± 2 Weeks	Week 30 ± 4 Weeks
Informed Consent	X							
Medical History/Concomitant Medications	X							
Inclusion/Exclusion Criteria	X							
Treatment Site ID	X							
Pregnancy Test	X	X	X	X	X			
Skin Biopsy (Optional)		X	X	X	X	X	X	X
Telephone Contact*		X	X	X	X			
Photography		X	X	X	X	X	X	X
Laser Treatment		X	X	X	X			
Subject Pain Score		X	X	X	X			
Subject Satisfaction			X	X	X	X	X	X
Safety Assessment (LSR, ADE, UADE)		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Study Exit								X

*10 Days post-treatment (+/- 7 Days)

12. Study Compliance

This study will be conducted in compliance with this Protocol, guidelines as provided by the device manufacturer, Candela Corporation, in the PicoWay® User Manuals and Treatment Guides, Sponsor Standard Operating Procedures (SOP), and other applicable guidance as provided by 21CFR 812, ICH GCP EC(R2), or other local regulatory authorities. Confidentiality and privacy of subjects' medical information will be maintained in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

13. Study Device

13.1. PicoWay® Laser System

The PicoWay® laser system is an alexandrite laser pumped, solid-state Neodymium:Yttruium Aluminum Garnet (Nd:YAG) laser emitting energy at user selectable wavelengths of 1064 nm, 532 nm, 785 nm or 730 nm [redacted]

At the 1064 nm and 532 nm wavelengths the ZOOM handpiece is provided that allows the spot size of the beam delivered to the treatment area to be adjusted from a [redacted] in increments of [redacted]

At the 785 nm and 730 nm wavelengths Titanium:Sapphire full surface handpieces are provided with selectable distance gauges that allow selection of [redacted] spot sizes.

At the 1064 nm and 532 nm wavelengths, a Resolve™ fractional handpiece is provided which transforms the laser beam [redacted]

At the 1064 nm and 532 nm wavelengths, a Resolve™ Fusion fractional handpiece is provided which transforms the laser beam into a fractional 10 X 10 array of 101 individual microbeams equally spaced within a 6 mm X 6 mm square spot size. Each microbeam produced by the Resolve™ Fusion handpiece consists of a central beam of energy surrounded by an annular “ring beam”.

Safety Eyewear is provided with each laser system and must be worn by all personnel in the treatment room while the laser is being used, including the patient.

13.2. Technical Specifications

Technical specifications for the PicoWay® Laser System are provided in Table 2.

Table 2: Laser System Technical Specifications

PicoWay™ Laser System

Parameter	Specifications
Wavelength	[redacted]
Pulse Duration (nominal)	[redacted]
Maximum Radiant Energy	[redacted]
Pulse Repetition Rate	[redacted]
Fluence (max) **ZOOM** handpiece	[redacted]
Fluence (max) **Ti:Sapphire** handpiece	[redacted]
Energy (max) **Resolve™** handpiece	[redacted]
Energy (max) **Fusion** central beam Fluence (max) **Fusion** ring beam	[redacted]
Safety Eyewear (minimum)	[redacted]
Spot Size	[redacted]
Delivery System	[redacted]
Aiming Beam	[redacted]

[redacted due to confidential information]

13.3. Device Training

Qualified, designated study personnel at each investigational site will receive device specific training from the Sponsor on the PicoWay® laser system prior to performing study laser treatments.

14. Regulatory Approvals

The base system of the PicoWay® Laser System and handpieces at the 1064 nm, 785 nm and 532 nm wavelengths have received multiple 510(k) market clearances by the U.S. Food and Drug Administration (FDA) as shown in Table 3. Specific cleared indications for use are also listed below.

The 730 nm and Resolve™ Fusion handpieces planned for use in this study are at this time considered Investigational Devices by the Food and Drug Administration and will therefore be labeled with the following statement:

"CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

Table 3: FDA 510(k) Premarket Notifications for Candela PicoWay® Laser System

510(k) Number	Device Name
[redacted]	PicoWay Laser
[redacted]	PicoWay Laser
[redacted]	PicoWay Laser
[redacted]	PicoWay Laser
[redacted]	PicoWay Laser
[redacted]	PicoWay Laser

14.1. Indications for Use

The PicoWay® Laser System is indicated for the following at the specified wavelength:

532nm: Removal of tattoos for Fitzpatrick skin types I-III to treat the following colors: red, yellow and orange.

