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Protocol Title:	Clinical Evaluation of a Nonablative Fractional 1940 nm Diode Laser for Treatment of Pigmented Lesions
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Study Synopsis

Protocol Number	FRX19005
Protocol Title	Clinical Evaluation of a Nonablative Fractional 1940nm Diode Laser for Treatment of Pigmented Lesions
Short Title	FRAX 1940 Pigment
Device Description	FRAX 1940 is a fractional 1940 nm solid-state diode laser that delivers linear arrays of microbeams to create nonablative microscopic treatment zones (MTZs) in the skin
Study Design	Prospective, open-label
Primary Objective	Evaluate the safety and efficacy of the FRAX 1940 nm fractional diode laser handpiece for treatment of pigmented lesions such as, but not limited to lentigos (age spots), solar lentigos (sunspots) and ephelides (freckles)
Study Population	Up to 60 enrolled subjects
Investigative Sites	Up to five 5) investigational sites
Study Treatment Areas	Face, hands, arms, back, chest or legs
Study Treatment Visits	• One (1) test spot visit (Phase I) • Up to three (3) treatment visits 4 ± 1 weeks apart (Phase II)
Follow-Up Visits	Phase I – Following Test Spots • 4 ± 2 days after test spots • 14 ± 7 days after test spots (Phase II may begin, pending subject's skin response) • 28 ± 7 days after test spots (if required) Phase II – Following Treatments • 7 ± 3 days after each treatment • Optional interim visits if required to assess adverse events • 1 months (4 ± 1 week) after final treatment • 3 months (12 ± 1 weeks) after final treatment • Additional visits beyond 12 weeks if required to assess adverse events
Measurement Instruments	• Pigment Improvement Score • Subject Numerical Pain Scale • Global Assessment Improvement Scale (GAIS) • Subject Satisfaction Questionnaire
Primary Efficacy Endpoint	Blinded assessment of improvement in clearance of pigmented lesions such as, but not limited to lentigos (age spots), solar lentigos (sunspots) and ephelides (freckles)
Secondary Efficacy Endpoint	• Blinded assessment of textural improvement using a 5-point Global Aesthetic Improvement Scale (GAIS) • Subject assessment of improvement using a 5-point Global Aesthetic Improvement Scale (GAIS) • Subject satisfaction with treatment results will be characterized using a 5-point scale
Primary Safety Endpoint	Incidence, severity and relatedness of adverse events

Abbreviations

AE	Adverse Event
cm, cm^2	Centimeter, Square Centimeters
CFR	Code of Federal Regulations
Ø	Diameter
FDA	Food and Drug Administration
FST	Fitzpatrick Skin Type
GCP	Good Clinical Practice
GUI	Graphic User Interface
Hz	Hertz
IRB	Institutional Review Board
J	Joule
MEND	Micro Epidermal Necrotic Debris
µbeam	Microbeam
µm	Micron
MTZ	Microscopic Treatment Zone
mJ	Millijoule
mm	Millimeter
ms	Millisecond
NAF	Nonablative Fractional
nm	Nanometer
NSR	Non-Significant Risk
UADE	Unanticipated Adverse Device Effect
SOP	Standard Operating Procedure
SPF	Sun Protection Factor
Tx	Treatment

Objective

This study is intended to evaluate the efficacy and safety of a 1940 nm diode fractional laser handpiece for treatment of pigmented lesions such as, but not limited to lentigos (age spots), solar lentigos (sunspots) and ephelides (freckles).

Background and Rationale

The use of lasers to selectively target chromophores in the skin was first described by Anderson and Parrish in 1983.[1] Since then several lasers have been developed with wavelengths in the near to mid-infrared spectrum that are selectively absorbed by water contained in the skin which raise the temperature of the skin in a nonablative manner to coagulate structures of the epidermis and dermis and promote new collagen formation. Initially these nonablative lasers were used with a flat beam profile for skin resurfacing[2]. Starting in 2004, these technologies were followed by the introduction of nonablative fractional (NAF) lasers that deliver the energy to the skin as arrays of microscopic treatment zones (MTZs) for indications ranging from skin resurfacing, to treatment of wrinkles and fine lines, pigmented lesions, scars, and other dermatological indications.[3,4,5,6,7,8] The microscopic arrays allow the laser energy to leave discrete microscopic zones of thermal epidermal and dermal injury separated by areas of untreated skin. This energy delivery technique allows for less healing time compared to traditional flat beam laser treatments.

