NCT03767972 (20174054) Energy Devices for Rejuvenation (Document date: 10/27/2021)

STUDY PROTOCOL

Background & Purpose of the Research

Primary Outcome:

1. To compare the efficacy of different non-ablative and ablative energy-based therapies for improvement in skin and skin appendages of the scalp, face, neck/décolletage, hands, upper and lower extremities, trunk and vagina.

Secondary Outcomes:

1. To use multi-photon microscopy (MPM) to monitor the epidermal thickening and collagen remodeling of the face after treatment with non-ablative and ablative energy-based therapies.

Exploratory Outcomes:

1. To compare patient satisfaction with different non-ablative and ablative energy-based therapies for rejuvenation of the scalp, face, neck/décolletage, hands, upper and lower extremities, trunk and vagina.
2. To determine the adverse event profile for different non-ablative and ablative energy-based therapies for rejuvenation of the scalp, face, neck/décolletage, hands, upper and lower extremities, trunk and vagina.

As the majority of the population ages, therapies for the improvement of skin and skin appendage disordersare becoming ever more popular for patients to ask for, and for clinicians to provide. Currently there are multiple options for skin improvement including non-invasive, minimally invasive and invasive surgery. Invasive surgeries often provide the most impressive results, however are also accompanied by a greater adverse event profile. Non-invasive therapies such as topicals (e.g. vitamin A, vitamin C, anti-oxidant serums) and chemical peels, provide nominal side effects, however results obtained using these treatments are often slight and unimpressive. Minimally invasive procedures such as fillers, botulinum toxin, radiofrequency, lasers and microneedling offer the best of both worlds with adequate results and a minimal adverse events profile with little down-time post-procedure.

The use of non-ablative (including UV lasers) and ablative devices for skin improvement is a “hot topic”. This encompasses the correction of wrinkles/rhytides, dyspigmentation, redness, skin texture (elasticity and laxity), epidermal thinning, hyper- and hypopigmentation, and skin appendage disorders. By creating minimal injury to the epidermis, these devices initiate the wound healing process, collagen remodeling and neocollagenesis, all leading to a refreshed and rejuvenated look. Advancements in technology has allowed for a boom in devices including non-ablative and ablative lasers, as well as radiofrequency. These devices have been used with efficacy for the treatment of the scalp, face, neck/décolletage, hands, trunk, and vagina in humans. In this study we would like to compare these devices in human subjects to determine which devices provide the most results with the least amount of adverse events.

We will be comparing the Fraxel Restore, Halo, Helios III, Vbeam, and Pico lasers for skin rejuvenation of the face, neck/décolletage, trunk, hands, upper and lower extremities. We will be comparing the ThermiVa and the DiVa for rejuvenation of the vagina. Lastly, we will assess the use of the PALLAS UV laser for scalp and skin appendage diseases as well as hypopigmentation disorders on the body.

To date, there are several therapeutic options for patients with signs of aging (wrinkles, uneven skin texture, laxity, dyspigmentation, redness, and follicular-based disorders) including non-invasive topicals, surgical options and minimally-invasive procedures such as energy-based devices using light, laser, radiofrequency, ultrasound, or microscopic physical damage (microneedling). Laser therapy is a safe therapeutic option for skin types I to III with little downtime and minimal side effects. New advances in technology have allowed for the development of hybrid ablative/non-ablative fractional lasers which may be safe to use in darker skin types as well. Fractionated ablative and non-ablative laser treatments have been shown to efficaciously decrease wrinkles and age spots/solar lentigines, while stimulating collagen production due to the development of microthermal treatment zones to improve on skin laxity and increase elasticity. Furthermore, non-ablative lasers, such as pulse dye lasers and targeted UV lasers can help reduce inflammation within the epidermis and dermis, thus improving redness and skin appendage or follicular-based skin disorders. Sides effects of non-

ablative lasers are often minimal and reported as discomfort/pain during the procedure, erythema and edema post-procedure. Ablative lasers carry a higher risk of side effects secondary to stripping of the epidermis. Fractional technology has minimized these adverse events, however if the procedure is done incorrectly, patients and physicians have reported crusting and blistering. Radiofrequency heats the dermal collagen to induce collagen remodeling and production. With an increased dermal structure, this non-ablative technology improves skin laxity, texture, elasticity and wrinkles. Side effects of radiofrequency have also been reported as minimal with discomfort/pain during the procedure, erythema and edema post-procedure. Currently all of the non-ablative and ablative technologies to be explored in this research protocol have been well-tolerated by patients and have reports of high patient satisfaction.

Primary, secondary and exploratory outcome variables will depend on the adherence of patients to post-procedure care instructions and proper sun protection (sunscreen, protective clothing, sun avoidance) that will be provided at the end of their first visit (Visit 1, Day 1). There are no predictors to be applied to our outcomes.