785nm: Removal of tattoos for Fitzpatrick skin types II-IV to treat the following tattoo colors: green and blue.

1064nm: Removal of tattoos for all skin types (Fitzpatrick I-VI) to treat the following tattoo colors: black, brown, green, blue, and purple.

The PicoWay® Laser System is also indicated for benign pigmented lesions removal for Fitzpatrick Skin Types I-IV.

The Resolve™ handpiece (1064nm) is also indicated for the treatment of acne scars in Fitzpatrick Skin Types II-V.

The Resolve™ handpieces are also indicated for treatment of wrinkles in Fitzpatrick Skin Types I-IV.

15. Non-Significant Risk Determination

In accordance with the definition of "Significant Risk Device" provided in the U.S. Code of Federal Regulation 21 CFR 812.3, each device to be used in the study has been determined to be a Non-Significant Risk (NSR) device 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

16. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This study will begin enrollment of subjects only after receiving written approval from the appropriate Institutional Review Board (IRB), Independent Ethics Committee (IEC) or other regulatory authorities deemed necessary depending on specific country or local requirements. Any sites selected outside of the United States will need to meet the country requirements for conducting human research studies.

17. Study Endpoints

17.1. Primary Effectiveness Endpoints

Benign Pigmented Lesions
Mean difference from Baseline to final 12-Week follow-up visit in Pigment Clearance Score as determined by blinded evaluators from clinical photographs.

Wrinkles
Mean difference from Baseline to final 12-Week follow-up in Fitzpatrick Wrinkle Score as determined by blinded evaluators from clinical photographs.

17.2. Primary Safety Endpoint

Analysis of the incidence, severity and relatedness of local skin responses and anticipated adverse device effects (ADE) and unanticipated adverse device effects (UADE).

17.3. Secondary Endpoints

1. Benign Pigmented Lesions
   Percentage of subjects demonstrating Pigment Clearance Score (PCS) of 3 or 4 (> 50% improvement) comparing baseline to 12-week follow-up as determined by blinded physician evaluators from clinical photographs

2. Wrinkles
   Percentage of subjects demonstrating $\geq$ 1 score improvement in Fitzpatrick Wrinkle Score (FWS) from baseline to 12-week follow-up visit as determined by agreement of 2 out of 3 blinded physician evaluators from clinical photographs

3. Subject Satisfaction
   Mean and distribution of Subject Satisfaction Scores at all visits beyond Treatment Visit #1

4. Subject Pain
   Mean and distribution of Subject Pain Scores following each treatment

17.4. Exploratory Endpoints

Histological analysis of laser-tissue effects and/or healing response from pre- and post-treatment skin biopsies using light microscopy and/or scanning electron microscopy.

18. Blinded Evaluation

Efficacy endpoints will be determined from the data gathered by blinded evaluators scoring clinical photography. Three qualified, non-treating clinicians will be trained to independently review Baseline and post-treatment photograph sets for each subject. The identity of the subjects will be masked when possible. No information will be provided to the evaluators that may allow them to determine the Baseline from the post-treatment photography. Evaluators will then examine pairs of Baseline and post-treatment photographs presented in a randomized fashion, and be asked to identify which is the Baseline, and to rate any perceived improvement using the Pigment Clearance Scale or Fitzpatrick Wrinkle Scale as appropriate for the condition treated.

19. Statistical Methods

19.1. Statistical Plan Overview

The study will be conducted with two separate strata (pigment, wrinkles) which will be evaluated. Benign pigmented lesions including dyschromia (Group A) and wrinkles including fine lines (Group B) will be separately powered and analyzed for efficacy and safety while both groups will further be combined for safety analyses. All study sites will be eligible to enroll subjects into each stratum; no subject will be enrolled into both strata.