Study Design

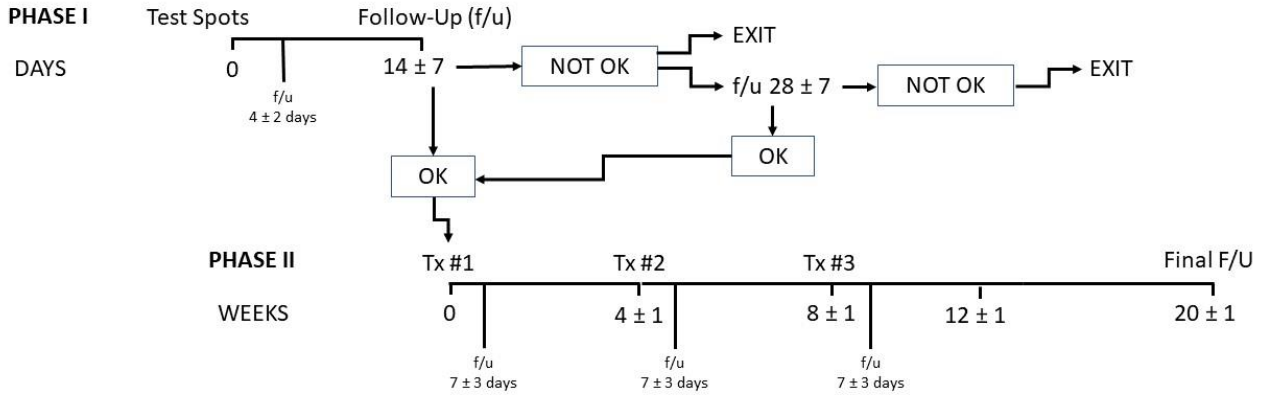
This study is a prospective, open-label, clinical trial to study the effects of the FRAX 1940 nonablative, fractional 1940 nm wavelength diode laser for treatment of pigmented lesions. Secondarily, textural improvement of the treated area (s) will be assessed.
Up to 60 enrolled subjects who agree to have treatment of pigmented lesions will be enrolled at up to five 5) investigational sites. After meeting all inclusion criteria and not meeting any of the exclusion criteria, as well as providing signed informed consent, a subject will be considered enrolled in the study and assigned a unique study identification number.

Subjects will initially receive up to four (4) test spots on the face, hands, arms, back, chest or legs using the FRAX 1940 laser to help the Investigator or study staff determine appropriate treatment settings for each individual subject. The test spots are performed to check for safety of the parameter settings. Each test spot area will not be larger than approximately 2 inches by 2 inches (5 cm x 5 cm).

Subjects will be scheduled for a follow-up visit at 4 ± 2 days (Follow-Up Visit #1) and 14 ± 7 days (Follow-Up Visit #2) after the test spots. Based on the observed skin responses and healing seen at Follow-Up Visit #2, the Investigator or study staff will determine if a subject is an appropriate candidate to proceed with the full treatment of the pigmented lesions. The full treatment will be performed immediately following Follow-Up Visit #2 or will be scheduled at a future time point during a 14 to 21-day period following the test spots.

If it is determined by the Investigator or study staff at the 14 ± 7 day visit following test spots that the skin response seen exhibits adverse events such that full treatment is not prudent, then the subject will either be exited from the study, or be asked to return approximately two weeks later for further evaluation. A study flow chart for subject intake through final follow-up is shown in **Figure 1**.

Figure 1: Study Flow Chart



KEY	OK	Subject may proceed to full face resurfacing treatment. Adequate healing of test spots observed without adverse events.
	NOT OK	Subject should not proceed to full face resurfacing at this time. Longer follow-up or study exit recommended.
	EXIT	Test Spot healing indicates subject is not a good candidate for full face resurfacing at this time. Subject should be exited from the study.

After receiving Treatment #1, subjects will be scheduled for a follow-up visit for clinical evaluation and photography at 7 ± 3 days. Treatment #2 will be scheduled 4 ± 1 weeks after Treatment #1 if skin assessment is acceptable; and Treatment #3 will be scheduled 4 ± 1 weeks after Treatment #2. Additional interim follow-up visits may be required between treatment visits at the discretion of the Investigator or study staff to monitor the treated area(s), and possibly after final treatment if lingering adverse events need to be monitored to resolution.

