



Protocol Title: Clinical Evaluation of a Nonablative Fractional 1940 nm Diode Laser for Skin Resurfacing and Treatment of Pigmented Lesions

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#### STATEMENT OF CONFIDENTIALITY

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**Study Synopsis**

|                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Protocol Number             | FRX19004 v 2.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Protocol Title              | Clinical Evaluation of a Nonablative Fractional 1940nm Diode Laser for Skin Resurfacing and Treatment of Pigmented Lesions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Short Title                 | FRAX 1940 Skin Resurfacing and Pigment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Device Description          | The 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, clinical trial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Objective                   | Evaluate the safety and efficacy of the FRAX 1940 nm fractional diode laser handpiece for skin resurfacing and treatment of pigmented lesions such as, but not limited to lentigos (age spots), solar lentigos (sun spots) and ephelides (freckles)                                                                                                                                                                                                                                                                                                                                                                                                 |
| Study Population            | Up to 60 enrolled subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Investigative Sites         | Up to three (3) investigational sites                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Study Treatment Visits      | <ul style="list-style-type: none"> <li>1 test spot visit (Phase I)</li> <li>Up to three (3) treatment visits <math>4 \pm 1</math> weeks apart (Phase II)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Follow-Up Visits            | <p>Phase I – Following Test Spots</p> <ul style="list-style-type: none"> <li><math>4 \pm 2</math> days after test spots</li> <li><math>14 \pm 7</math> days after test spots</li> <li><math>28 \pm 7</math> days after test spots (if required)</li> </ul> <p>Phase II – Following Treatments</p> <ul style="list-style-type: none"> <li><math>7 \pm 3</math> days after each resurfacing treatment</li> <li>Optional interim visits if required to assess adverse events</li> <li>4 weeks after final treatment</li> <li>12 weeks after final treatment</li> <li>Additional visits beyond 12 weeks if required to assess adverse events</li> </ul> |
| Measurement Instruments     | <ul style="list-style-type: none"> <li>Subject Numerical Pain Scale</li> <li>Global Assessment Improvement Scale (GAIS)</li> <li>Subject Satisfaction Questionnaire</li> <li>Pigment Improvement Score</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Primary Efficacy Endpoint   | <ul style="list-style-type: none"> <li>Formation and healing times of micro epidermal necrotic debris (MENDs) as measured in days</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Secondary Efficacy Endpoint | <ul style="list-style-type: none"> <li>Improvement in clearance of pigmented lesions, such as, but not limited to lentigos (age spots), solar lentigos (sun spots), and ephelides (freckles).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Primary Safety Endpoint     | <ul style="list-style-type: none"> <li>Incidence, severity and relatedness of adverse events</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

**Abbreviations**

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

## Objective

This study is intended to evaluate the efficacy and safety of a 1940 nm diode fractional laser handpiece for skin resurfacing and treatment of pigmented lesions. In addition to demonstrating skin resurfacing, a secondary goal of this study is to generate data with the 1940 nm diode fractional laser handpiece to support a regulatory submission for treatment of pigmented lesions, such as, but not limited to lentigos (age spots), solar lentigos (sun spots), 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.<sup>1</sup> 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 enough 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<sup>2</sup>. Starting in 2004, these technologies were followed by the introduction of nonablative fractional 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.<sup>3,4,5,6,7,8</sup> 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 skin resurfacing.

Up to 60 enrolled subjects who agree to have skin resurfacing will be enrolled at up to three (3) 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.

