

**Feasibility Study of a Novel Cooling Device for Pain
Management During Treatment of Skin with Radio-Frequency
Microneedling Device**

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I. BACKGROUND AND SIGNIFICANCE

The Profound® System, a radiofrequency (RF) microneedling device marketed and sold by Candela™, is commercially available and FDA cleared. The Profound System is comprised of an RF generator with graphical user interface, a handpiece, and a single-use, disposable sterile cartridge. The reusable handpiece and disposable cartridges are available in two configurations, Dermal or SubQ. The Dermal handpiece includes a small cooling plate to provide contact cooling during treatment via a thermoelectric cooling mechanism.

RF energy is delivered from the RF generator through the handpiece to needles in the Dermal or SubQ cartridge. The needles are deployed into the dermal layers of the skin and bipolar RF energy is delivered between independent needle pairs. The Dermal configuration inserts 5 pairs of needles (10 needles total) at a 25-degree angle for a shallower penetration depth while the SubQ handpiece inserts 7 needle pairs (14 needles total) at a 75-degree angle for a deeper penetration to treat the deeper dermis. The Profound System is programmable to deliver bipolar RF energy to achieve thermal heating of tissue at a specific target tissue temperature and application time; the treatment parameters are controlled by the physician.

This feasibility study will use the Profound System with the Dermal handpiece to treat the dorsal thigh area. Candela, the manufacturer of the Profound device, has previously treated the thigh area using the Profound Dermal handpiece in a clinical trial registered under NCT02489994 to assess use of the device for the treatment of cellulite (in support of FDA clearance for this indication, K161043).

When using the Profound RF device, physicians typically numb the area to be treated using both topical anesthetic (e.g., EMLA cream) and tumescent anesthesia injected into the tissue prior to treatment. The tumescent anesthesia procedure requires about 45 minutes to perform and can be painful for patients. The Profound Dermal handpiece, described above, also includes a small cooling plate that cools the skin at the point of contact during the RF microneedling treatment with thermoelectric cooling (TEC). The cooling provided by the cooling plate is generally considered inadequate for pain management which is why topical and tumescent anesthesia are routinely used.

This feasibility study is designed to assess an alternative cooling method to determine the potential for improved pain management during RF microneedling procedures. The alternative cooling method, an evaporative cooling technology, uses the vaporization of a refrigerant (in a closed system) to provide more intense contact cooling to tissue than the thermoelectric cooling technology currently in use. We believe the dermal cooling device utilizing evaporative cooling and configured as a cooling plate that attaches to the Profound Dermal handpiece, will offer improved pain management during RF microneedling as compared to the thermoelectric cooling plate currently provided with the Profound

Dermal handpiece. We further hypothesize that the evaporative cooling technology may be sufficient to eliminate the need for tumescent anesthesia prior to the RF microneedling procedure.

The study will take place at MGH's Clinical Unit for Research Trials & Outcomes in Skin (CURTIS) at 50 Staniford Street, Suite 240 Boston, MA 02114 or Translational Clinical Research Center (TCRC) on the 12th floor of the White Building.

II. SPECIFIC AIMS

This study proposes to evaluate a novel dermal cooling device for pain management during treatment with an FDA-cleared RF microneedling device. During this study, the novel dermal cooling device may be evaluated as an attachment to the RF microneedling dermal handpiece OR as a separate entity during RF microneedling treatment.

The study will use the commercially available Profound System (Candela Corporation, California) with the Dermal handpiece to deliver RF energy during treatment of skin on the dorsal thigh area. The study will compare the pain management capability of the thermoelectric cooling plate (TEC) of the commercially available Profound System to a novel evaporative cooling technology (EC) developed by the Manstein Lab. This comparison will be accomplished by the removing the existing cooling plate on the Profound Dermal handpiece and using the experimental EC plate as the sole cooling mechanism. (This modification is made prior to making the device available for the study; no change to the Profound Dermal handpiece is required by the investigator at the time of use.)

During Phase 1 of the study, pain scores are recorded when the microneedles are deployed without radiofrequency. To complete Phase 1 and accurately analyze the cooling efficiency of the experimental EC device, the deployed needles will record the internal temperature distribution of the tissue. Candela added the ability for the RF Profound device to measure tissue temperature at the deployed needles without delivering any radiofrequency to the subject with dummy loads. See *Measuring Tissue Temperature with the RF Microneedling Device*. In Phase 2 of the study, the dummy load will be replaced with a second modified dummy load so that radiofrequency is delivered to the 3 front pairs of microneedles. Figure 2 shows the orientation of the microneedles in the dermal cartridge and identifies which needle pairs will deliver radiofrequency and which will not. No other changes will be made to the FDA-cleared RF microneedling device.

The dorsal thigh area to be treated is shown in Figure 1a below. A template of treatment areas, spaced appropriately so that the cooling areas of the skin do not

overlap, is shown in Figure 1b. The template will be used to mark the treatment areas on subjects' thighs prior to commencing any treatments. Markings will be performed with a surgical marker, which is designed not to come off with regular washing but will fade over time. This study includes a maximum of 15 treatment areas per thigh.