Subjects participating in the pigment treatment stratum will be evaluated using the Pigment Clearance Score (Appendix A) while subjects participating in the wrinkle treatment stratum will be evaluated using the Fitzpatrick Wrinkle Score (Appendix B). All study subjects will also be evaluated using the Subject Pain Scale (Appendix C), Subject Satisfaction Survey (Appendix D), the Local Skin Response (Appendix E), and will be evaluated for safety according to 21 CFR Part 812 as well as ICH guidelines (E3 and E6) and ISO 14385:2016 as applicable.

A statistical analysis plan (SAP) will be finalized prior to study initiation. The database will be constructed using Microsoft Office Excel (Microsoft, Redmond, WA). The database will be locked following a review of all protocol deviations to be classified as a major or minor deviation. Major and minor protocol deviations will be reviewed once all data undergo source document verification and prior to database lock. The independent biostatistician will determine major vs. minor protocol deviations.

Data analyses will be performed using SAS Version 9.3 or later (SAS Institute, Cary NC) and StatXact Version 10 or later (StatXact, Cambridge MA). All analyses will be performed in a GCP environment controlled by SOPs.

19.2. Hypotheses

Null and alternative hypotheses are stratum specific. They assess the change from Baseline to Week 12/study exit.

Pigment effectiveness (5-point ordinal scale, 5 is best) will be evaluated according to the following null and alternative hypotheses for Group A:

- Null Hypothesis: Less than 50% experience good to excellent improvement in the Pigment Clearance Score (PCS)
- Alternative Hypothesis: At least 80% experience good to excellent improvement in PIS.

Fitzpatrick Wrinkle Score (9-point ordinal scale, 1 is best) will be evaluated separately for peri-orbital wrinkles and peri-oral wrinkles as well as the sum according to the following null and alternative hypotheses for Group B:

- Null Hypothesis: There is no mean improvement in the Fitzpatrick Wrinkle Score (FWS)
- Alternative Hypothesis: There is at least a 2-point mean improvement in FWS.

19.3. Sample Size

The following summarizes the sample size required to achieve 80% power separately for pigmentation Group A and Group B for their respective primary efficacy endpoints.

From Kung, et al, 2018, Graph 1 indicates that for clearance of pigmentation, 0% experienced complete improvement (Grade 5: >95%), 53.8% experienced excellent (Grade 4: 75-94%) improvement, while 30.8% experienced good (Grade 3: 50-74%) improvement from baseline. With 30 evaluable subjects, there is 80% power to reject a 50% improvement rate in favor of a 75% improvement rate according to a two-sided exact binomial test with 5% Type I error. Statistical significance will be achieved if [redacted]% improvement is observed at 12 week follow-up / study exit visit.

From Fitzpatrick, et al, 1996, Table 2 indicates for peri-orbital and peri-oral wrinkles, the mean changes from baseline to study exit were 2.34 points and 2.25 points with standard deviations < 2 points. With 34 evaluable subjects, there is 80% power to detect a 1-point improvement from baseline according to a two-sided paired t-test with 5% Type I error. Statistical significance will be achieved if a [redacted] mean improvement is observed from Baseline to 12 week follow-up / study exit with a 2-point standard deviation.

19.4. Effectiveness Analyses

The skin pigmentation score will be evaluated using a paired t-test separately for the peri-orbital, peri-oral, and combined outcomes from baseline to study exit. In addition, the percentage achieving a 1-point improvement will also be displayed with two-sided 95% confidence intervals to support regulatory submissions requiring 1-point improvement analyses.

Wrinkle score improvement will be evaluated using a two-sided exact binomial test.

The Subject Pain Scale and Subject Satisfaction Score will be evaluated by displaying the distributions with the range, mean, and two-sided 95% confidence intervals provided. Results will be displayed separately for Groups A and Group B.

The effectiveness analyses will be performed using a Per Protocol (PP) population which excludes subjects with major protocol deviations such as subjects withdrawn prior to final evaluation.

19.5. Safety Analyses

Safety will be evaluated using the Local Skin Response (Appendix E) which will specifically assess the following nine pre-defined safety endpoints: erythema, edema, whitening, petechiae, pinpoint bleeding, purpura, crusting, blistering, burn, as well as other to be graded on a 5-point ordinal score.