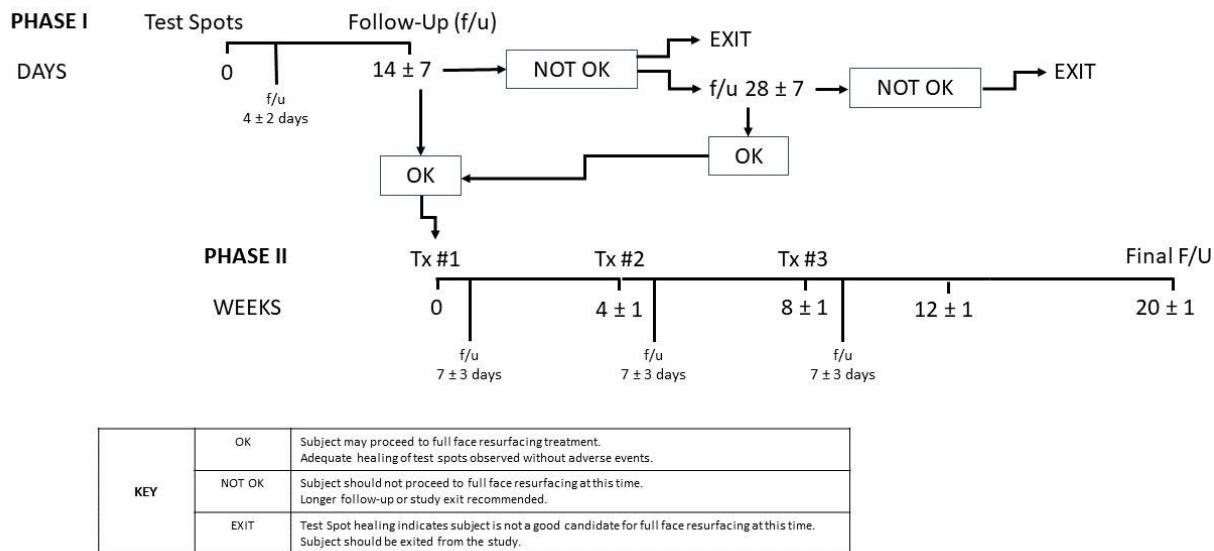
Subjects will initially receive up to four (4) test spots on their face and up to four (4) test spots on other anatomical locations (e.g., hands, arm, back, chest) using the FRAX 1940 laser to help the study clinicians determine appropriate treatment settings for each individual subject. The test spots are administered to check for safety of the parameter settings. Each test spot area will typically 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  $4 \pm 2$  days and  $14 \pm 7$  days (Follow-Up Visit #1) after the test spots. Based on the observed skin responses and healing seen at Follow-Up Visit #1, the Investigator or study staff will determine if a subject is an appropriate candidate to proceed with the skin resurfacing treatment on the face which will be administered either at this same visit, or scheduled at a future time point during a 14 to 21 day period following administering the test spots. Additional skin resurfacing treatment

may be also administered in other locations that contain pigmented lesions on the face, hands, arms, legs, back, and/or chest.

If it is determined by the Investigator or study staff at the  $14 \pm 7$  day visit after test spots that the skin response seen exhibits adverse events such that treatment of the entire face 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



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

A follow-up visit will be scheduled approximately  $4 \pm 1$  weeks (1 month) after the final treatment, typically Treatment #3.

A final follow-up visit will be scheduled approximately  $12 \pm 1$  weeks (3 months) after the final treatment, typically Treatment #3. Note: Fewer than three treatments may be required at the discretion of the Investigator or study staff.

A Study Schedule of Events is provided in Table 1.

Table 1: Study Visit Schedule of Events

|                                                                                                                      | Phase 1      |                             |                             |                              | Phase 2                                     |                                 |                                   |                                                    |
|----------------------------------------------------------------------------------------------------------------------|--------------|-----------------------------|-----------------------------|------------------------------|---------------------------------------------|---------------------------------|-----------------------------------|----------------------------------------------------|
|                                                                                                                      | Screening    | Baseline/<br>Test<br>Spots* | Follow<br>Up Visit<br>#1    | Follow<br>Up Visit<br>#2     | Treatment<br>#1**                           | Follow Up<br>Visits             | Treatments<br>#2 & #3             | Follow Up<br>Visits***<br>#1 & #2                  |
| Activity                                                                                                             | 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 | 4 ± 1 Weeks And 12 ± 1 Weeks after final Treatment |
| Exclusion Criteria                                                                                                   | X            |                             |                             |                              |                                             |                                 |                                   |                                                    |
| Informed Consent                                                                                                     | X            |                             |                             |                              |                                             |                                 |                                   |                                                    |
| Assign Study ID                                                                                                      |              | 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 beyond 12 weeks to monitor resolution of adverse events               |              |                             |                             |                              |                                             |                                 |                                   |                                                    |

## 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 image, confidential]

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.