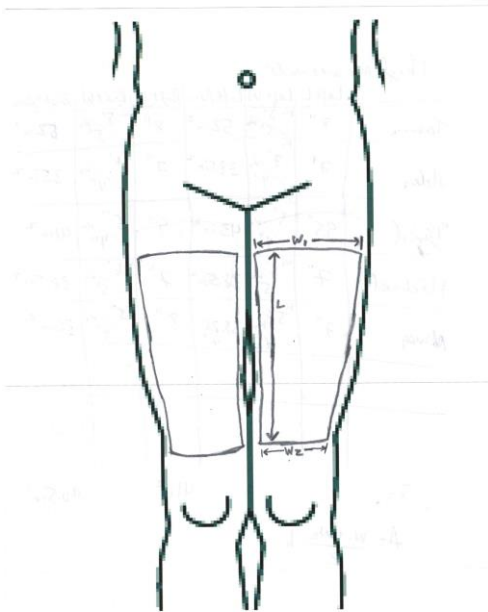


Figure 1a - Thigh Treatment Areas

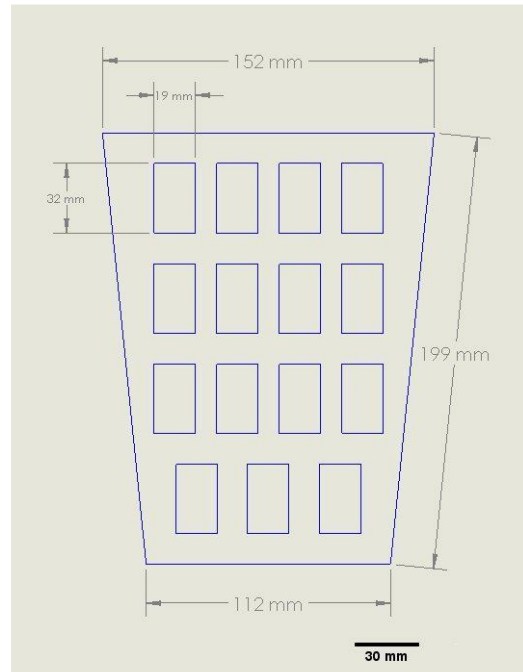


Figure 1b - Thigh Treatment Area Layout

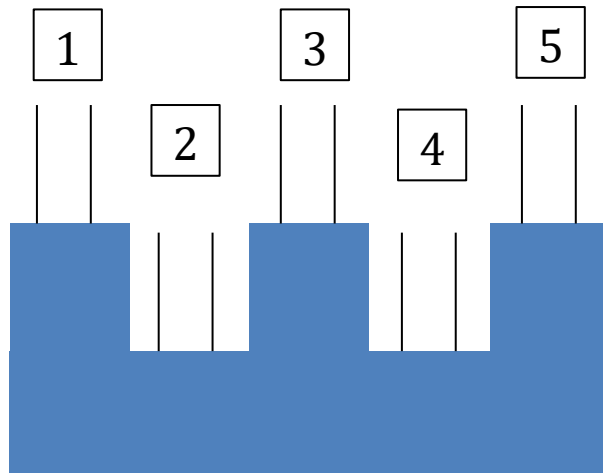
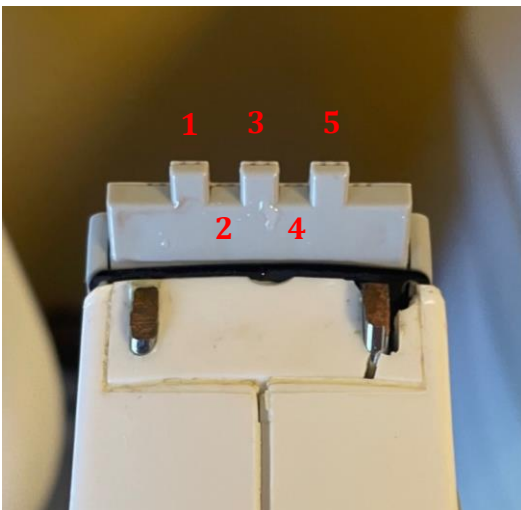


Figure 2 – Dermal Cartridge Needle Pairs

This feasibility study will be divided into two phases.

- Phase 1 will focus on collecting information about the *in vivo* time/temperature cooling profile of the EC device.
- Phase 2 will focus on comparing the pain tolerance to RF microneedling treatment using the EC device compared to the existing TEC device.

Subjects will be enrolled in Phase 1 until Phase 1 is complete (i.e., until the required number of subjects are enrolled, and the follow-up period has been completed). When Phase 1 is complete, enrollment in Phase 2 will begin. Subjects enrolled in Phase 1 may be enrolled in Phase 2 if they choose to do so.

The specific aims of the study are as follows:

Aim 1. Using the EC device, evaluate the cooling rate of *in vivo* tissue and the temperature profile of the tissue with various pre-cooling times (Phase 1).

Aim 2. Using the EC device, evaluate the cooling time that is required to provide analgesia during RF microneedling at different energies (Phase 2).

Aim 3. Evaluate the pain management capability of the EC device compared to the TEC device during RF microneedling when using topical anesthesia only (Phase 2).

Aim 4. Determine if the EC device can eliminate the need for tumescent anesthesia and/or topical anesthesia prior to RF microneedling (Phase 2).

Aim 5. Evaluate the operability and ease of use of the EC device for clinicians (Phase 2).

III. SUBJECT SELECTION

Subjects will be screened to determine if they meet all the eligibility criteria specified below.

We will recruit and screen up to 30 subjects with the goal of having 6 subjects complete Phase 1 and 10 subjects complete Phase 2 of the study.

a. Inclusion/Exclusion Criteria

Inclusion Criteria

- Signed informed consent to participate in the study.
- Female subjects, ≥ 18 and ≤ 60 years of age at the time of enrollment.
- Fitzpatrick Skin Type I to III.

- Not pregnant or lactating and must be either post-menopausal, surgically sterilized, or using a medically acceptable form of birth control at least 3 months prior to enrollment.
- Negative urine pregnancy test prior to treatment.
- General good health confirmed by medical history and skin examination of the area to be treated.
- Willing to receive the Profound RF microneedling treatment:
 - Without radiofrequency, with or without EMLA cream for topical anesthesia and with the EC device during Phase 1.
 - With radiofrequency and with or without EMLA cream for topical anesthesia and with the EC device during Phase 2.
- Willing to follow the treatment and post-treatment care instructions.
- Willing to have photographs and videos taken of the treated areas to be used de-identified in evaluations, publications and presentations.
- Subjects must be able to read and understand English.