A follow-up visit will be scheduled approximately 4 ± 1 weeks (1 month) after the final treatment (usually after Treatment #3).

A final follow-up visit will be scheduled approximately 12 ± 1 weeks (3 months) after the final treatment (usually after Treatment #3).

Note: Subjects may undergo fewer than three treatments, as decided by the Investigator or study staff.

1. Inclusion and Exclusion Criteria

Subjects will be enrolled at the discretion of the Investigator after determining that each potential subject (1) meets all inclusion criteria, (2) does not meet any exclusion criteria, and (3) provides signed informed consent.

Inclusion Criteria

1. Male or Female
2. Age 21 to 70
3. Fitzpatrick Skin Type I to VI
4. Willingness to have test spots and up to three (3) treatments for pigmented lesions on or off the face which are rated at baseline as *moderate or higher* per Investigator or study staff
5. Provide signed informed consent to participate in the study
6. Adhere to study treatment and follow-up schedules
7. Willing to have hair removed from the intended treatment area prior to treatment and/or photography
8. Avoid sun exposure to all treated areas and use of sunscreen with sun protection factor (SPF) 30 or greater throughout the duration of the study
9. Adhere to post-treatment care instructions
10. Allow photography of treated areas and to release their use for scientific and/or promotional purposes

Exclusion Criteria

1. Pregnant, planning to become pregnant, or breast feeding during the study
2. Allergy to lidocaine or similar medications
3. Excessively tanned skin in the intended treatment area
4. Open wound or infection in the intended treatment area
5. Tattoo(s) or permanent make-up in the intended treatment area
6. Skin condition in the intended treatment area that could interfere with treatment or evaluation of safety or efficacy
7. Presence or history of melasma
8. Presence or history of skin cancer within the treatment area
9. History of keloid or hypertrophic scar formation
10. History of herpes simplex virus (HSV) or similar condition in the intended treatment area unless treated with prophylactic medication
11. Diagnosed coagulation disorder
12. Immunosuppression disorder
13. Presence of any medical condition that in the opinion of the Investigator could impair healing or outcome as a result of treatment
14. Use of systemic retinoid therapy (e.g. Accutane) during the past six (6) months
15. Use of topical retinoid therapy in the intended treatment area during the past two (2) weeks
16. Use of oral corticosteroid therapy during the past four (4) weeks
17. Prior treatment, such as surgery, light, laser or radiofrequency (RF) procedures in the intended treatment area during the past three (3) months
18. Prior injectable dermal fillers (e.g. collagen, hyaluronic acid) in the intended treatment area within the past 12 months

19. Prior injectable toxins (e.g. Botox) in the intended treatment area within the past three (3) months
20. Subjects who in the opinion of the Investigator are unwilling or unable to adhere to the study requirements, or who are otherwise not a good candidate for the study

Compliance

This study will be conducted in compliance with this protocol, the manufacturer guidelines as provided in the FRAX 1940 User Manual, and other guidelines as required by Good Clinical Practices (GCP), IRB, 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).

Materials and Equipment

The FRAX 1940 handpiece is one of several that can be connected to a main base system such as the NORDLYS or Ydun manufactured by Ellipse, a subsidiary of Candela Corporation, Wayland, MA. The NORDLYS and Ydun base systems and FRAX 1940 non-ablative handpiece are shown in **Figure 2**. The FRAX 1940 handpiece consists of a 1940 nm solid-state, diode laser [redacted]

The FRAX 1940 is also equipped with an integrated cold air delivery system contained in the base system that blows cold air onto the treatment area to provide patient comfort.

Safety Eyewear designed for use with the FRAX 1940 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.

Figure 2: NORDLYS and Ydun Base Systems (left) and FRAX 1940 Handpiece (right)

Figure 3: Fractional Beam Patterns Selectable from [redacted] micro thermal zones (MTZ) per line

[redacted due to confidential information]

Technical specifications for the FRAX 1940 laser are identical whether it is connected to the NORDLYS or Ydun base system and are provided in **Table 2**.

