A Prospective, Multicenter, Single Arm Clinical Study Evaluating the Use of the Renuvion Dermal System for Dermal Resurfacing

Clinical Study Protocol

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LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CRO	Clinical Research Organization
DCF	Data Clarification Form
DRM	Data Review Meeting
ESU	Electrosurgical Generator Unit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSS	Fitzpatrick Skin Scale
FWS	Fitzpatrick Wrinkle and Elastosis Scale
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICH	International Conference for Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IFU	Instructions for Use
IPR	Independent Photographic Reviewer
IRB	Institutional Review Board
ITT	Intent-to-Treat
NSAID	Non-steroidal Anti-Inflammatory Drug
PP	Per Protocol
PSR	Plasma Skin Resurfacing
PPS	Per Protocol Set
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

1 STUDY SYNOPSIS

Study Title	A Prospective, Multicenter, Single-Arm Clinical Study Evaluating the Use of the Renuvion® Dermal System for Dermal Resurfacing
Study Device	Renuvion® Dermal System
Study Population	The study population will consist of males and females, 30 years of age or older, requesting a procedure for the purpose of improving facial appearance by reducing facial wrinkles and rhytides. Those subjects who meet eligibility criteria and agree to provide written informed consent will be invited to participate.
Study Objective	The study objective is to demonstrate the safety and effectiveness of the Renuvion® Dermal System for use in dermal skin resurfacing.
Study Design	This is a multi-center, single arm, evaluator-blind prospective study of up to 55 study subjects who are seeking a procedure to reduce the appearance of wrinkles and rhytides from up to 5 investigational centers in the United States. Each study subject will receive one procedure with the Renuvion® Dermal System at enrollment. Follow-up will occur immediately following the procedure, at 1 day, at 6 (±2) days, at 10 (-1/+4) days, 30 (±7) days, 90 (±10) days, and 180 (±14) days after study treatment.
Study Endpoints	**Primary Effectiveness Endpoint** is the proportion of subjects with at least one-point improvement from baseline in the Fitzpatrick Wrinkle and Elastosis Scale (FWS) at 90 days as determined by 2 out of 3 blinded Independent Photographic Reviewers**.** **Primary Safety Endpoint** is the evaluation of adverse events up to the 3-month visit after treatment. **Secondary Safety Endpoint** is the evaluation of the change in pain and discomfort after treatment (baseline, within 60 minutes following the procedure) as reported by the subject on a visual analog scale (VAS)experienced in the period up to the 10-day follow-up visit. Any pain or discomfort will be recorded daily by each participant in a diary using an 11-point Visual Analogue Scale (VAS).
Additional Endpoints	1. Whether or not (yes/no) at least 2 out of 3 blinded Independent Photographic Reviewers (IPRs) correctly identify the 90-day image of a subject from the pair of baseline and 90-day images. 2. Magnitude of improvement measured by the mean change in FWS from baseline to 90-day visit as determined by Investigators. 3. Subject modified GAIS at 90-day FUV (follow-up visit). 4. Investigator modified GAIS at 90-day FUV. 5. Subject satisfaction with procedure recorded at the 90-day visit. 6. Achievement of re-epithelialization by facial zone and across all facial zones at the 10-day, 30-day and 90-day follow-up visits as reported by the investigator. **7.** Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject.
Planned Study Duration	Study enrollment is expected to occur over 3-6 months. Imaging and study assessments will continue through 3 months post-procedure, with long term subject follow-up and data collection through 6 months post-procedure. Moreover, study subjects will be followed until each adverse event is resolved to ensure their safety. Total study duration is expected to be approximately 9-12 months. It is expected that the 510(k) application for the device will be submitted based on 3-month post-

	procedure results. However, this clinical trial will continue until every enrolled subject has reached 6 months following their procedure. At that time, the trial will be considered complete, the final results will be analyzed, and a final report will be prepared.

2 STUDY ADMINISTRATIVE STRUCTURE

Study Sponsor:

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Proprietary Notice:

This document contains mainly unpublished data and is the sole property of the Sponsor. Therefore, it is provided to you in strict confidence as an investigator, potential investigator, or consultant. The information may be reviewed by you, your staff, and your institutional review board. It is understood that this information will not be disclosed to others without written authorization from the study Sponsor except to the extent necessary to obtain informed consent from those persons to whom the investigational device may be implanted.