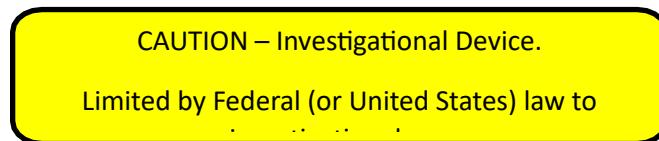
Table 2: Technical Specifications – FRAX 1940 Handpiece

| 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 <sup>8</sup> | [REDACTED]     |
| Delivery System                | [REDACTED]     |

[redacted information above 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:



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 (e.g. Mottled Pigmentation, Ephelides [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.
  - Periungual and subungual 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.

## **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 V
4. Willingness to have test spots and up to three (3) skin resurfacing treatments on the face
5. Presence of pigmented lesions to be treated off the face must be rated at baseline as *moderate or higher* per Investigator or study staff
6. Provide signed informed consent to participate in the study
7. Adhere to study treatment and follow-up schedules
8. Willing to have hair removed from the intended treatment area prior to treatment and/or photography
9. 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
10. Adhere to post-treatment care instructions
11. 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(s)
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
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 skin resurfacing treatment, such as surgery, light, laser or radiofrequency (RF) procedures in the intended treatment area during the past six (6) months
18. Prior injectable dermal fillers in the intended treatment areas within the past twelve (12) months
19. Prior injectable toxins (Botox) in the treated areas 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

### **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**

#### *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 typically 60 to 90 minutes.

Clinical photography will be taken of treated areas at baseline and all treatment and follow-up visits using a non-contact digital camera. Flash photography is not typically 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.

#### *Subject Enrollment*

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

#### *Test Spot and Skin Resurfacing Treatment Procedures*

Prior to receiving skin resurfacing 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 typically not exceed approximately 2 inches X 2 inches (50 mm X 50 mm) 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 skin resurfacing 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 skin resurfacing treatments will be administered 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 skin resurfacing 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.

Subjects with presence of benign pigmented lesions off the face may also receive treatment on the hands, arms, chest, back, or legs. 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.

If an appropriate clinical response is seen from the test spots at  $14 \pm 7$  days after test spots (Follow-Up #2), then subjects will be scheduled to receive up to three (3) skin resurfacing treatments. All subjects will receive resurfacing treatment performed on the face.

Additionally, subjects with presence of pigmented lesions of at least moderate severity off the face on the hands, arms, back, chest, or legs may also receive up to three (3) treatments in these areas.

The skin resurfacing 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  $14 \pm 7$  days for re-evaluation (a total of  $28 \pm 7$  days after initial test spots). Subjects who are still not exhibiting good candidacy for full face treatment at this subsequent visit will be exited from the study.

Facial skin resurfacing treatment will be avoided very close to the eyes, or directly on the lips. Total treatment times will be noted on the appropriate CRF.

Following each test spot and each skin resurfacing 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 each treatment, 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] |
| Facial Skin Resurfacing/<br>Off Face Pigmented Lesions | [REDACTED]     | [REDACTED]     | [REDACTED] | [REDACTED] |

#### Follow-up Visits: Test Spot

Subjects will be scheduled to return for a follow-up visit  $4 \pm 2$  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  $14 \pm 7$  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 and resurfacing of the skin. If an appropriate clinical response is seen from the test spots at this visit, then subjects may proceed to receive up to three (3) skin resurfacing treatments on the face.

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  $14 \pm 7$  days (a total of  $28 \pm 7$  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: Treatments*

Subjects will be scheduled to return for a follow-up visit  $7 \pm 3$  days after each skin resurfacing treatment in order to evaluate the 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 visit will be scheduled approximately  $4 \pm 1$  weeks (1 month) and  $12 \pm 1$  weeks (3 months) after the final treatment, typically Treatment #3. NOTE: Fewer than three treatments may be administered 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**

The primary efficacy endpoint for the skin resurfacing treatment will be based on the formation of MENDs and the skin's healing response as measured in days.

Following test spots digital photography and clinical evaluation will be performed at a minimum approximately 4 and 14 days after test spots (Test Spot Follow-up Visits #1 and #2).

Following skin resurfacing treatments digital photography and clinical evaluation will be performed at a minimum approximately 7 days after treatment, and just prior to any subsequent treatment which occurs at an approximate 4 week interval.