Table 2: Technical Specifications – FRAX 1940 Handpiece

Parameter	Specifications
Wavelength (nm)	[redacted]
Energy per MTZ (mJ)	[redacted]
MTZ Diameter (microns)	[redacted]
Scan Width	[redacted]
MTZ per scan line	[redacted]
Pulse Duration (ms)	[redacted]
Pulse Repetition Rate (Hz)	[redacted]
Aiming Beam	[redacted]
Treatment Cooling[8]	[redacted]
Delivery System	[redacted]

[redacted due to confidential information]

Regulatory Status

Use of the FRAX 1940 nm wavelength handpiece is considered an investigational device by FDA. As a result, to meet the criteria for an Investigational Device it will be labeled with the following statement:

CAUTION – Investigational Device.

Limited by Federal (or United States) law to

The NORDLYS and Ydun base systems and a family of handpieces that includes intense pulsed light (IPL), Nd:YAG 1064nm laser, and a nonablative fractional 1550 nm laser have received prior 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.

Table 3: FDA 510(k) Market Clearances for NORDLYS Base System

510(k) Number	Device Name
[redacted]	Ellipse Ydun
[redacted]	Frax 1550 for Ellipse Nordlys/Ellipse Nordlys+, Ellipse Sirius, Ellipse Infinity, Ellipse Mjolner, Ellipse Nordlys Ultra
[redacted]	Ellipse Nordlys

510(k) Cleared Indications for Use: NORDLYS and Ydun Base Systems and Family of Handpieces

Ellipse Ydun system is intended to be used in dermatology, as tabled below:
• Ydun is indicated for use in dermatological procedures requiring the coagulation of soft tissue, as well as for skin resurfacing procedures

Ellipse NORDLYS system is intended to be used in dermatology, as tabled below:

- Permanent Hair Reduction (defined as the long-term, stable reduction in the number of hairs re-growing when measured at 6, 9, and 12 months after the completion of a treatment regime) (overall 600-950nm).
- Treatment of Telangiectasias (530-750nm or 555-950nm).
- Treatment of Port Wine Stains (530-750nm or 555-950nm).
- Treatment of Benign Pigmented Lesions (eg Mottled Pigmentation, Ephilides [sic]) and Benign Vascular Lesions (e.g. Diffuse Redness) (530-750nm or 555-950nm).
- Treatment of Rosacea (530-750nm or 555-950nm).
- Treatment of Poikiloderma of Civatte (530-750nm or 555-950nm).
- Treatment of Benign Epidermal Pigmented Lesions (e.g. Lentigo Solaris) (400-720nm).
- Treatment of Inflammatory Acne Vulgaris (530-750nm).

Using Nd:YAG Laser, (1064 nm):

- Treatment of Leg vessels (0.1 -3.0 mm diameter).
- Treatment of Benign Vascular Lesions.
- Treatment of Venous Lakes.
- Treatment of Port Wine Stains.
- Treatment for Clear Nail defined as: Temporary increase of clear nail in patients with onychomycosis (e.g., dermatophytes Trichophyton rubrum and T. mentagrophytes, and/or yeasts Candida albicans, etc.).
- Treatment of benign cutaneous lesions, such as warts.
- Podiatry (ablation, vaporization, incision, excision, and coagulation of soft tissue), including:
    - Matrixectomy
    - Periungal and subungal warts
    - Plantar warts

Using Frax 1550 Laser, (1550 nm):

- The Frax 1550 nm laser is indicated for use in dermatological procedures requiring the coagulation of soft tissue, as well as for skin resurfacing procedures.

Non-Significant Risk Determination

The Sponsor believes the 1940 FRAX laser handpiece does not meet the criteria of a significant risk device. In accordance with the definition of “Significant Risk Device” provided in the U.S. Code of Federal Regulation 21 CFR 812.3, the 1940 FRAX laser handpiece 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 and does not present a potential for serious risk to the health, safety, or welfare of a subject; or
d) Otherwise, use of the device does not present a potential for serious risk to the health, safety, or welfare of a subject.

Institutional Review Board (IRB)

This study will begin enrollment of subjects at each investigational site only after receiving written approval from the appropriate Institutional Review Board (IRB) or other regulatory authorities deemed necessary depending on specific country or local requirements.

Study Visits

A Study Visit Schedule of Events is provided in **Table 1**.