Exclusion Criteria

- Subject has had a surgical procedure(s) in the intended area of treatment in the last 6 months.
- Pregnant or planning to become pregnant, having given birth less than 3 months ago, and/or breast feeding.
- Known allergy to lidocaine, prilocaine, 3 or more antibiotics, or glycerol.
- Active malignancy or history of malignancy in the past 5 years.
- Having any active electrical implant anywhere in the body, such as a pacemaker or an internal defibrillator.
- Suffering from significant concurrent illness, such as cardiac disorders, diabetes (type I or II), lupus, porphyria, or pertinent neurological disorders (i.e. any disease state that in the opinion of the Principal Investigator would interfere with the topical anesthetic, treatment or healing process).
- Having a known anticoagulative or thromboembolic condition or taking anticoagulation medications one week prior to and during the treatment course (to allow inclusion, temporary cessation of use as per the subject's physician discretion)
- Subject has a history of bleeding disorder or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
- History of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or currently using immunosuppressive medication.
- Suffering from hormonal imbalance, whether related to thyroid, pituitary, or androgen.
- History of significant lymphatic drainage problems.
- History of cancer which required lymph node biopsy or dissection.
- Suffering from significant skin conditions in treatment areas or inflammatory skin condition, including but not limited to open lacerations or abrasions, hidradenitis, or dermatitis of the treatment area prior to

- treatment (duration of resolution as per the Principal Investigator's discretion) or during the treatment course.
- History of keloid scarring, abnormal wound healing, forming marked post-inflammatory hyper or hypopigmentation, and /or prone to bruising.
 - History of epidermal or dermal disorders (particularly if involving collagen or micro vascularity) including collagen vascular disease or vasculitic disorders.
 - Use of isotretinoin (Accutane) within 6 months of treatment or during study.
 - Subject on systemic corticosteroid therapy 6 months prior to or during the study.
 - Dysplastic nevi in the area to be treated.
 - Subject has palpable lymphadenopathy at any visit. Standard palpation techniques will be used.
 - Subjects with history of severe edema.
 - Subject is unable or unwilling to comply with the study requirements.
 - Subject is currently enrolled or has been enrolled within the prior 3 months in a clinical study of any other unapproved investigational drug or device.
 - Any other condition that would, in the professional opinion of the investigator, potentially affect the integrity of the data or would pose an unacceptable risk to the subject.
 - Known history of cold urticaria.
 - Fitzpatrick skin type IV – VI.

b. Source of Subjects and Recruitment Methods

The study will be posted on the Rally recruitment website, the Partner's clinical research web page (rally.partners.org/) and on bulletin boards around the hospital to reach an economically and socially diverse population.

IV. SUBJECT ENROLLMENT

a. Method of Enrollment

All subjects will undergo a telephone prescreening by study staff before scheduling the initial consenting visit. All subjects who sign an informed consent form (ICF) and are screened will be documented on a screening log, which will also include a note of explanation for any subjects who do not subsequently qualify for enrollment in the study. All subjects who qualify for the study after screening and who are enrolled in the study will be documented on the enrollment log. A note will be made in the source documentation verifying that the subject has willingly signed the ICF prior to participation in any study procedures.

b. Informed Consent Form (ICF)

One of the licensed physician investigators listed on the protocol will consent and

inform the potential study subject of all aspects of the study and answer their questions. Sub-investigators (e.g., nurse practitioner or study staff) may assist in the consent process. If the subject agrees to be a study subject, they will document consent in electronic or written form by signing the informed consent form via Adobe eSign or in person. Subjects who need more time to decide whether they would like to participate will have access to the electronic consent form prior to their informed consent call or visit with the licensed physician investigator if they are interested in participating in the study.

The investigator is responsible for using a consent form that has been approved by the IRB/Partner's HRC and is the most current version. If a new version of the consent form is approved by the IRB/Partner's HRC while a subject is still participating in the study and there are major changes to any component of the consent form, then the subject will be informed of the changes and, if the subject agrees to continue study participation, they should sign the updated form.

Electronic or written informed consent will be obtained by trained study staff prior to performance of any protocol-specific procedures.

V. STUDY PROCEDURES

a. Study visits and procedures

A urine pregnancy test will be given to the fertile WOCBP prior to radiofrequency microneedling treatments. In the case of a positive test result, all study procedures will be discontinued, and the subject will be unenrolled from the study. In addition, any woman of childbearing age who is seeking to become pregnant, is breastfeeding or who suspects she may be pregnant will not be enrolled in the study.

Consenting visit (Phone call or in person visit)

During the consenting visit, the investigator will discuss with each subject the nature of the study, its requirements, and its restrictions. This call or visit will last up to 1 hour.

The following will be performed to determine eligibility:

- Review of inclusion/exclusion criteria
- Medical history and demographics
- Review of medications

Subjects who qualify for the study will be consented by a licensed physician investigator and scheduled for Visit 1. Subjects who fulfill all inclusion and exclusion criteria may enroll and begin the Visit 1 procedures that same day.

Phase 1: Temperature Cooling Profile

Phase 1 is intended to provide data on the temperature cooling profile of the experimental EC device and to evaluate the cooling time required to provide analgesia during the delivery of RF energy with the Profound microneedling system.

Phase 1 Visit 1

This visit is expected to last approximately 2 hours. Subjects will be instructed to change into disposable shorts provided by study staff.

The following assessments will be performed during Visit 1 prior to the procedure:

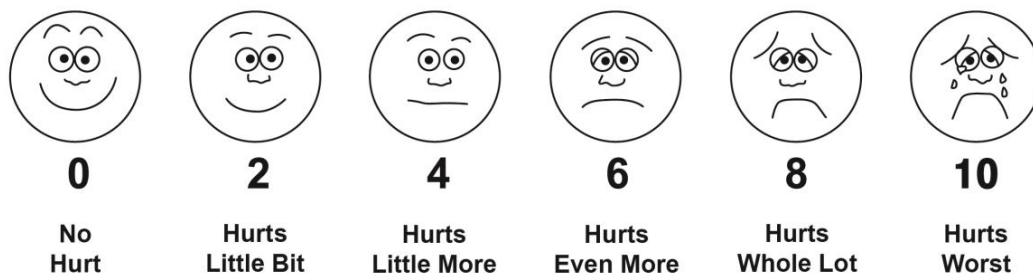
- Review of eligibility criteria
- Review of medical history and medications
- Urine pregnancy test (for female subjects of childbearing potential)
- Measurement of height, weight, and blood pressure

All treatments in Phase 1 will be done with the Profound System with the Dermal handpiece and EC device. These two devices may be used together (connected to each other) or separately (disconnected) during the procedure. During Phase 1 the RF Profound System will only be used with the dummy loads to prevent the delivery of radiofrequency to the deployed microneedles.