Ethics Statement:

The study will be completed in accordance with applicable regulations and standards to provide public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

3 INTRODUCTION

3.1 Study Background

Physiological skin aging is multi factorial and results from both intrinsic and extrinsic factors. Genetics is one example of an intrinsic factor; others include hormone and metabolic processes that can cause the skin to age. Exposure to chronic light, radiation, pollution, chemicals and toxins, are examples of extrinsic factors. Since skin health and beauty is contemplated as one of the representations of overall "well-being" and "health", several anti-aging therapies have been developed during the recent years. The goal of these therapies is to achieve a healthy, smooth, blemish-free, translucent and resilient skin. [1]

Skin resurfacing or peel procedures have become an established non-surgical method for reducing certain skin imperfections such as wrinkles, rhytides, dark spots, scars, or blemishes. Traditional fully ablative and fractional lasers are the most commonly used devices for skin resurfacing.

The skin is composed of three layers: the epidermis, the dermis, and the hypodermis. The dermis contains well-organized and oriented collagen fibers that contribute to the firmness and smoothness of the skin. As people age, these collagen fibers reduce in number and become less organized, resulting in sagging and/or wrinkled skin. When esthetic procedures are scheduled for older adults, the rate of the epidermal turnover associated with a slower wound healing and less effective desquamation (shading of outer layers of the skin), needs to be taken into consideration.[1]

In most skin resurfacing procedures, an energy source (heat, radiofrequency energy, etc.) is used to selectively damage the skin and prompt a healing response that stimulates the growth of new collagen fibers in the dermis that are well-organized. The healing response and new collagen formation results in skin that is smoother and firmer.

There are numerous traditional fully ablative and fractional lasers on the market today used for skin resurfacing. Traditional and fractional lasers differ in their method of treatment. Traditional lasers have a single beam that burns or damages all of the epidermis within the treatment area of the beam. Fractional lasers divide the beam into multiple smaller beams and treat only a "fraction" of the epidermis to affect changes in the deeper epidermis or dermis. This results in multiple small cores of laser damage surrounded by areas of healthy tissue. When compared to traditional lasers, fractional lasers deliver a more superficial treatment resulting in less risk for complications and reduced time for healing. However, this also means more treatments may be required to achieve the desired results especially in areas of deep lines or wrinkles. Healing times vary by amount of treatment, but fractional laser recovery time is typically one week compared to three to four weeks for traditional lasers.

In the wake of the demonstrated safety and effectiveness of laser skin resurfacing, multiple additional treatment modalities have been developed for this application including the use of radiofrequency (RF) energy. The fractionated radiofrequency results in epidermal and subepidermal ablation under the conductive pins that reproduces similar effects as a fractional CO_2 laser with dermal heating, seen in the non-ablative lasers and devices.[2] The combination of epidermal ablation and dermal heating with radiofrequency, called sublative resurfacing in some studies, is suitable for skin types I–IV, for the treatment of skin laxity, wrinkles, enlarged pores, pigmented lesions, acne, telangiectasias, and scarring from trauma or acne. Subject recovery and

down time periods are significantly lower when compared with ablative laser healing times, with minimal adverse effects.[3]

3.2 Study Rationale

An emerging method utilizing the state of matter known as plasma to create a thermal effect on the skin through the use of positively ionized gasses is plasma skin resurfacing (PSR).[4] As this plasma comes in contact with the resurfacing target, the positive ions capture back electrons while energy is released. With PSR, an inert gaseous source is used to form a plasma that releases thermal energy that eliminates oxygen from the targeted skin surface. [5,6] PSR is not dependent on a chromophore for its use and does not vaporize tissue as ablative lasers do. This resurfacing modality has been hypothesized to function by forming a layer of desiccated epidermis creating a natural barrier that facilitates accelerated healing with generation of new epidermis. PSR also penetrates to the upper dermis resulting in thermal denaturation of surrounding collagen, thereby increasing fibroblast activity, which has been shown to continue up to a year after the plasma treatments.[7] Plasma resurfacing has been safely used in Fitzpatrick skin types I–IV. It has been approved for the treatment of many skin conditions including photoaging, acne scars, rhytides, dyschromias, skin laxity, as well as the treatment of actinic keratosis and seborrheic keratosis. In contrast to the ablative laser, plasma resurfacing treatments have a very low incidence of side effects such as permanent hypopigmentation, scarring, or prolonged erythema.[8]