Table 1: Study Visit Schedule of Events

	Phase I				Phase II			
Activity	**Screening**	**Baseline/ Test Spots***	**Follow Up Visit #1**	**Follow Up Visit #2**	**Treatment #1****	**Follow Up Visits**	**Treatments #2 & #3**	**Follow Up Visits*****
	Day -14 to 0	Day 0	4 ± 2 Days after test spots	14 ± 7 Days after test spots	14 ± 7 Days or 28 ± 7 Days after test spots	7 ± 3 Days after *each* Treatment	4 ± 1 Weeks after *prior* Treatment	1 Month (4 ± 1 Weeks) and 3 months (12 ± 1 Weeks) after *final* Treatment
Eligibility Criteria	**X**							
Informed Consent	**X**							
Assign Study ID, Identify Treatment Location		**X**						
Photography		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Test Spots		**X**						
Treatment				**X****	**X**		**X**	
Subject Pain Score		**X**			**X**		**X**	
Subject Satisfaction Questionnaire								**X**
GAIS Subject								**X**
Skin Response Adverse Event Documentation		**X**	**X**	**X**	**X**	**X**	**X**	**X**
*Screening, Baseline/Test Spots may occur at the same visit								
**Treatment #1 may occur at same visit as Follow-Up Visit #2 if acceptable clinical endpoint is seen from Test Spots								
***Additional follow-up visits may be required to monitor resolution of adverse events								

Subject Enrollment

Once a qualifying subject is enrolled into the study, their visits will be scheduled as illustrated in the Study Flow Chart (**Figure 1**) and study activities as described below.

Screening and Baseline Visits

Subjects will be evaluated against the inclusion and exclusion criteria at the Screening Visit for eligibility to participate in the study.

Eligible subject will be scheduled for a baseline visit during which they will be asked to read and sign the Informed Consent Form, receive a unique study identification number, and receive their baseline photography. The baseline visit may occur on the same visit as screening.

Enrolled subjects may also receive the study test spots during the same combined screening and baseline visit. The total duration of a combined screening and baseline visit with test spots is approximately 60 to 90 minutes.

Clinical photography will be taken of treatment areas at baseline before treatment, at all treatment and follow-up visits using a non-contact digital camera. Flash photography is not required. As the treatment areas may be directly on or near the face, photography may contain identifying features. However, efforts will be made to de-identify images if used for scientific/research or promotional purposes.

All subjects must agree to have photography performed and released for research purposes since the photographs are used to assess the primary endpoint of the study. Additionally, subjects will be asked if their photographs can be released for commercial marketing purposes.

Test Spot and Treatment Procedures

Prior to receiving treatments subjects will receive up to four (4) test spots at the Test Spot Visit. The Investigator or study staff will deliver FRAX 1940 laser energy in or near the intended treatment area(s) as test spots to evaluate the reaction of the skin. This helps the Investigator or study staff determine that the laser is set to a safe setting, or whether more or less energy should be used to achieve clinical endpoint, typically slight edema or erythema.

Each test spot area size will not exceed approximately 5 cm X 5 cm and will be treated beginning with low energy and low coverage settings. One or both of these settings may be increased as needed in order to achieve a desired clinical endpoint.

Before receiving test spots or treatment, the areas of the skin intended to be exposed to the laser energy may need to be shaved to avoid any influence of hairs absorbing the treatment laser energy.

Some subjects may be offered anesthesia to minimize discomfort during treatment in the form of a topical cream containing lidocaine/prilocaine (EMLA), benzocaine/lidocaine/tetracaine (BLT), or similar product that would be applied 30 to 60 minutes in advance and removed before laser treatment.

Both the NORDLYS and Ydun base systems incorporate a design feature to blow cool air on the skin during treatment to increase patient comfort that subjects may choose to use this during their treatments. Subjects may also choose the use of no anesthesia.

Subjects and clinical staff will always be required to wear safety eyewear during study treatment to protect the structures of the eye from possible injury due to the laser beam energy.

Test spots and treatments will be performed in accordance with general guidelines and parameters provided by the manufacturer for the FRAX 1940 handpiece. Specific laser

parameters will be determined by the Investigator through the skin response and healing response of test spots.

The test spots and treatments will be performed by passing the handpiece of the FRAX 1940 laser along the skin using a rolling mechanism in the handpiece which activates the fractional laser pulses. Exact treatment parameters are also guided by factors such as Fitzpatrick Skin Type (FST), location on the body, or other factors.

If an appropriate clinical response is seen at 14 ± 7 days after test spots (Follow-Up #2), then subjects will be scheduled to receive up to three (3) treatments of pigmented lesions on the hands, arms, back, chest, or legs. Pigmented lesions will include, but not be limited to, lentigos (age spots), solar lentigos (sunspots) and ephelides (freckles).