This study group will consist of patients seeking improvement of either the scalp, face, neck/décolletage, hands, upper and lower extremities, trunk and/or vagina.

List up to ten relevant references/articles to support the rationale for the research:

1. Gold, MH. The future of non-invasive rejuvenation technology: devices. JDD, 16(6):s104-7, 2017.
2. Gold, MH, Sensing, W, Biron, J. Fractional Q-switched 1064 nm laser for the treatment of photoaged-photodamaged skin. J Cosmet Laser Ther, 16(2):69-72, 2014.
3. Magon, N, Alinsod, R. ThermiVa: the revolutionary technology for vulvovaginal rejuvenation and noninvasive management of femail SUI. J Obstet Gynaecol India, 66(4):300-2, 2016.
4. Peet, JJ. Evaluation of the safety and efficacy of hybrid fractional 2940 nm and 1470 nm lasers for treatment of vaginal tissue: pilot study. 2600-003-15 Rev. A, Sciton, Inc.
5. Pozner, J, Robb, C. Hybrid fractional laser: the future of laser resurfacing. 2600-003-13 Rev A, Sciton, Inc.
6. Tanzi, EL, Wanitphakdeedecha, R, Alster, TS. Fraxel laser indications and long-term follow-up. Aesthet Surg J, 28(6):675-8, 2008.
7. Beggs S, Short J, Rengifo-Pardo M, Ehrlich A. Applications of the Excimer Laser: A Review. Dermatol Surg. 2015;41(11):1201-1211. doi:10.1097/DSS.0000000000000485.
8. Gordon JR, Reed KE, Sebastian KR, Ahmed AM. Excimer Light Treatment for Idiopathic Guttate Hypomelanosis: A Pilot Study. Dermatol Surg. 2017;43(4):553-557. doi:10.1097/DSS.0000000000000996
9. Liu A, Moy RL, Ross EV, Hamzavi I, Ozog DM. Pulsed dye laser and pulsed dye laser-mediated photodynamic therapy in the treatment of dermatologic disorders. Dermatol Surg. 2012 Mar;38(3):351-66. doi: 10.1111/j.1524-4725.2011.02293.x. Epub 2012 Jan 23. PMID: 22269028.

Research Procedures

We expect that screening patients for inclusion in this study will take two to three months total. Subjects will be screened for participation from the patient population of the UC Irvine, Department of Dermatology. Once a subject is chosen as a possible candidate, the research study team will discuss with the patient whether they would like to participate in a research study comparing non-ablative and ablative energy devices for skin improvement. It will be made clear to patients that modalities such as Fraxel, Halo, Helios, Vbeam, and Pico have been found to be efficacious for improvement of the skin of the face or body while ThermiVa and DiVa have been found to be efficacious for rejuvenation of the vagina, and PALLAS for the scalp or hypopigmentation disorders. Patients will be told that photographs of their scalp, face, neck/décolletage, trunk, hands, upper and lower extremities, and /or vagina depending on the treatment site will be taken and will possibly be used for publications and presentations in the future; it will be made clear to patients that all efforts will be taken to de-identify the photographs. Risks will be explained thoroughly to patients. If patients decide that they would like to participate, they will be given a copy of the informed consent either to take home and read for up to 2 weeks, or if they feel comfortable reading in a private room to read for a maximum of 2 hours before obtaining a signature. Once patients consent to participation, they will be scheduled for their first visit, which may be as early as on the same day as their screening visit.

If eligible, patients may opt to have multiple sites treated during the study.

At their first visit (Visit 1, Day 1), patients' inclusion/exclusion criteria will be reviewed, demographic information will be obtained, physician-assessment performed, vitals assessed, and photographs (before and after treatment) will be taken. Patients will then receive the energy-based treatment in one or more areas. Information regarding the area treated, the device used and the machine settings will be recorded in detail. Patients will be given a diary to fill out to assess for side effects and the timeline of resolution.

The patients receiving laser treatments other than with the UV laser (PALLAS) will be instructed to return to the office in 2 weeks (Visit 2, Day 14 +/- 3 business days) for their next appointment where subject and physician assessments will occur and photographs will be taken. The patients will be instructed to return to the office in 2 weeks for their next appointment where subject and physician assessments will occur and photographs will be taken (Visit 3, Day 30 +/- 3 business days). The patients will be instructed to return to the office in 1 month for their next appointment where subject and physician assessments will occur and photographs will be taken (Visit 4, Day 60 +/- 3 business days). The patients will be instructed to return to the office in 1 month for their next appointment where subject and physician assessments will occur and photographs will be taken (Visit 5, Day 90 +/- 3 business days). This will be the last visit for the patients. Please refer to the attached study schedule Table 1 above for further clarification.