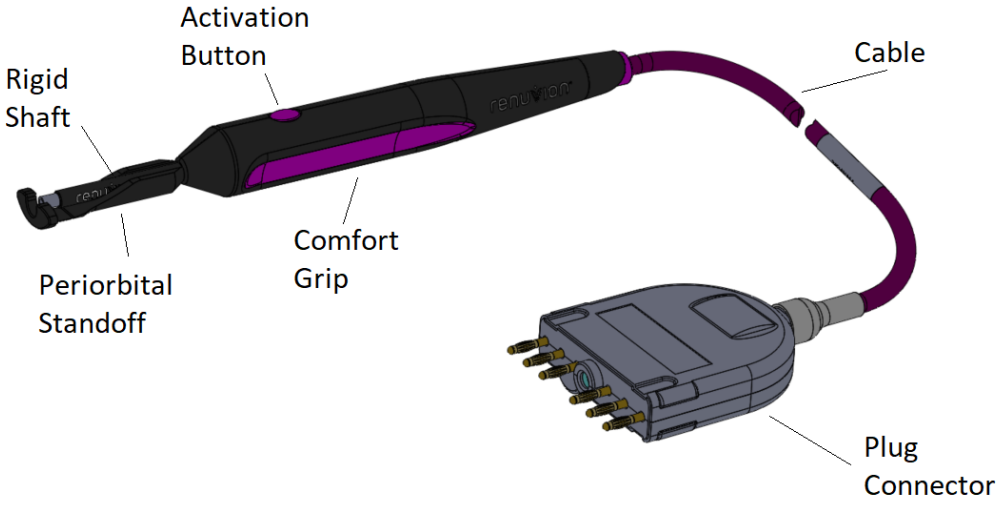
As an alternative treatment modality for skin resurfacing, Apyx Medical Corporation has developed the Renuvion® Dermal System that delivers RF energy in a controlled fashion with similar depth of thermal effect as predicate devices currently on the market for dermal resurfacing and wrinkle reduction procedures. [9,10,11] A potential benefit of this single-treatment low-risk technology is reducing wrinkle appearance and enhancing well-being by improving satisfaction and perception of having a more youthful appearance.

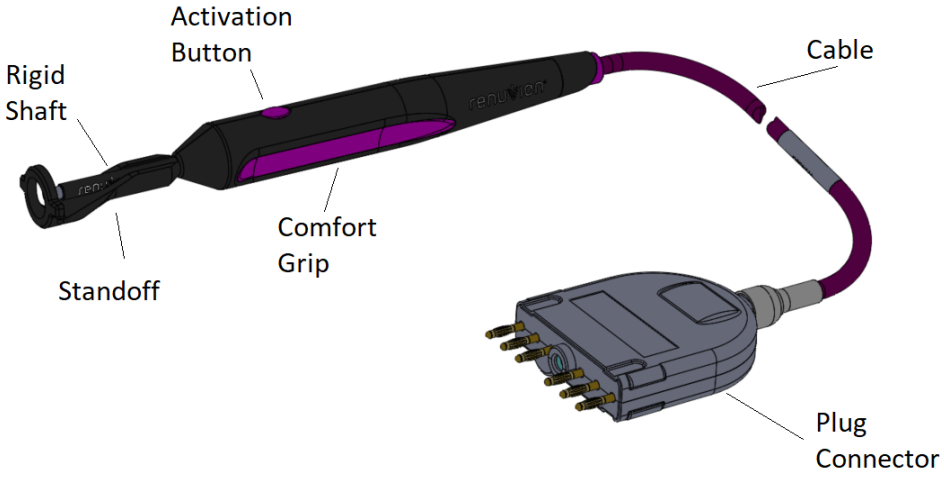
3.3 Study Device Description

The Renuvion® Dermal System consists of an electrosurgical generator unit (ESU, Figure 1), a handpiece with detachable standoffs (Figure 2), and a supply of helium gas. RF energy is delivered to the handpiece by the ESU and used to energize an electrode. When helium gas is passed over the energized electrode, a helium plasma is generated which allows for conduction of the RF energy from the electrode to the subject in the form of a precise helium plasma beam.

Figure 1: Electrosurgical generator unit

Figure 2: Handpieces with Standoffs





Apyx Medical Corporation's Renuvion® helium-based plasma technology has received FDA clearance (K112233, K151325, K152570, and K170188) for the cutting, coagulation, and ablation of soft tissue.

Pre-clinical studies comparing Renuvion (formerly known as J-Plasma®) to other energy sources such as CO_2 laser and RF energy demonstrated less or comparable lateral and depth of thermal spread for Renuvion® in porcine peritoneum, bladder, and small intestine.[12]

Additionally, a pre-clinical study comparing Renuvion to the NeoGen PSR System (K132754) when ablating/resurfacing the skin in a naive swine model was conducted. A single animal was utilized in the study to evaluate both devices at an acute time point. At the treatment settings used in this study, the maximum depth of thermal effect measured for tissue treated using the Renuvion® System were statistically equivalent to or lower than the maximum depth of thermal effect for tissue treated using the NeoGen PSR System. These results support the safety of Renuvion® for this application and equivalent tissue effects for the two technologies.