Off-face treatment areas will be limited in size per the Investigator or study staff decision depending on factors including but not limited to practical treatment times, amount of topical anesthetic required, expected duration of anesthesia effect.

The treatment(s) may occur during the same visit as the test spot Follow-Up #2 visit if appropriate skin responses and healing are observed by the Investigator or study staff. If further observation of the test spot healing is deemed necessary, the subject may be scheduled for a subsequent follow-up visit after another 14 ± 7 days for re-evaluation (a total of 28 ± 7 days after initial test spots). Subjects who are still not exhibiting good candidacy for full study treatment at this subsequent visit will be exited from the study.

Treatment will be avoided in the periorbital region, or directly on the lips. Total treatment times will be noted on the appropriate CRF.

Following test spots and each treatment, the study subjects will be asked to rate the amount of pain they may have experienced during their test spots or treatment on an

11-point pain scale (0=No Pain to 10=Extreme Pain) which will be recorded on the appropriate case report form (CRF) by the Investigator or study staff. A sample of the Subject Reported Numerical Pain Scale to be used is provided in Appendix A.

Following all test spots and treatments, the treated area will be examined and photographed, and immediate skin responses (Adverse Events) will be recorded on the appropriate CRF.

Appropriate post-treatment care instructions will be provided as deemed appropriate by the Investigator or study staff.

Suggested treatment parameter ranges are provided in **Table 4**.

Table 4: Suggested Treatment Parameters FRAX 1940 Handpiece

Treatment Area	Minimum Energy	Maximum Energy	Line Width	Coverage
Test Spots	[redacted]	[redacted]	[redacted]	[redacted]
Pigmented Lesion Treatment	[redacted]	[redacted]	[redacted]	[redacted]

Follow-up Visits: Test Spot

Subjects will be scheduled to return for a follow-up visit 4 ± 2 days (Follow Up #1) after receiving their test spots in order to evaluate the skin response and have photography performed of the test spot areas. It is anticipated that test spot areas will exhibit the formation of MENDs at this visit.

Subjects will also be scheduled to return for a follow-up visit 14 ± 7 days (Follow Up #2) after receiving their test spots in order to evaluate the skin response and have photography performed of the test spot areas. It is anticipated that any MENDs observed at the prior visit will have begun to show resolution or disappearance at this visit, indicating healing of the skin and possibly clearance of the pigmented lesions treated. If an appropriate clinical response is seen from the test spots at this visit, then subjects may proceed to receive up to three (3) treatments of their pigmented lesions.

Subjects not showing adequate healing or adverse events at Follow Up #2 may be scheduled to return for a subsequent follow-up visit after an additional 14 ± 7 days (a total of 28 ± 7 days after initial test spots). After again evaluating the skin response and having photography performed of the test spot areas, the Investigator or study staff at this time point may decide that a subject exit the study.

Follow-up Visits: Pigmented Lesion Treatment

Subjects will be scheduled to return for a follow-up visit 7 ± 3 days after each treatment in order to evaluate skin response and perform photography of the treated area(s).

Treated areas will also be evaluated just before receiving Treatment #2 and Treatment #3.

Follow-up visits will be scheduled approximately 4 ± 1 weeks (1 month) and 12 ± 1 weeks (3 months) after the final treatment. **Note:** Fewer than three treatments may be performed at the discretion of the Investigator or study staff due to adverse events or complete clearance of the pigmented lesion(s).

Study Endpoints

Primary Effectiveness Endpoint

Improvement in the clearance of pigmented lesions as determined by three (3) blinded evaluators comparing photographs taken at Baseline and 1 Month Follow-Up (post final treatment) using a validated 5-Point Pigment Improvement Score:
0 = 0% (No Improvement) to 4 = 75-100% (Excellent Response).[10] (Appendix D)

Primary Safety Endpoint

The primary safety endpoint will be an analysis of the incidence and severity of the reported Adverse Events.

Secondary Effectiveness Endpoints

1. Blinded assessment of textural improvement using a 5-point Global Aesthetic Improvement Scale (GAIS) (1 = Very Much Improved, 5 = Worse) at the 1 month and 3-month follow-up visit (Appendix B).
2. Subject assessment of improvement using a 5-point Global Aesthetic Improvement Scale (GAIS) (1 = Very Much Improved, 5 = Worse) at the 1 month and 3-month follow-up visit (Appendix B).
3. Subject satisfaction with treatment results will be characterized using a 5-point scale (1 = Not Satisfied, 5 = Very Satisfied) at the 1 month and 3-month follow-up visit (Appendix C).