The following procedures and evaluations will be performed:

- The subject may or may not have EMLA cream applied to one or both thighs. If EMLA cream is applied, we will wait an hour while the EMLA cream numbs the thighs. We will not exceed the maximum dose of 60 grams of EMLA cream on a patient (See FDA label).*
- The subject will lay in a supine position for the procedures.
- If necessary, any hair in the treatment area will be shaved off.
- Subject's thighs will be marked with the template to outline the treatment areas with a surgical marker.
- Subjects will be instructed how to report a pain score for each needle insertion cycle. A visual 10-point pain scale will be used.

Wong-Baker FACES® Pain Rating Scale



- The licensed physician investigator will perform the microneedling insertion procedure (without the use of RF energy) to the thigh for each of the specified test conditions and subject feedback pain scores will be recorded for each insertion.
- Glycerol will be applied to the subject's thighs prior to the microneedling procedure.**
- If at any time the subject requests to stop a test sequence or stop the study, the investigator will stop treatments and document at what point the test sequence or study was stopped.
- Upon completing each of the test sequences, the treatment area will be wiped with gauze and a mild cleanser.
- Upon completion of all treatments, the treatment area will be covered with a wound dressing and the subject will be provided with aftercare instructions, remuneration and parking voucher if needed. Subjects will be asked not to remove the template markings for medical photography.
- Study staff will document any anticipated side effects or Adverse Events that occur during the study visit.
- Photos of the treatment area will be taken with an encrypted iPhone before and after the procedure.
- Video will be taken of the treatment area during the procedure.
- Video with the Flir A655SC Thermal Camera A600 Series will be taken of the treatment area during the procedure.

*EMLA cream is applied several minutes before the cold exposures as it needs approximately one hour to provide its numbing effects. This applies to the test sites where EMLA cream is used. Some test sites use the effects of cooling as the only localized analgesic.

**The application time point of the glycerol (as the experience from selective cryolipolysis procedures show) is not critical, and therefore, glycerol is applied shortly before the cold application. If EMLA cream had been applied previously, any residual excess of EMLA cream will be removed from the skin surface before glycerol is applied.

Additional details for Phase 1 follow.

Test 1 – The Profound Dermal handpiece and the EC device will be applied to the subject's thigh, and the microneedles inserted without the application of RF energy. The Profound System will be used to record the temperature data at the inserted needle tips while the EC device is held on the thigh for up to 45 seconds. The Dermal handpiece and EC device will then be moved to a new non-cooled area of the thigh, and the test repeated. This test will be repeated once more for a total of 3 times per subject.

Test 2 – The Profound Dermal handpiece and the EC device will be applied to the subject's thigh to pre-cool the test areas for various times ranging from 5

seconds to 45 seconds. The microneedles will be inserted without the application of RF energy and the temperature will be recorded at the inserted needle tips. The Dermal handpiece and the EC device will then be moved to a new non-cooled area of the thigh where pre-cooling will occur again for between 5 to 45 seconds, the microneedles will be inserted, and the temperature at the inserted needle tips recorded. This will be repeated with different pre-cooling times.

Test 3 – The Profound Dermal handpiece and the EC device will be applied to the subject's thigh in a stamping motion. The first test area will include up to 45 seconds of pre-cooling prior to microneedle insertion. The temperature at the inserted needle tips will be recorded. Following this, the Dermal handpiece and EC device will be shifted to the pre-cooled area and held in place for between 5 and 45 seconds prior to microneedle insertion and temperature recording. The number of times the needles are inserted in this stamping fashion will be limited so as not to exceed the maximum total number of treatments which is 30 locations (15 per thigh). This complete test will be repeated up to three times.

Test 4 – The Profound Dermal handpiece will be applied to the subject's thigh without any cooling, The microneedles will be inserted into the skin and the temperature will be recorded to establish a baseline temperature of the skin without any cooling. This test will be repeated for a total of 3 times per subject.

During treatment of each test area, the subject will be asked if they feel any sensation (pain, tingling, burning, etc), how any pain they feel rates on the Wong-Baker pain scale and their answers recorded. If at any of the cooling times, the subject feels pains or is uncomfortable continuing, the treatment will be discontinued at the current setting and move on to milder treatment settings. If at any time the subject requests to stop the study, no further treatments will be applied and the subject will be given after care instructions, etc.

Phase 1 Follow-up Call 1 (1-3 days after Phase 1 Visit 1)

Study staff will call the subject 1-3 days after Phase 1 Visit 1 to check-in and inquire about any post-procedure pain or other observations related to the treatment area. All subjects who have procedures done during Visit 1, even if they request to stop study procedures during the visit, will undergo the follow-up process. Items to be discussed include: any lumps or indentation in skin, rating post-procedural pain (1-10), redness, swelling, burns, continued bleeding, darkening or scarring. This call is expected to last approximately 30 minutes. The subject will have the option to send photos of the numbered treatment area via Patient Gateway.

The subject requires an in-person follow-up if: reported pain is greater than 7, moderate or severe redness, moderate or severe swelling, or there are burns, continued bleeding, darkening or scarring. Additional stipend will be given as needed.

Phase 1 Follow-up Call 2 (1 week after Phase 1 Visit 1)

Study staff will call subjects one week (± 2 days) after Phase 1 Visit 1 to inquire about any post-procedure pain, other observations related to the treatment area or any side effects. All subjects who have procedures done during Visit 1, even if they request to stop study procedures during the visit, will undergo the follow-up process. Items to be discussed include: any lumps or indentation in skin, rating post-procedural pain (scale 1-10), redness, swelling, burns, continued bleeding, darkening or scarring. This call is expected to last approximately 30 minutes. The subject will have the option to send photos of the treatment area via Patient Gateway and the option for an in-person visit for assessment.

The subject requires an in-person follow-up if: reported pain is greater than 7, moderate or severe redness, moderate or severe swelling, or there are burns, continued bleeding, darkening or scarring. Additional stipend will be given as needed.

Phase 2: Comparison of Procedural Pain with EC to TEC

Phase 2 is intended to provide a comparison in the pain tolerance of subjects during the microneedling treatment with the experimental EC device and the current Profound Dermal handpiece cooling (TEC).