These pre-clinical study results demonstrate safety and effectiveness of the Renuvion® Dermal System in the ablation of soft tissue within its current FDA cleared indications in an animal model, therefore making the Renuvion® Dermal System a viable technology for dermal skin resurfacing.

4 STUDY DESIGN

4.1 Study Objective

The study objective is to demonstrate the safety and effectiveness of the Renuvion® Dermal System for use in dermal skin resurfacing.

4.2 Study Design

This is a multi-center, single arm, evaluator-blind prospective study of up to 55 study subjects who are seeking a procedure to reduce the appearance of wrinkles and rhytides at up to 5 investigational centers in the United States. The maximum enrollment per site is 20 subjects.

Study subjects that meet study eligibility criteria and have provided informed consent will be enrolled in the study. During the procedure, the investigators will use the Renuvion® Dermal System on applicable facial zones to reduce wrinkles and rhytides.

Study subjects will be followed immediately following the procedure, at 1 day, at 6 (±2) days, at 10 (-1/+4) days, 30 (±7) days, 90 (±14) days, and 180 (±30) days after study treatment for study assessments.

Study enrollment is expected to occur over 3-6 months. Imaging and study assessments will continue through 6 months post-procedure. Total study duration is expected to be approximately 9-12 months. It is expected that the 510(k) application for the device will be submitted based on 90-day post-procedure results. However, this clinical trial will continue until every enrolled subject has reached 180 days following their procedure and all adverse events are resolved. At that time, the trial will be considered complete, the final results will be determined, and a final report will be prepared.

4.3 Study Endpoints

The following endpoints will be assessed in this study.

4.3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the proportion of subjects with at least one-point improvement from baseline in the Fitzpatrick Wrinkle and Elastosis Scale (FWS) at 90 days as determined by 2 out of 3 blinded Independent Photographic Reviewers**.** Three experienced, blinded Independent Photographic Reviewers (IPRS) will perform an analysis/review of the pre-treatment and post-treatment sets of images of each subject in a blinded and randomized order.

4.3.2 Primary Safety Endpoint

The primary safety endpoint is the evaluation of adverse events up to the 90-day visit after treatment.

4.3.3 Secondary Safety Endpoint

The secondary safety endpoint is the evaluation of the change in pain and discomfort after treatment (baseline, within 60 minutes following the procedure) experienced in the period up to the 10 (-1/+4) day follow-up visit. Pain or discomfort will be recorded daily by each participant in a diary using an 11-point Visual Analogue Scale (VAS).

4.3.4 Additional Endpoints

Other endpoints to be evaluated include:

1. Whether or not (Yes/No) at least 2 out of 3 blinded Independent Photographic Reviewers (IPRs) correctly identify the 90-day image of a subject from the pair of baseline and 90-day images.
2. Magnitude of improvement measured by the mean change in FWS from baseline to 90-day visit as determined by Investigators.
3. Subject modified GAIS at 90-day FUV.
4. Investigator modified GAIS at 90-day FUV.
5. Subject satisfaction with procedure recorded at the 90-day visit.
6. Achievement of re-epithelialization by facial zone and across all facial zones at the 10 day, 30 days and 90 days follow-up visits as reported by the investigator.
7. Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject.

5 INVESTIGATORS SELECTION AND STUDY POPULATION

5.1 Investigator Selection

Participating Investigators will be qualified based on professionals experienced in treatment of wrinkles, such as dermatologists or plastic surgeons. Investigators will be selected based on interest and availability for participation in the study; ability to provide qualified subjects; adequate support staff; experience conducting clinical research; and willingness to comply with the protocol, IRB requirements, regulatory requirements (including the signed investigator agreement and statements disclosing any financial relationship investigators might have with Apyx Medical Corporation), and FDA regulations.

5.2 Study Population

All subjects requesting a procedure for the purpose of improving facial appearance by reducing facial wrinkles and rhytides from each participating investigator's subject population will be considered as candidates for the study. Those subjects who meet eligibility criteria and agree to provide written informed consent will be invited to participate.

Subjects will be considered enrolled into the study when they have signed an approved informed consent form. Enrolled subjects who meet all study criteria and have undergone a procedure with the Renuvion Dermal System will be part of the full analysis set.