Safety will be evaluated in the Intent to Treat (ITT) population which includes all treated subjects. Safety results will be displayed separately for Groups A and Group B. Analyses will include a summary of the incidence, severity, and relatedness of all reported local skin responses, adverse device effects, and unanticipated adverse device effects. In addition, the percentage with no adverse device effects will also be reported as well as the percentage according to worst overall degree; a similar evaluation will be performed for the worst degree for those at least related to the study treatment. The percent reporting each ordinal score per safety endpoint will be presented separately for each stratum and combined.

20. Histological Analysis

20.1. Light Microscopy

Skin biopsies will be processed for routine hematoxylin and eosin (H&E) tissue staining to allow light microscopy analysis of laser-tissue effects such as acute skin and pigment changes, wound healing, or other morphologic changes.

20.2. Scanning Electron Microscopy

Skin biopsies may be processed for scanning electron microscopy (SEM) by a third-party laboratory to allow analysis of laser-tissue effects such as acute skin and pigment changes, wound healing response, or other morphologic changes.

21. Risks and Benefits

21.1. Potential Risks

The study treatments to be administered in this trial carry risks of local skin responses that are common, expected, and at times even desired with study treatments. The skin responses are typically only trace to moderate, and transient in nature, resolving within a few days after treatment.

Common local skin responses or side effects of treatment include erythema, edema, whitening, petechiae, pinpoint bleeding, purpura, crusting, blistering, and burning following the treatment.

Examples of less common but potentially more severe or lingering local skin responses associated with PicoWay™ laser treatment include hyperpigmentation, hypopigmentation, herpes virus activation, infection and scarring.

Allergic reactions to the topical or injectable anesthesia products are also possible.

There is also a risk of eye injury associated with the use of any laser device. This risk is very uncommon as it is easily prevented if proper safety eyewear is used as required.

21.2. Potential Benefits

Subjects may benefit from participation in this study by experiencing partial or complete clearance of their benign pigmented lesions including dyschromia, or their wrinkles including fine lines. However, there is no guarantee that subjects will experience any beneficial clinical result at all.

22. Adverse Device Effects

22.1. Definitions

The following occurrences will be documented and reported as required for compliance with applicable regulations including 21CFR 812 and ICH GCP EC(R2).

Adverse Device Effect

An adverse device effect (ADE) is an adverse event related to the use of an investigational medical device in a subject, whether it is expected or unexpected.

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if

that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

22.2. Reporting

Anticipated device effects (ADE) and unanticipated adverse device effects (UADE) are collected from the time of subject consent until the subject exits the study. A description of the adverse event or device effect, date of onset, severity, action taken, relationship to study treatment and outcome are documented in the case report form. All adverse events or adverse device effects are followed until resolution.

The Investigator will submit to Candela and to the reviewing IRB a report of any unanticipated adverse device effect (UADE) that might have led to a serious adverse event if suitable action had not been taken, intervention had not been made; or if circumstances had been less fortunate within 48 hours but in no event later than 10 working days after first learning of the effect.

The Sponsor, upon learning of any unanticipated adverse device effect, shall immediately conduct an evaluation and report the results to IRB within 10 working days.

22.3. Rating

The Investigator will assess the severity and relationship of all adverse effects. The following definitions will be used for severity assessment:

For all ADE and UADE reported, the Investigator will assign independent ratings for Severity and Relatedness to laser treatment in accordance with the descriptions found in Table 4 and Table 5, respectively.

Table 4: Severity Rating System for ADE/UADE

Score	Severity	Definition
0	None	Normal
1	Trace	Very minimal reaction resolved within 24 hours. Does not require medical intervention. No effect on daily activities.
2	Mild	Noticeable reaction expected to resolve within 7 days. Does not require medical intervention. No effect on daily activities.
3	Moderate	Noticeable reaction lasting more than 2 weeks. Possibly requires some medical intervention. May interfere with some daily activities.
4	Severe	Significant skin reaction lasting more than 6 months, or deemed permanent by Investigator. Requires significant medical or surgical intervention. Debilitating and prevents normal everyday activities

Table 5: Relatedness Rating System for AE/UADE

Score	Relatedness to Treatment	Definition
0	Not Related	Clearly related to other factors and not to laser treatment
1	Possibly Related	A reasonable temporal sequence from the time of study treatment but could have been produced by other factors
2	Probably Related	A reasonable temporal sequence from the time of study treatment but cannot be reasonably explained by other factors.
3	Related	A reasonable temporal sequence from the time of on stopping the investigational product, or reappears on repeat exposure, or there is a positive reaction at the application site.
U	Unable to Determine	Insufficient information to make a rational determination.