Phase 2 Visit 1

Visit 1 is expected to last approximately 2 hours. Subjects will be instructed to change into disposable shorts provided by study staff.

The following assessments will be performed during Visit 1:

- Review of eligibility criteria
- Review of medical history and medications
- Urine pregnancy test (for female subjects of childbearing potential)

All treatments in Phase 2 will be done with the Profound System with the Dermal handpiece. During Phase 2, the RF Profound System will only be used with the second modified dummy load to allow the delivery of radiofrequency to the front three needle pairs identified in Figure 2. For test areas using the Profound System current cooling plate (TEC), the Dermal handpiece, as supplied by Candela, will be used. For the test areas using the experimental EC device, the Profound System with the modified Dermal handpiece will be used.

Topical EMLA cream will be applied to one of the subject's thighs one hour prior to treatment. For all of the tests, the radiofrequency will be delivered for up to 3s and up to 65°C. The treatments of the study subjects will be divided into test categories:

Test 1 – The EC device will be applied to the EMLA thigh for 45s to pre-cool the skin. The EC device will continue to cool the skin while radiofrequency is delivered. (Note: if subject stops here, the study will not proceed to tests 2 through 6.) This will be repeated twice.

Test 2 – The EC device will be applied to the EMLA thigh for 30s to pre-cool the skin. The EC device will continue to cool the skin while radiofrequency is delivered. (Note: if subject stops here, the study will not proceed to tests 3 through 6.) This will be repeated twice.

Test 3 – The EC device will be applied to the EMLA thigh for 15s to pre-cool the skin. The EC device will continue to cool the skin while radiofrequency is delivered. (Note: if subject stops here, the study will not proceed to tests 4 through 6.) This will be repeated twice.

Test 4 – The EC device will be applied to the non-EMLA thigh for 45s to pre-cool the skin. The EC device will continue to cool the skin while radiofrequency is delivered. (Note: if subject stops here, the study will not proceed to tests 5 and 6.) This will be repeated twice.

Test 5 – The EC device will be applied to the non-EMLA thigh for 30s to pre-cool the skin. The EC device will continue to cool the skin while radiofrequency is delivered. (Note: if subject stops here, the study will not proceed to test 6.) This will be repeated twice.

Test 6 – The EC device will be applied to the non-EMLA thigh for 15s to pre-cool the skin. The EC device will continue to cool the skin while radiofrequency is delivered. This will be repeated twice.

Test 7 - The TEC device will be applied to the EMLA thigh for up to 45s to pre-cool the skin. The TEC device will continue to cool the skin while radiofrequency is delivered. This will be repeated twice.

RF microneedling treatments will be performed according to the FDA-cleared parameters available on the Profound System. During treatment of each test area, the subject will be asked to report any sensation (pain, tingling, burning, etc) and a pain score based on the Wong-Baker pain scale.

If at any point during the delivery of radiofrequency the subject reports a pain score of 6 or higher, the radiofrequency delivery will be immediately stopped and the total time of radiofrequency delivery will be recorded.

The following procedures and evaluations will be performed:

- One of the subject's thighs will be numbed with topical EMLA cream and the subject will wait for one hour for numbing to occur prior to the first treatment*

- The subject will lay in a supine position for the treatments.
- If necessary, any hair in the treatment area will be shaved off.
- Subject's thighs will be marked with the template to outline the treatment areas.
- Subjects will be instructed how to report a pain score for each insertion/heating cycle. A visual 10-point pain scale will be used.



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- The licensed physician investigator will perform the RF microneedle treatment to the thigh for each of the test groups above and subject feedback pain scores will be recorded for each insertion.
- Glycerol will be applied to the subject's thighs prior to the microneedling procedure**
- If at any time the subject requests to stop a test group or stop the study, the investigator will stop treatments and document at what point the test group or study was stopped. If the subject requests to stop Test 1, then the study will not proceed further.
- Upon completing each of the four test groups of the study, the treatment area will be wiped with gauze and a mild cleanser.
- Upon completion of all treatments, the treatment area will be covered with a wound dressing and the subject will be provided with aftercare instructions, remuneration and parking voucher if needed. Subjects will be asked not to remove the template markings for medical photography.
- Study staff will document any Adverse Events that occur during the study visit.
- Photos of the treatment area will be taken with an encrypted iPhone before and after the procedure.
- Video will be taken of the treatment area during the procedure.
- Video with the Flir A655SC Thermal Camera A600 Series will be taken of the treatment area during the procedure.

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the test sites where EMLA cream is used. Some test sites use the effects of cooling as the only localized analgesic.

******The application time point of the glycerol (as the experience from selective cryolipolysis procedures show) is not critical, and therefore, glycerol is applied shortly before the cold application. If EMLA cream had been applied previously, any residual excess of EMLA cream will be removed from the skin surface before glycerol is applied.

Phase 2 Follow-up Call 1 *(1-2 days after Phase 2 Visit 1)*

Study staff will call the subject 1-2 days after Phase 2 Visit 1 to check-in and inquire about any post-procedure pain or other observations related to the treatment area. All subjects who have procedures done during Visit 1, even if they request to stop study procedures during the visit, will undergo the follow-up process. Items to be discussed include: any lumps or indentation in skin, rating post-procedural pain (1-10), redness, swelling, burns, continued bleeding, darkening or scarring. This call is expected to last approximately 30 minutes. The subject will have the option to send photos of the numbered treatment area via Patient Gateway.

The subject requires an in-person follow-up if: reported pain is greater than 7, moderate or severe redness, moderate or severe swelling, or there are burns, continued bleeding, darkening or scarring. Additional stipend will be given as needed.

Phase 2 Follow-up Call 2 *(1 week after Phase 2 Visit 1)*

Study staff will call subject one week (± 2 days) after Phase 2 Visit 1 to inquire about any post-procedure pain, other observations related to the treatment area or any side effects. All subjects who have procedures done during Visit 1, even if they request to stop study procedures during the visit, will undergo the follow-up process. Items to be discussed include: any lumps or indentation in skin, rating post-procedural pain (scale 1-10), redness, swelling, burns, continued bleeding, darkening or scarring. This call is expected to last approximately 30 minutes. The subject will have the option to send photos of the treatment area via Patient Gateway and the option for an in-person visit for assessment.