Subject reported pain during treatment as scored on an 11-point scale (0=None, 10= Extreme) will be recorded after Test Spots and after each Treatment. (Appendix A)

Study Data Analysis Methods and Statistical Analysis Plan

Safety will be evaluated on the Intent to Treat (ITT) population, defined as all subjects enrolled, and will include a summary of the incidence, severity, and resolution of all reported adverse events. Clinical assessments will be performed at each treatment and follow-up visit.

Safety data analyses will be performed using Microsoft Office Excel (Microsoft, Redmond, WA) or similar statistical software.

Risks and Benefits

Potential Risks

The study treatments to be administered in this trial carry risks of skin reactions that are anticipated or in some cases desired endpoints. These skin responses are typically trace to mild in severity, and transient in nature, resolving within a few days to a few weeks after treatment, and localized to the treated area(s). Examples include edema, erythema, blanching, sloughing, and bronzing (transient darkening).

An additional type of anticipated local skin response unique to nonablative fractional laser treatment is the formation of micro epidermal necrotic debris (MENDs) which appear as

patterns of small brown dots on the skin surface about the size of the MTZ diameter. These are not only common but represent a desired clinical endpoint. MENDs typically resolve within 7 to 14 days after laser exposure[3] though in some cases may last a few weeks.

Examples of less common but potentially more severe or lingering adverse events may include blistering, burning, scarring, herpes simplex virus (HSV) activation, acne eruptions, telangiectasia formation, or pigmentary changes such as hypopigmentation or post-inflammatory hyperpigmentation (PIH) that persist beyond one month.

There is a risk of eye injury associated with the use of the FRAX1940 laser. This risk will be eliminated by the subject wearing the appropriate protective eyewear during laser treatment.

Potential Benefits

There is no guarantee of a positive clinical result or any other benefit by participating in this study. No significant clinical benefit is expected from receiving test spots. However, subjects may experience improvement in the appearance of pigmented lesions.

Adverse Events

To evaluate safety of the FRAX1940 laser treatments, all adverse events, whether expected or less common, will be recorded and scored (see **Tables 5 and 6**) throughout the duration of the study. Skin assessments will be performed at Baseline, immediately before and after each treatment, and at each follow-up visit. All Adverse Events (AE) that occur in the study will be documented on the appropriate CRF.

Anticipated adverse events as a result of laser treatment include edema, erythema, blanching, MENDs, sloughing, and bronzing (transient darkening). Less common adverse events include blistering, burning, scarring, herpes simplex virus (HSV) activation, acne eruptions, telangiectasia formation, or pigmentary changes such as hypopigmentation or post-inflammatory hyperpigmentation (PIH).

All local skin responses and adverse events (AE) will be documented as required on the appropriate case report form. The severity of AE will be scored using a numerical scale from 0 (none) to 4 (severe) as shown in **Table 5**. The relatedness of AE to study treatment will be scored using the relatedness scale as shown in **Table 6** from 0 (unrelated) to 3 (related), including a choice of U (unable to determine if related).

Any Unanticipated Adverse Device Effect (UADE) occurring during this study will be reported as soon as possible to the sponsor and IRB, but no later than 10 working days after the Investigator first learns of the event as outlined in 21 CFR part 812.150(a)(1). However, the Sponsor requests that all Investigators notify the sponsor within 48 hours of first learning of the event. UADE is defined as any serious adverse event affecting the 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 application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

A serious adverse event (SAE) is any adverse event that:

a) led to death,
b) resulted in life-threatening illness or injury
c) resulted in permanent impairment of a body structure or body function
d) resulted in int hospitalization or prolongation of existing hospitalization,
e) resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function, or
f) led to fetal distress, fetal death, congenital abnormality or birth defect

Table 5: Severity Rating System for AE

Numerical Score	Severity
0	None
1	Trace
2	Mild
3	Moderate
4	Severe

Table 6: Relatedness Rating System for AE

Numerical Score	Relatedness to Treatment
0	Not Related
1	Possibly Related
2	Probably Related
3	Related
U	Unable to Determine if Related

Investigational Sites

Up to four to five (4-5) Investigational Sites may be included in this study after signed Clinical Trial Agreements are in place with the Sponsor, and IRB/EC approval for the study has been received.