23. Investigational Sites

Investigational sites will be identified by the Sponsor and pre-qualified for participation prior to site initiation or subject enrollment.

24. Compensation

Subjects will receive PicoWay™ laser treatments in this study at no cost. Subjects will also receive a one-time honorarium of $100.00 upon completion of the scheduled 12-week follow-up visit. Subjects consenting to skin punch biopsies will receive $250.00 for each biopsy taken.

25. Monitoring Plan

Study Monitoring will be performed by qualified personnel from or designated by the Sponsor to ensure data integrity, adherence to the protocol and protection of study subjects. It is anticipated that at least three study monitoring visits will be scheduled per site during this study, though the Sponsor may determine that additional monitoring visits are required.

26. Protocol Deviation Reporting

Subjects enrolled without meeting inclusion/exclusion criteria, enrolled without providing informed consent and any other major deviations from the protocol will be reported to the Sponsor as soon as possible after becoming aware of the deviation. Protocol deviations will be reported to the IRB in accordance with IRB guidelines.

27. Record Retention

The Investigator will retain a copy of all study records in accordance with applicable regulations for a period of two (2) years after the study is terminated or completed. It is the responsibility of the Investigator to retain study records in a secure location at the site.

28. Publication Policy

Study Investigators agree not to publish the results from, or disclose confidential information related to, this study as described in the Clinical Trial Agreement without prior written agreement from the study Sponsor, Candela Corporation. If the Sponsor agrees to publish the results from this study, the Investigators will provide the Sponsor publication manuscript(s) for review at least thirty (30) days before submission for publication. Investigators will also provide the Sponsor advance at least (30) days' notice of any planned presentation of study results.

29. References

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30. Appendices

Appendix A: Pigment Improvement Score (PIS)
Appendix B: Fitzpatrick Wrinkle Score (FWS)
Appendix C: Subject Pain Scale
Appendix D: Subject Satisfaction Survey
Appendix E: Local Skin Response

30.1. Appendix A: Pigment Clearance Score Pigment Score

Score	Clearance	Description
1	0% - 24%	Poor response
2	25 - 49%	Fair Response
3	50 - 74%	Good response
4	75 - 94%	Excellent response
5	≥ 95%	Complete response

30.2. Appendix B: Fitzpatrick Wrinkle Score (FWS)

Class	Wrinkling	Score	Degree of Elastosis
I	Fine wrinkles (rhytides)	1-3	Mild (fine textural changes with subtly accentuated skin lines)
II	Fine to moderate depth wrinkles,	4-6	Moderate (distinct papular elastosis [individual papules with yellow translucency under direct lighting] and
III	Numerous lines, with or without redund ant skin folds Fine to deep wrinkles.	7-9	Severe (multipapular and confluent elastosis [thickened yellow and pallid] approaching or consistent with cutis rhomboidalis)

30.3. Appendix C: Subject Pain Scale

Question: How much pain did you experience during the treatment today?										
No Pain										Extreme Pain
0	1	2	3	4	5	6	7	8	9	10

30.4. Appendix D: Subject Satisfaction Scale

Question: How satisfied are you with your pigment improvement at this point of the study?	
Score	Definition
-2	Extremely Dissatisfied
-1	Somewhat Dissatisfied
0	Neither Satisfied nor Dissatisfied
1	Somewhat Satisfied
2	Extremely Satisfied

30.5. Appendix E: Local Skin Response

Local Skin Response Assessment				
❑ None ❑ N/A				
❑ **Erythema**	❑ **Edema**	❑ **Whitening**	❑ **Petechiae**	❑ **Pinpoint Bleeding**
❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe
❑ **Purpura**	❑ **Crusting**	❑ **Blister**	❑ **Burn**	❑ **Other:**
❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe
❑ **Other:**	❑ **Other:**	❑ **Other:** _____	❑ **Other:** _____	❑ **Other:**
❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe	❑ None ❑ Trace ❑ Mild ❑ Moderate ❑ Severe