The subject requires an in-person follow-up if: reported pain is greater than 7, moderate or severe redness, moderate or severe swelling, or there are burns, continued bleeding, darkening or scarring. Additional stipend will be given as needed.

Drugs to be used

No therapeutic drugs will be used in this study. Topical EMLA cream will be used to numb the subject's thigh(s) prior to insertion or RF treatment with the

microneedling device.

Devices to be used

Candela Profound System with Dermal Handpiece

The Profound System, an RF microneedling device marketed and sold by Candela (previously known as Syneron), is commercially available and FDA cleared. The Profound System is comprised of an RF generator with graphical user interface, a reusable Dermal or SubQ handpiece and disposable sterile Dermal or SubQ cartridges. The Dermal handpiece has a small cooling plate that provides contact cooling during treatment via a thermoelectric cooling mechanism.

RF energy is delivered from the RF generator, through the handpiece, to needles in the Dermal or SubQ cartridge that are deployed into the dermal layers of the skin and bi-polar RF energy is delivered between independent needle pairs. The Dermal configuration inserts 5 pairs of needles (10 needles total) at a 25-degree angle for a shallower penetration depth while the SubQ handpiece inserts 7 needle pairs (14 needles total) at a 75-degree angle for a deeper penetration to treat the deeper dermis. The Profound System is programmable to deliver bipolar RF energy to achieve thermal heating of tissue at a specific target tissue temperature and application time.

Flir A6555SC Thermal Camera A600 Series

A thermal camera will be used to detect temperature of the skin treatment area before, during, and after the procedure. Video will be taken of the treatment area starting when the glycerol is applied to the skin prior to the first treatment and ending at the conclusion of the procedure.

Experimental Dermal Cooling Device

The experimental dermal cooling device is intended to facilitate pain management during the Profound RF microneedling treatment. Like the current Profound System, the cooling feature in the experimental dermal cooling device is activated prior to and during the delivery of RF energy. The experimental dermal cooling device, however, includes a larger contact surface area and a different cooling mechanism; it uses an evaporative cooling mechanism as the tissue cooling method rather than the thermoelectric cooling mechanism of the Profound System.

The experimental patient applicator is comprised of a cooling assembly with disposable, titanium foil and thermoplastic patient contact components coupled with a non-disposable copper cooling chip through which R-1234yf refrigerant is flowing. The EC device cools the subject's skin on contact through a liquid to gas phase change of R-1234yf creating a rapid, evaporative cooling effect. The refrigerant is completely contained within the sealed system and does not come into contact with the subject or escape into the treatment room.

The copper cooling chip operates at a temperature at $-8^{\circ}\text{C} \pm 2^{\circ}\text{C}$, which is monitored by the use of a temperature sensor in the cooling chip. The cooling chip temperature is displayed on the device and the device will alarm if the cooling chip temperature is out of range. Data from the temperature sensor is recorded via an integrated data logger and can be retrieved from the device via a USB port. The experimental dermal cooling device is controlled entirely by discrete hardware and does not depend on software for any controls.

The handpiece for inserting needles and delivering RF energy to be used for this study is a modified Profound System Dermal handpiece. The thermoelectric cooling plate on the commercial Profound System Dermal handpiece is removed so that the only cooling mechanism during treatment is the experimental patient applicator. This modification is done prior to making the dermal cooling device available for the study procedures; no change to the Profound Dermal handpiece is required by the investigator at the time of use. No other changes will be made to the Profound System.

b. Data to be collected and when data is collected

Study data will be collected during screening and each study visit. Study data to be collected includes subject blood pressure, height and weight (Visit 1 only), and visual assessments of treated areas.

Data collected during Phase 1 includes:

- Cooling chip temperature information from the datalogger for each subject's test sequence will be downloaded as an Excel file, labeled with the subject's number and stored in the subject's data file.
- Profound System data for RF needle temperature will be collected for each subject after each treatment visit, labeled with the subject's number and stored in the subject's data file.
- Subject's reported pain scores with Wong-Baker pain rating scale (visit 1, follow-up call 1, follow-up call 2)
- Before and after images of the treated area.
- Video of the treated area during the procedure.
- Thermal camera video of the treated area.

Data collected during Phase 2 includes:

- Cooling chip temperature information will be collected for each subject after each treatment visit, labeled with the subject's number and stored in the subject's data file.
- Profound System data for RF needle temperature and energy delivered will be collected for each subject after each treatment visit, labeled with the subject's number and stored in the subject's data file.
- Subject's reported pain scores with Wong-Baker pain rating scale (visit 1, follow-up call 1, follow-up call 2)
- Before and after images of the treated area.

- Video of the treated area during the procedure.
- Thermal camera video of the treated area.

Information about side effects in the treatment area or any adverse events will be collected during the follow-up calls and visit 1.

c. Remuneration

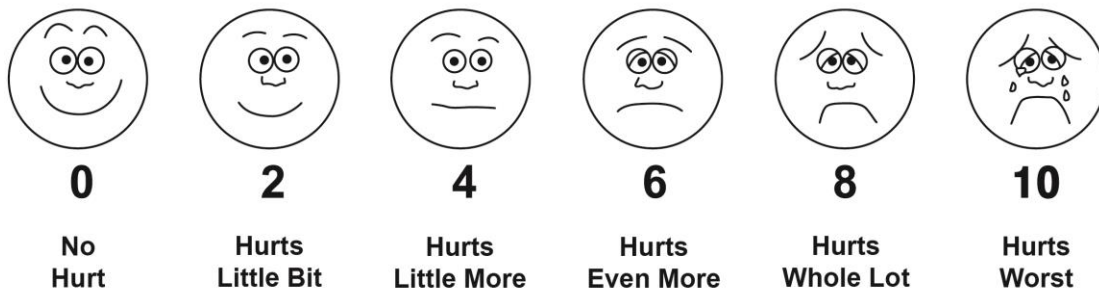
Remuneration for Phase 1 and Phase 2 subjects will be the same across study visits. Subjects will receive \$300 for completing Visit 1 or \$150 if the subject elects not to continue at any point after Visit 1 treatment has begun. All subjects will be requested to complete follow-up visits if any treatment was performed. Subjects will receive \$50 for completing follow-up call 1 (1-2 days after visit 1) and \$50 for completing follow-up call 2 (1 week after visit 1). If the subject needs to come in person for follow-up 1 and follow-up 2 instead of a phone call, they will be compensated with an additional \$20 stipend per visit. The total remuneration amount will be up to \$440 for completion of all study visits and up to \$290 for those who did not complete but started Visit 1. We will also provide a parking voucher for each visit upon request.