#### **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. Subject reported pain during treatment as scored on an 11-point scale (0=None, 10=Extreme) will be recorded after Test Spots and each Treatment . (Appendix A)
2. Subject assessment of improvement using a 5-point Global Aesthetic Improvement Scale (GAIS) at each follow-up visit. (Appendix B)
3. Subject satisfaction with treatment results will be characterized using a 5-point scale (1 = Not Satisfied to 5 = Very Satisfied) at each follow-up period. (Appendix C)
4. Improvement in the clearance of pigmented lesions (if treated) as determined by three (3) blinded evaluators comparing photographs taken at Baseline and Final Follow-Up using a validated 5-Point Pigment Improvement Score: 0 = 0% No Improvement) to 4 = 75 - 100% (Excellent Response). <sup>10</sup> (Appendix D)

### **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 special type 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<sup>3</sup> 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 treated for skin resurfacing may experience improvement in the appearance of fine lines, wrinkles, or general tone, texture or appearance of the skin; or clearance of pigmented lesions (if included).

#### **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 4 and 5) 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 three (3) Investigational Sites may be included in this study after signed Clinical Trial Agreements are in place with the Sponsor, and IRB 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 monitoring required 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.

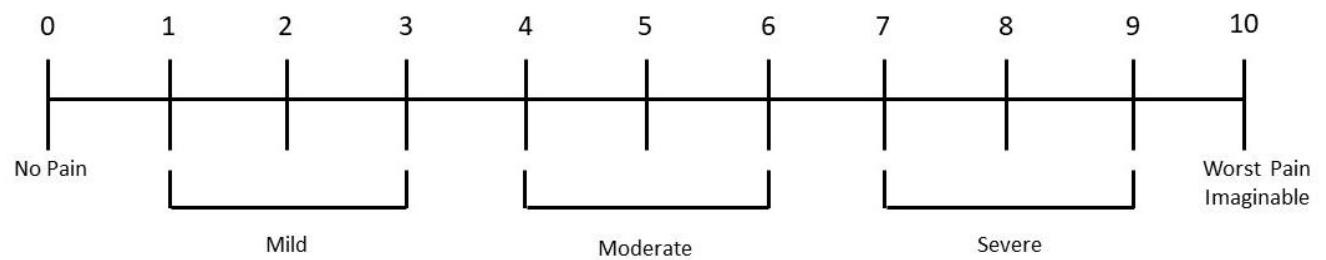
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## Appendix A - Numerical Pain Rating Scale

### Pain Score 0 – 10 Numerical Rating Scale (NRS)



**Appendix B – Global Aesthetic Improvement Scale (GAIS)**

| GAIS                       | Rating                    | Description                                                                                              |
|----------------------------|---------------------------|----------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> 1 | <b>Very Much Improved</b> | Optimal cosmetic result in this subject                                                                  |
| <input type="checkbox"/> 2 | <b>Much Improved</b>      | Marked improvement in appearance from the initial condition, but not completely optimal for this subject |
| <input type="checkbox"/> 3 | <b>Improved</b>           | Obvious improvement in appearance from initial condition, but a re-treatment is indicated                |
| <input type="checkbox"/> 4 | <b>No Change</b>          | The appearance is essentially the same as the original condition                                         |
| <input type="checkbox"/> 5 | <b>Worse</b>              | The appearance is worse than the original condition                                                      |

### Appendix C - Subject Satisfaction Questionnaire

| Score                      | Rating                    |
|----------------------------|---------------------------|
| <input type="checkbox"/> 1 | <b>Not Satisfied</b>      |
| <input type="checkbox"/> 2 | <b>Little Satisfied</b>   |
| <input type="checkbox"/> 3 | <b>Somewhat Satisfied</b> |
| <input type="checkbox"/> 4 | <b>Satisfied</b>          |
| <input type="checkbox"/> 5 | <b>Very Satisfied</b>     |

### Appendix D - Pigment Improvement Score

| Score                      | Clearance | Description                                                  |
|----------------------------|-----------|--------------------------------------------------------------|
| <input type="checkbox"/> 0 | 0%        | No Improvement                                               |
| <input type="checkbox"/> 1 | 1% - 24%  | Trace to mild improvement of some lesions                    |
| <input type="checkbox"/> 2 | 25 - 49%  | Moderate Response: Some lesions lighter                      |
| <input type="checkbox"/> 3 | 50 - 74%  | Good response: Some lesions much lighter                     |
| <input type="checkbox"/> 4 | 75 - 100% | Excellent response: Most or all lesions much lighter or gone |