5.2.1 Inclusion Criteria

Potential subjects must meet all of the following inclusion criteria:

1. Male or female subjects ≥30 years of age.
2. Subject is seeking improvement of facial appearance by reducing facial wrinkles and rhytides.
3. Subject with a facial wrinkle score rating of at least 4 on the FWS.
4. Subject with a Fitzpatrick Skin Scale score ≤III.
5. Subjects who are willing and able to take protocol allowed medications prescribed at investigator discretion which may include Keflex or Z-pack as an antibiotic, Acyclovir or Valtrex as an antiviral, Diflucan as an antifungal, Ativan or Valium for anxiety during treatment, Norco or Ultram for pain control during or post-procedure, Gabapentin, Tylenol with Codeine or NSAIDS for post-procedure pain control, and/or Antihistamines for itching during healing.
6. Subjects who are willing to have polycarbonate eye shields placed for study treatment.
7. Subject is willing and able to provide written informed consent.
8. Subject is willing and able to comply with protocol requirements, including obtaining study-required images/photos and assessments, post-care instructions, and returning for follow-up visits.
9. Subject is willing to maintain baseline skin care regimen during study participation with the exception when protocol specified ointments, moisturizers, and cleansers are required during healing stage (through approximately the 30-day follow-up). Sunblock is required throughout the study starting on approximately day 10.

10. Subject is willing to release rights to study Sponsor for the use of the photos, including in potential publication.
11. Subject is willing to abstain from other facial cosmetic procedures through the 6-month follow-up visit; examples include, but are not limited to, laser or chemical re-surfacing, dermabrasion, neuromodulator and/or filler injections, aesthetic facial surgery, etc.

5.2.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Subject with a Fitzpatrick Skin Scale score ≥IV.
2. Subject is pregnant or lactating.
3. Active HSV-1 or diabetes mellitus.
4. Active cut, wound, or infection on the skin of the face.
5. Subject has used, within 30 days prior to screening or plans to use during study participation, Accutane, Retinol, or any medication that can cause dermal hypersensitivity.
6. Subject has used, within 10 days prior to study treatment, aspirin or NSAIDs.
7. Subject has a history of autoimmune disease (excluding Hashimoto's thyroiditis).
8. Subject with a known bleeding disorder or who is on blood thinning medication that may be at risk for bleeding.
9. Subject has a known adverse reaction to lidocaine and/or epinephrine.
10. Subjects with active skin disease of the facial area or known connective tissue disease.
11. Subjects with known susceptibility to keloid formation or hypertrophic scarring.
12. Subjects with present cancerous or pre-cancerous lesions in the area to be treated.
13. Subject who, for any reason, suspects that they will not be able to complete the prescribed follow-up assessment(s).
14. Subject has had concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety and effectiveness of the study treatment method.
15. Subject is not willing to release rights to study Sponsor for the use of the photos, including in potential publication.
16. Subject is enrolled in another investigational (drug or device) clinical trial that can interfere with this study's assessments.
17. Subject has undergone a facelift procedure within 12 months prior to the screening visit.
18. Subject has received IPL, microneedling, or chemical peels within 3 months prior to the screening visit.
19. Subject has received microneedling with RF or any facial treatment with an energy-based device within 6 months prior to the screening visit.
20. Subject has received facial injections with BOTOX® or other toxins within 6 months prior to the screening visit.
21. Subject has received hyaluronic acid or calcium hydroxylapatite fillers within 4 months prior to the screening visit.
22. Subject who is a family member or employee of the investigator or sponsor.
23. Participation in any other investigational study within 30 days prior to consent.
24. Subject who, in the opinion of the investigator, is not an appropriate candidate for the study.

6 STUDY PROCEDURES

6.1 Informed Consent

The Investigator must ensure that written informed consent to participate in the study and written authorization for use and disclosure of protected health information is obtained before including any individual as a subject in the study, and before conducting any study-related assessments. The Investigator must provide the prospective subject with enough opportunity to consider whether or not to participate and minimize the possibility of coercion or undue influence.

To participate in the study, a subject must sign and date an IRB-approved consent document. The original, signed documents will be kept with the subjects' files and copies will be provided to the subjects. The informed consent process must be followed, and the subject's participation in the study, must be documented in the subject's medical record/chart.

6.2 Pre-Procedure

The subjects will have verification of eligibility criteria, a brief general examination including medical history, and wrinkles/rhytides assessment completed within 30 days prior to undergoing the study procedure. In response to the ongoing coronavirus disease (COVID-19) pandemic, preoperative testing can be completed at the Investigator's discretion. Pre-operative testing should be performed as close to the scheduled study procedure as feasible, but in time to get results. Up to two urine pregnancy tests must be obtained prior to study procedure for females with child-bearing potential (one at pre-procedure screening and one on the day of the procedure prior to the procedure. Screening and procedure will not be performed on the same day).