VI. BIOSTATISTICAL ANALYSIS

Pain Scoring Analysis

The Wong-Baker FACES Pain Rating Scale will be used to score subject pain in Phase 1 Test 2; Phase 2 Tests 1, 2, 3 and 4; and follow-up calls for both phases.

Wong-Baker FACES® Pain Rating Scale



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Statistical methods

This device feasibility study is intended to gather empirical data about the pain management capability of the dermal cooling device from a limited number of subjects. Descriptive statistics may be performed (e.g., averages, min/max, etc.) on this limited data set to describe the results and observations from the study and may inform the design of future larger studies.

VII. RISKS AND DISCOMFORTS

a. Complications of surgical and non-surgical procedures

Subjects may experience erythema, edema, bruising, post-treatment pain, discomfort, dryness, or flaking at the site of treatment over the 3 weeks following the procedure; these are transient, anticipated effects of microneedling. Rare instances of infection at the treatment site may develop during the week after treatment. Additional potential complications of microneedling procedures, although also rare, include bleeding, burns, pigmentation changes, scarring. In the event of any such complications, subjects will be instructed to contact study staff for a follow-up visit to evaluate and determine a treatment plan.

b. Drug side effects and toxicities

EMLA cream will be applied topically to the upper dorsal thighs of subjects during this study. There is a possibility of allergic reaction to EMLA cream or glycerol, which may manifest as dizziness or drowsiness. In the event of an adverse reaction (e.g., allergy), appropriate measures will be taken by study staff to manage the reaction. Although the incidence of systemic adverse reactions with use of EMLA cream is very low, high systemic levels and toxic effects (eg, methemoglobinemia, irregular heartbeats, respiratory depression, seizures, death) have been reported in patients who (without supervision of a trained professional) have applied topical anesthetics in large amounts (or to large areas of the skin), left these products on for a prolonged time, or have used wraps/dressings to cover the skin following application. We will not exceed the maximum dose of 60 grams of EMLA cream on a patient (See FDA label). We will not apply to broken or inflamed skin, open wounds, or near the eyes. We will avoid inadvertent trauma to the treated area (eg, scratching, rubbing, exposure to extreme hot or cold temperatures) until complete sensation has returned. The event will be recorded in the Adverse Events Log and subjects will be instructed to contact study staff for a follow-up visit to evaluate and determine a treatment plan. In the event of post-treatment pain, subjects will be counseled to use whatever over-the-counter pain products they currently use.

c. Device complications/malfunctions

The Profound RF microneedling device

The Profound RF microneedling procedure and devices are FDA cleared and millions of procedures have been performed worldwide. The device is used worldwide by physicians and rarely malfunctions. Some operator errors that may occur include inserting the needles too close to bone. In this case, the needles are unable to fully extend, and the system will alarm so that the clinician can retract the needles and reposition the applicator.

We performed a search of the MedSun Medical Product Safety Network database over the period of 5/1/2015 – 5/1/2020 using search terms ‘Candela’, ‘Profound’, ‘Syneron’, ‘ePrime’, and ‘radiofrequency microneedling’ and no adverse events have been reported over this period. Syneron and

ePrime are the former company and product names for Candela and Profound respectively so these terms were included in the search.

We also searched the MAUDE database over the period of 5/1/2015 – 5/1/2020 using the 'Profound' brand name and 'ePrime' and 'Primaeva' which are brand names of earlier versions of the Profound device. There was a total of 25 reports in the database during that time period, at least several of which appeared to be duplicative. All reports were related to treatment on the face, submental and/or neck area. There were no reports related to treatment of the thighs. Reported adverse events included significant swelling and edema, hyperpigmentation, nodules/granulomas, local infection at the treatment site, scar tissue/pitting, and excessive bruising/pustules and peeling skin. The causes were attributed to reaction/allergic hypersensitivity or improper needle insertion.

The experimental dermal cooling device

The experimental dermal cooling device is designed to operate with a cooling chip temperature of $-8^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The system has a hardware-based alarm (visual and audio) if the applicator temperature reaches -11°C or below. It is known from other commercially available cooling systems that temperatures down to -11°C for up to 30 minutes will not cause harm to human skin if glycerol is used on the skin as an interface between the cooling surface and the skin (Kilmer, 2017).

Glycerol is an established, well-tolerated cryoprotectant which is used to minimize tissue damage by preventing/minimizing ice crystal formation in tissue. The PI has extensive experience for over a decade with the use of glycerol in combination with skin cooling as he invented and studied selective cryolipolysis (SC or also known as CoolSculpting), which is a non-invasive method to remove localized subcutaneous fat tissue by external cold application to the treatment area. During selective cryolipolysis, glycerol is applied to the skin surface shortly before cold exposure, which is accomplished by a cold applicator set at -11°C for a skin contact time of approximately half an hour. SC is an FDA-approved procedure, which and does typically not produce any epidermal skin damage (absence of frost bites, epidermal damage, blistering, or hypopigmentation and potentially necrosis of the skin). The cold application in this protocol, as compared to selective cryolipolysis procedures, is characterized by less cold applicator temperatures (-7°C to -11°C) and a substantially shorter cold exposure time period (less than a minute), glycerol applied to the skin shortly before cold exposure is used for both procedures. Such less cold and substantially shorter cold exposure times (as compared to SC) are not expected to cause any fat loss and are also safe for the skin (less cold exposure).

If the dermal cooling device fails to maintain the cooling chip temperature needed for adequate analgesia at the treatment site, the subject may feel pain.