Investigational sites for this study will be identified by the Sponsor and pre-qualified for participation prior to enrolling subjects in this study. In-service training on all devices will be provided to delegated study personnel at each site prior to or at the time of study initiation.

Study Monitoring

It will be the responsibility of the Sponsor to develop and execute an adequate Monitoring Plan for this study. Qualified personnel will be identified by the Sponsor to perform required monitoring visits. It is anticipated that three (3) monitoring visits per site should be adequate to ensure site compliance for this study, though additional visits may be scheduled at the discretion of the Sponsor.

Protocol Deviation Reporting

Subjects enrolled without meeting inclusion/exclusion criteria, enrolled without providing informed consent and all other deviations from the protocol should be reported immediately to the Sponsor. The Investigator, Study Monitor, or study staff are responsible for deviations to the Sponsor. Each protocol deviation will be investigated by the Sponsor.

Record Maintenance

All completed case report forms including the Subject Satisfaction Questionnaire will be sent by the clinical site to the Sponsor throughout the duration of the study.

The Investigator will retain a copy of all study records in accordance with applicable regulations for a period of two (2) years following completion or discontinuation of the study. It is the responsibility of the Investigator to retain study records in a secure location within the investigational site.

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.

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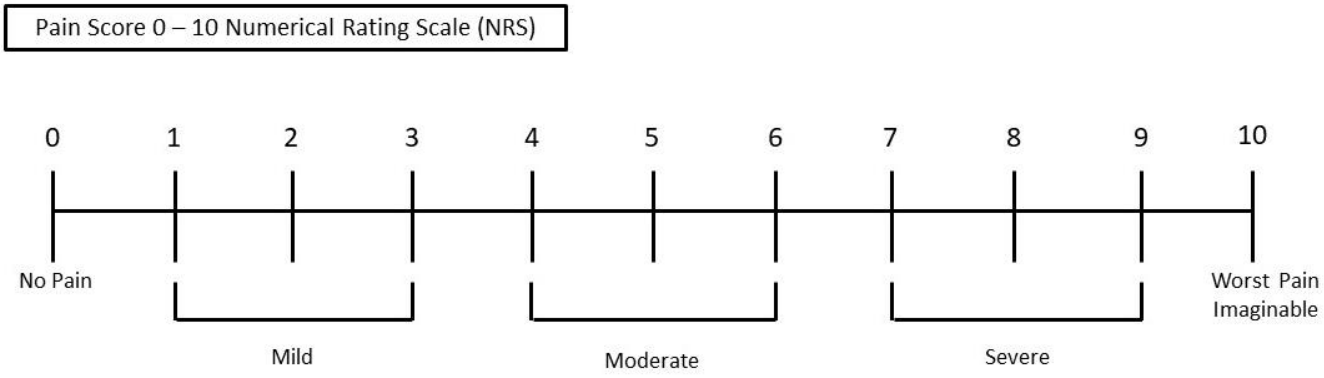
Appendix A - Numerical Pain Rating Scale



Appendix B - Global Aesthetic Improvement Scale (GAIS)

GAIS	Rating	Description
❑ 1	**Very Much Improved**	Optimal cosmetic result in this subject
❑ 2	**Much Improved**	Marked improvement in appearance form the initial condition, but not completely optimal for this subject
❑ 3	**Improved**	Obvious improvement in appearance from initial condition, but a re-treatment is indicated
❑ 4	**No Change**	The appearance is essentially the same as the original condition
❑ 5	**Worse**	The appearance is worse than the original condition

Appendix C - Subject Satisfaction Questionnaire

Score	Rating
❑ 1	Not Satisfied
❑ 2	Little Satisfied
❑ 3	Somewhat Satisfied
❑ 4	Satisfied
❑ 5	Very Satisfied

Appendix D - Pigment Improvement Score

Score	Clearance	Description
❑ 0	0%	No Improvement
❑ 1	1% - 24%	Trace to mild improvement of some lesions
❑ 2	25 - 49%	Moderate Response: Some lesions lighter
❑ 3	50 - 74%	Good response: Most lesions much lighter
❑ 4	75 - 100%	Excellent response: Most or all lesions much lighter or gone