Additionally, photographs of the area to be treated with the study device will be taken using the Canfield Scientific Visia-CR system (see also Section 12.3 Data Management Responsibilities and Section 12.4 Data Capture Methods) for each subject to document the appearance of their facial wrinkles and rhytides. The same standardized photography views will be used throughout the study as documented in the Canfield User Manual document developed for the study. Subjects will specifically be instructed to lightly rest their chin on the chinrest rather than resting heavily and distorting the chin appearance.

All screening images will be reviewed by the Sponsor prior to study treatment to ensure enrollment criteria are met and study baseline images are high quality.

The study subjects may be given medication for the prophylactic treatment of bacterial and viral infections including herpes simplex based on investigator's discretion; allowed medications include:

- Antibiotics: Keflex 500mg BID (first dose just prior, within 90 minutes, to procedure) x 7 days. Alternative, Z-pack.
- Antivirals: Acyclovir 400mg BID (start 1 day prior and continue for 10 days). Alternative, Valtrex 1 gram every day for 10 days (start 1 day prior).
- Antifungals: Diflucan 150mg (1 day prior).

Medications subject is taking upon entry into the study should also be documented in the Case Report Forms (CRF). Documentation should include medications and supplements that study subjects take on an elective basis in addition to prescribed medications. Medication used for analgesia and/or anesthesia should be recorded as concomitant medication as well. To ensure the capture of the foregoing information on pre-existing conditions, sites should also be attentive to the need to document without limitation and whenever discovered: (1) all chronic, episodic or 'as needed' medications used before study enrollment; (2) prior episodic or 'as needed' therapeutic interventions, procedures or hospitalizations; and, (3) recent or planned surgical procedures.

6.3 Study Procedure

On the day of the procedure and prior to the study procedure, female subjects with child-bearing potential must complete a urine pregnancy test (result must be obtained prior to the procedure). Additionally, subjects must complete a VAS pain assessment pre-procedure and immediately following the procedure (within 60 minutes after the procedure).

Prior to study treatment, the following medications may be administered at investigator's discretion:

- Ativan 2mg or Valium 10-20mg.
- Norco 5-10mg or Ultram 200mg.

A responsible driver (friend or family member) is required if these medications are prescribed.

The skin in the treatment area will be prepped by wiping the area with 70% isopropyl alcohol, then cleaned with 0.012% Hypochlorous Acid, then the entire area will be wiped clean with sterile saline.

Facial Nerve Blocks will be done prior to infiltration of tumescent anesthesia to the ophthalmic nerve (v1), the maxillary nerve (V2), and the mandibular nerve (V3) using 1%-2% lidocaine with epinephrine (1:100,000).

Regional blocks and local tumescent anesthesia (an anesthetic) will be used during the study procedure. The local anesthetic is commonly referred to as Klein's Solution. Per standard of care, this Klein's Solution is prepared at the time of use and contains USP injection grade saline solution, USP injection grade Lidocaine for pain, and injection grade Epinephrine for vasoconstriction. A 0.2% concentration (double Klein solution) will be utilized in this study. The Tumescent solution is made by adding the following to 500 cc of normal saline:

1. 50cc of 2% Lidocaine = to 1000mg
2. 0.5cc of 1 mg/ml Epinephrine (1:1000)

Tumescent local and regional anesthesia will be injected percutaneously infused with a 22 Gauge spinal needle. The total volume of tumescent used should be between 250 – 500cc for the entire treatment area at investigator's discretion and will be documented in the CRFs.

Polycarbonate plastic eye shields will be used as per product IFU during study treatment. Numbing eye drops may be used to place eye shields at investigator's discretion.

During the study procedure, the face of each subject will be treated by the study investigator using the Renuvion Dermal System according to the Instructions for Use (IFU; see Appendix F) and procedures described in this section. The face will be divided into 6 zones: Zone 1 (perioral), Zone 2 (periorbital), Zone 3 (forehead), Zone 4 (nose), Zone 5 (cheeks), and Zone 6 (jawline/mandibular border) – see Appendix G: Facial Zones.

The plasma beam will be used to ablate the tissue in each Zone using a consistent movement of the beam. Zones 1, 3, 4, and 5 (perioral, forehead, nose, and cheeks, respectively) will be treated with two (2) passes of the plasma beam at 40% power and 4 liters/minute helium flow utilizing the appropriate standoff with one pass done horizontally and the other pass done perpendicular. Zone 2 (periorbital) will be treated with one (1) or two (2) passes, 20% power, and 4 liters/minute helium flow utilizing the appropriate standoff with up to 2 passes done horizontally or only in one direction. Zone 6 (jawline/mandibular border) will be treated with one (1) or two (2) passes, based on the investigator's discretion, at 20% - 40% power and 4 liters/minute helium flow using the appropriate standoff and a treatment pattern in a variable motion to achieve blending. Special care must be taken to not pass over any treated area more than twice. Areas that are treated with 1 pass (optional for Zone 2 and/or Zone 6) are not wiped after the pass. For areas that will be treated with a 2nd pass, the eschar will be wiped away entirely prior to start of the 2nd pass. Pat skin dry prior to performing 2nd pass. Do not wipe eschar away in areas that are treated with only 1 pass. Do not wipe eschar away following 2nd pass.