Subjects receiving the UV laser treatment for scalp/skin appendage disorders or hypopigmentation disorders will follow up biweekly for a total of 24 treatments (see attached study schedule table 2). Photography, clinical/patient assessments, and adverse events will be collected at each even visit. A final follow up visit will occur one month after the treatment period has completed for final clinician/patient assessments.

As optional research activities, patients will be asked if they are willing to undergo imaging using the MPM. If patients agree, they will be able to obtain baseline imaging prior to their Day 1 visit. Post-treatment imaging will be completed after 2 weeks (Visit 2), 1 month (Visit 3) and 3 months (Visit 5).

Once all subjects have completed the all visits, non-identifiable data will be complied on the industry-standard RedCAP on a secure network computer located at Hewitt Hall. Data analysis will be carried out by the personnel at the UC Irvine Dermatology Clinical Research Center. The photographs that were collected will be assessed by a blinded physician. Once data is analyzed, we hope to be able to write and publish articles summarizing our findings. Once analysis and publication is completed, non-identifying photographs and patient information will be destroyed. PHI will be maintained for 6 years after study completion.

To further validate the use of energy-based devices for improvement of the skin and skin appendages, we will also include retrospective chart review of patients that had previously been treated with one of the aforementioned modalities. Physician notes and photographs will be used to determine patients' progress post-treatment. Medical records will be accessed by the physician who previously treated the patient at Gottschalk Medical Plaza. The physician will record the type of device used, the parameters under which the device was used, the area that was treated and the number of treatments received by the patient. If there are photographs available, the photos will be assessed by one of the non-treating physicians for improvement post-treatment. There will be no collection of PHI during this retrospective chart review.

The DiVa will use both wavelengths 2940 nm and 1470 nm (fractional ablative Er:YAG and non-ablative laser diode) for vaginal rejuvenation. The Fraxel Dual 1927 nm and the 1550 nm (fractional non-ablative thulium and pulsed dye) will be used for treatment of pigmentation and wrinkle reduction. The Fraxel Re:Pair 10600 nm (fractional ablative CO_2) will be used for resurfacing of the skin. The resurfacing handpieces will be utilized in this study. The Halo will use both wavelengths 2940 nm and 1470 nm (fractional ablative Er:YAG and non-ablative laser diode) for skin rejuvenation. The Helios III will use the 1064/532 nm (fractional non-ablative Nd:YAG) for removal of pigmented lesions and telangiectasias. The PicoWay will use the 1064/532 nm (dual wavelength pico laser) for removal of pigmented lesions. The ThermiVa will use radiofrequency to achieve electrocoagulation in the vagina and induce rejuvenation. The PALLAS will use the wavelengths 308/311 nm (UV laser system) will be used for scalp and skin appendage disorders as well as hypopigmentation of the body. The Vbeam is a pulsed dye laser, wavelength 595nm, which will be used for treatment of vascular lesions or pigmented lesions on the face or body.

The number of passes, size of treated area, spot size and energy level will be determined by the treating physician/investigator. Parameters will be adjusted depending on the area being treated, the aging concern being addressed, skin type, and patients' tolerance during treatment again based on the treating physician's/investigator's discretion. The treating physicians have the appropriate knowledge and experience to be able to make these decisions during the study visit. This information will be recorded meticulously to ensure that the patient receives the proper treatment and will provide the physician/investigator with the necessary information for proper patient care and follow-up.

Subject will receive 24 treatments over 12 weeks (Visits 1-24), with patient and clinician assessments and clinical photos taken at every other visit (Visit 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24). Photographs of the subjects' scalp, faces, neck/décolletage, trunk, hands, upper and lower extremities, and/or vagina will be taken during this study. Photographs will be taken using secured cameras available for clinical photography at the Gottschalk Medical Plaza and Hewitt Hall. These photos will be uploaded immediately onto a secure server for access only by the study team.

The subject will participate in the study treatment period for 3 months. Including screening and follow up period, we expect a maximal participation period of 6 months.

Study Design
This study will be designed as a prospective clinical trial to compare various energy-based devices for the improvement of the scalp, face, neck/décolletage, trunk, hands, upper and lower extremities, and vagina. If patients meet the inclusion and exclusion criteria for multiple treatment areas, they will be allowed to receive treatment for multiple areas. The treating physician will decide which energy-based device is best-suited to address the patients' aging concerns; although patient preference will be taken into account, ultimately the treating physician is responsible for the correct assessment of the patients' needs, the use of the appropriate energy-based devices, and the final treatment. Although this may lead to some bias, patients will be treated in the most appropriate manner for their disease. Patients will be followed for 3 months post-treatment to determine if the procedure was efficacious for rejuvenation of the treatment anatomical area.