Subjects will be instructed by study staff to immediately report any pain to the study physician performing the treatment. The subject has the right to stop the study at any time if they feel pain or otherwise wish to stop the study.

There is the risk of a freezing injury to a subject's skin, which could cause significant epidermal damage, possibly including a local area of inflammation, blistering, or hypopigmentation and potentially necrosis of the skin. To minimize the likelihood of such events, glycerol will be applied to the skin before the treatment procedure. In the event glycerol is not applied to the skin, the subject would typically feel a biting sensation as the skin is cooled. Subjects will be advised of this potential during the consent process and instructed to notify the study physician immediately if they ever feel this sensation during the study.

d. Psychosocial (non-medical) risks

There is a potential risk of loss of privacy. We will protect privacy by labeling samples, information, and data files only with a study subject number code and keeping the key to the code in a password protected database.

e. Radiation risks (statement provided by Radiation Safety Committee)

VIII. POTENTIAL BENEFITS

a. Potential Benefits to subjects

There are no medical or health benefits to subjects for participating in the study.

b. Potential Benefits to Society

Information gathered from this study may improve pain management for RF microneedling devices in the future. Current anesthesia procedures for RF microneedling involve administration of topical and tumescent anesthesia. Improved pain management using this advanced cooling technology may allow use of only topical anesthetic which is less invasive for patients.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

Experienced study personnel (study monitor) who are not assigned to complete procedures of this study will conduct monitoring after the first subject is enrolled and periodically thereafter. The monitor will be responsible for confirming the completion and correctness of the study procedures as well as record collection and keeping.

b. Safety monitoring

Prior to enrollment, subjects will be screened for eligibility at which time a complete medical history, including a baseline assessment of the subject's skin will be done. Evaluations will be ongoing throughout the study to detect adverse events and changes in existing medical conditions.

At any time after enrollment, a subject may be discontinued. Reasons for discontinuation of a subject from the study will include, but may not be limited to, the following:

1. Subject is noncompliant with protocol restrictions and requirements.
2. Subject develops an intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
3. Subject becomes pregnant while participating in the study.
4. Subject enrolls in another investigational study.
5. Subject requests to withdraw from the study.
6. The study staff decides to suspend or terminate the study.

If possible, a final set of assessments will be performed on all subjects whose participation is ended prior to study completion.

a. Outcome monitoring

The study will be conducted in accordance with applicable regulations and Good Clinical Practice Guidelines. Keeping files locked with access limited to study staff will ensure confidentiality and data integrity.

b. Adverse Event Reporting

Definition

Adverse Event (AE) is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect

- Is another medically important condition

Reporting and Documenting Adverse Events

All untoward medical occurrences that occur after the subject signs a consent form will be documented as an AE. The Investigator will ensure that all events that occur during the study period are recorded. All AEs will be followed until resolution or until, in the Investigator's judgment, they are chronic and stable. If an emergency situation should occur, appropriate medical measures should be taken to stabilize the subject.

Documentation of AEs includes date and time of onset and resolution of AE, intensity, frequency, seriousness, related interventions, and outcome. The Investigator will also evaluate the probability of a causal relationship of the AE to the study treatment as being: "definite, probable, possible, unlikely, or unrelated." Intensity of adverse events will be graded as mild, moderate, or severe according to the following criteria:

- Mild: symptoms that are easily tolerated and transient in nature with minimal or no impairment of normal activity
- Moderate: symptoms that are poorly tolerated, are sustained, and interfere with normal activity
- Severe: symptoms that are incapacitating and render the subject unable to work or participate in many or all usual activities

All SAEs will be reported to the IRB according to the IRB's requirements.

Adverse events will be reported to the PHRC as described in the PHRC policy on Unanticipated Problems Involving Risks to Subjects or Others Including Adverse Events, which can be found on the Partner's Research Navigator website.

XII. DATA MANAGEMENT

a. Data collection

Study data will be collected during screening and each study visit. Study data to be collected includes subject blood pressure, height and weight (Visit 1 only), and visual assessments of treated areas. Information about side effects in the treatment area or any adverse events will be collected during the follow-up calls and study visit 1. Details of data to be collected can be viewed in the "Data to be collected and when data is collected" section above.

All physical documentation will be stored in study binders maintained in restricted lab space only accessible by study staff and members of the Manstein Lab.

Digital data including images will be deidentified and stored on Partner's computers. Any identifiable information in photographs such as eyes and tattoos will be blacked out and deidentified. The images will be assigned a number that corresponds to the study subject number. All study documents containing PHI will be password encrypted, including the enrollment log and identification key, and stored in Partners Dropbox or in a locked cabinet with only study staff having access. An encrypted external hard drive will be used to store the data as a backup.

b. Record retention

The Investigator or designees will retain all study records in accordance with the hospital policy (MGB Human Subject Research Recordkeeping and Record Retention Requirements) and clinical trial regulations.

XIII. IRB REVIEW AND APPROVAL

The study will not begin prior to the receipt of written confirmation of approval by the IRB and any relevant regulatory authority. It is the responsibility of the Investigator to obtain the IRB approval (per the U.S. Code of Federal Regulations, Title 21, Part 56 and applicable ICH guidelines) for the protocol, amendments, informed consent, subject information sheet, questionnaires, and advertising materials used to recruit study subjects, if appropriate.

X. REFERENCES

RF Needle Array Publications

1. Alexiades-Armenakas, Macrene et. al., Prospective Multicenter Clinical Trial of a Minimally Invasive Temperature-Controlled Bipolar Fractional Radiofrequency System for Rhytid and Laxity Treatment. *Dermatol Surg.* 2013 Feb;39(2):263-73. Doi: 10.1111/dsu.12065. Epub 2012 Dec 28.
2. Berube, Dany et. al., A Predictive Model of Minimally Invasive Bipolar Fractional Radiofrequency Skin Treatment. *Lasers in Surgery and Medicine.* 41:473-478 (2009).

Safe Cold Exposure of the Skin

3. Kilmer, Suzanne., Prototype CoolCup Cryolipolysis Applicator With Over 40% Reduced Treatment Time Demonstrates Equivalent Safety and Efficacy With Greater Patient Preference. *Lasers in Surgery and Medicine.* 49:63-68 (2017).