6.4 Follow-up Procedures

At investigator's discretion, subjects may be given the following medications post-procedure ~~PRN or~~ and as needed:

- Gabapentin 300mg TID x 6 days.
- Tylenol with Codeine (T3) x 15 tablets.
- Norco 5-10mg x 15 tablets.
- NSAIDS and Antihistamines (e.g. Benadryl, Zyrtec)

Following the procedure, the research staff and the subject will care for the treated areas using the Post-Procedure Care Guidelines listed below:

<u>Post-Procedure Care Guidelines</u>

You will likely experience the following treatment effects from your procedure with the Renuvion Dermal System:

- Pain immediately after the procedure, decreasing substantially by 10 days post-procedure; and
- Swelling, crusting, and itching persisting approximately 7-14 days.
- Pin-point bleeding during the healing process resolving by 14 days.
- Temporary post-inflammatory hyperpigmentation (redness or darkening of the skin) resolving by 90 days,

Please following these Post-Procedure Instructions:

- Stage 1 (days 1-3)

- Tepid to cool showers multiple times/day
- Vinegar water soaks multiple times/day (wear gloves when doing vinegar soaks)
    - To make a vinegar water soak, fill a clean bowl with cold tap water and a few ice cubes and 1 tablespoon of white vinegar for every cup of water.
    - Using clean 4x4 gauze pads, wet them with the water solution and apply over the face, replacing them with new wet gauzes before they dry; alternatively, cold water may be repeatedly dripped over the gauze.
    - Continue soak for approximately 30 minutes.
    - The soak should not sting. Make sure the water stays chilled and replace when warm.
- After showering or applying vinegar soaks, apply Aquaphor or alternative Crisco. Wear gloves to apply Aquaphor or Crisco.

- Stage 2 (days 4-14)
    - Tepid to cool showers multiple times/day
    - Vinegar soaks as needed
    - Alcohol free cleansers (Neutrogena Fresh Foaming Facial Cleanser & Makeup Remover) and alcohol-free ointments (Aquaphor or Crisco) allowed

- Stage 3 (days 15 and beyond)
    - Sunblock (Neutrogena Sheer Zinc Oxide Dry-Touch Face Sunscreen with Broad Spectrum SPF 50)
    - No hydroquinone
    - No retinol
    - Use light moisturizer (Neutrogena Oil Free Moisture Daily Hydrating Facial Moisturizer & Neck Cream)

Following the study procedure, subjects will be asked to complete VAS pain assessment and return to the study site at 1 day, 6 days (4-8 days), 10 days (9-14 days), 30 days (23-37 days), 90 days (80-100 days), and 180 days (166-194 days) for post-procedure assessments and to complete study questionnaires. At the 1-day, 6-day, and 10-day follow-up visits, study staff may soak and debride the treatment area as needed.

Photographs of the treated areas will be taken at each study follow-up visit using the Canfield Scientific Visia-CR system (see also Section 12.3 Data Management Responsibilities and Section 12.4 Data Capture Methods) for each. Subjects may also text selfie pictures to study staff as needed for questions related to the healing process; these images will not be maintained by study sponsor.

Study subjects will be asked to report complications experienced post-procedure and complete daily VAS 0-11 scale pain assessments utilizing the Subject Diary (see Appendix E: Subject Diary), and date when study subject felt comfortable, willing and able to go in public following the procedure.

Table 1 illustrates study procedures that will occur at each visit.