Per statistical considerations outlined below we will be comparing non-ablative and ablative devices. For each body area studied, 10 patients will be enrolled each into the non-ablative and the ablative device groups. The decision to treat and which device will be used will be made by the physician after careful consideration of a subject's rejuvenation concern(s). Multiple devices may be used due on one subject; for instance, a subject may require facial, body and/or vaginal rejuvenation, in which case one of the devices such as the Fraxel, Halo, Helios, Vbeam, or PicoWay would be used to address the face or body with the device picked based on the subject's needs or concerns, while either the ThermiVa or the DiVa would be used for vaginal rejuvenation, and PALLAS would be used for the scalp or hypopigmentation concerns.

A retrospective electronic medical record review will also be completed as part of this study to capture patients who were previously treated with any of the aforementioned modalities for rejuvenation of either the face, neck/décolletage, hands, trunk, upper and lower extremities and/or vagina.

The study endpoint will be 3 months. Number of laser treatments needed during this time period will be based on the patient's clinical response to each treatment (as assessed by the physician). Evaluation will occur using various validated methods including photographs, MPM imaging, the Global Aesthetic Improvement Scale, the Visual Analogue Scale, the Modified Fitzpatrick Wrinkle Scale, the Wrinkle Severity Rating Scale, the Facial Laxity Improvement Scale, the Dyspigmentation Scale, the Mid-Clavicular Nipple Distance, the Fabi Bolton Chest Wrinkle Scale, the Merz Hand Grading Scale, the Vulvo-vaginal Laxity Questionnaire, Female Sexual Function Index, International Consultation on Incontinence Questionnaire – Short Form, Severity of Alopecia Tool, Psoriasis Scalp Severity Index, Patient Global Impression of Change, and Clinician Global Impression (based on which body site and laser are used).

There are no composite variables as the primary outcomes will only be determined by the physician and subject GAISs. Other criteria for evaluation (secondary and exploratory outcomes) include photographs, the Modified Fitzpatrick Wrinkle Scale, the Wrinkle Severity Rating Scale, the Facial Laxity Improvement Scale, the dyspigmentation scale, the mid-clavicular nipple distance, the Fabi Bolton Chest Wrinkle Scale, the Merz Hand

Grading Scale, the Visual Analogue Scale for pain, the patient diary, and the investigator-authored patient satisfaction survey.

At each study visit, the investigator/physician will collect physician and subject-reported data regarding the efficacy and adverse events associated with the procedure (Visits 2-5, Days 14-90). To define patient satisfaction, an investigator-authored survey will be completed at the last visit (Visit 5, Day 90). Photographs will be collected at all visits (Visits 1-5, Days 1-90).

Since use of the PALLAS laser is typically required twice weekly, treatment of scalp and hypopigmentation disorders will follow a separate schedule of events from the other energy-based devices. Subject will receive 24 treatments over 12 weeks (Visits 1-24), with patient and clinician assessments and clinical photos taken at every other visit (Visit 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24). A blinded clinician will also assess change in skin or hair at Visit 12 and 24. Visit 25 will consist of a one-month follow up after the three-month treatment period.

Micro-coring (Ellacor) treatments are typically recommended in one month intervals so it will follow a separate schedule. Subjects will receive three treatments over two months (day 0, 30 and 60). Followup visits will be conducted at 1 month and 3 month post-last treatment (day 90 and day 150, respectively.) Patient and clinician assessments and clinical photos will be taken at every other visit.

STATISTICAL ANALYSIS PLAN

Statistical analysis of the data will be limited given the small sample size. Given the scales used for evaluation, data will be recorded as continuous scores. Statistical analysis will be completed using non-parametric methods (with significant defined as $p < 0.05$) due to the subjective nature of the quantitative scales of improvement used and possible skew of results. Given that multiple areas will be treated and monitored for improvement over time, we may need to apply the Bonferroni Correction. If and when dependent samples are reported (i.e. longitudinal measures on individual patients), analysis will be completed with either the Mann-Whitney-Wilcoxon Test (two observations) or Friedman's test (more than two observations). When possible, trend evaluated over time will be assessed using a non-parametric test for trends over ordered groups. Bonferroni correction will be used to account for multiple comparisons. Analysis will be completed using STATA, version 13.

Power and sample size will be determined based on primary outcome- to compare the improvement between ablative and non-ablative therapy in face, décolletage, hands, trunk, upper and lower extremities, and vagina. Given the 7 regions to compare, Bonferroni correction was used to define the new significance level as $0.05/7=0.007$. Sample sizes of 10 in ablative and 10 in non-ablative group in each body region achieve 81% power to show a difference in means when there is a difference of 2.0 between the null hypothesis mean difference and the actual mean at the 0.007 significance level (alpha) using a two-sided Mann-Whitney-Wilcoxon Test.