Table 1: Study Required Procedures

Table 1: Study Required Procedures							
	Baseline/ Pre-Procedure Screening[1]	**Procedure**	**1 Day**	**6, 10 Days**	**30 Days**	**90 Days**	**180 Days**
			1 day	6±2 days and 10+4/-1 days	30±7 days	90±10 days	180±14 days
Informed Consent	√						
Assess Inclusion/Exclusion Criteria	√						
Urine Pregnancy Test[2]	√	√					
Medical History	√						
General Physical Exam	√						
Review Medications	√		√	√	√	√	√
Photographic Images[3]	√[9]		√	√	√	√[9]	√
Fitzpatrick Skin Type Scale (FST)	√						
Fitzpatrick Wrinkle and Elastosis Scale (FWS) [4]	√				√	√	√
Visual Analog Scale (11-point VAS) [5]		√	√	√	√	√	√
Study Procedure		√					
Debride Treatment Area (PRN)			√	√			
Subject Diary (11-point VAS)[6]		√	√	√			
Adverse Event Assessment		√	√	√	√	√	√
Re-epithelization and Down Time[7]			√	√	√	√	
Modified Global Aesthetic Improvement Scale (GAIS) [8]					√	√	√
Subject Satisfaction Survey						√	

[1] Pre-procedure Screening assessments to take place within 30 days prior to undergoing the procedure.
[2] Up to two urine pregnancy tests must be obtained prior to study procedure for females with child-bearing potential (one at pre-procedure screening and one on the day of the procedure prior to the procedure if screening and procedure are not performed on the same day).
[3]Digital photographs of the subject's face will be taken and labeled according to Photography Instructions.
[4]To be completed by Investigator.
[5] To be completed by the study subject on a day of the procedure (prior to the procedure and immediately following the procedure, e.g. within 60 minutes) and at specified follow-up visits.
[6] To be completed by the study subject daily starting from the day of procedure (after procedure, at home) until the 10-day follow-up visit.
[7] To be completed by Investigator to capture achievement of epidermal recovery status at follow-up visits; and date when study subject felt comfortable, willing and able to go in public following study procedure (assessed at the 10-day follow-up visit).
[8] To be completed by Investigator at all follow-up visits and study subject at the 30, 90, and 180-day follow-up visits.
[9] Images taken on this visit as primary endpoint for effectiveness.

6.5 Data Collection

Subject demographic information, procedural data, adverse events, device observations, and study required assessments will be documented on the CRFs. Study subjects will complete Visual Analog Scale and Modified Global Aesthetic Improvement Scale (GAIS): Subject Form at follow-up visits.

6.6 Confidentiality of Data

The Principal Investigator will oversee the conduct of the study and all data will be kept confidential. Confidentiality will be maintained by using subject identification numbers instead of names. Informed consent forms, data collection sheets and records, linking a subject's name with their ID number will be maintained in a locked cabinet or locked office. Information to be stored on the computer will be identified by subject ID and will be password protected.

Data disclosed outside the study team will be de-identified or will only include general group demographic information. Protected Health Information and/or identifiable study data will not be shared with anyone outside the study team or Health System, with the exception of the study sponsor, and federal regulators/ institutional officials for the purposes of auditing.

7 EVALUATION TOOLS

The following evaluation tools will be used in this study:

7.1 Fitzpatrick Skin Type Scale (FST)

Assessment of subject's skin color will be determined prior to study procedure by the Investigator using the FST. The scale delineates skin color into the categories as shown in Table 2.

Table 2: Fitzpatrick Skin Type Scale (FST)

Table 2: Fitzpatrick Skin Type Scale Evaluation	
Skin Type	**Description**
Type I	White skin that never tans and always burns easily
Type II	White skin that tans slightly and always burns easily
Type III	Light brown skin that tans gradually and can burn moderately
Type IV	Moderately brown skin that tans well and burns slightly
Type V	Dark brown skin that tans profusely and burns rarely
Type VI	Black skin with deep pigmentation that never burns

7.2 Fitzpatrick Wrinkle and Elastosis Scale (FWS)

Assessment of each subject's wrinkles at baseline and 30, 90, and 180-day follow-up visits will be performed by the Investigator. As well, assessment of each subject's baseline and the 90-day follow-up visit images viewed simultaneously will be performed by three board-certified dermatologists or plastic surgeons sourced and managed by Canfield Scientific and the Sponsor, called Independent Photographic Reviewers (IPRs), using the Fitzpatrick Wrinkle and Elastosis Scale (FWS) categories as shown in Table 3 (see also Section 12.3 Data Management Responsibilities and Section 12.4 Data Capture Methods). The FWS is a clinically validated

assessment tool used to assess skin wrinkle severity and elastosis on a scale from 1 through 9, where the lower score is considered better. Three Independent Photographic Reviewers will be blinded to the study subject's visit (baseline and follow-up visit) and will perform photographic assessments of each subject's wrinkle depth in the treated zones (identified only as "Zones to Evaluate" to the IPRs) using FWS and ignoring nasolabial folds and marionette lines (effects of gravity), and artifacts from the chin rest. The IPRs will assign a single FWS score per subject for both the right and left photo. Each photograph will have a unique identification number but sets of images will not be arranged in any specific order (i.e., randomized order).

Independent Photographic Review Evaluation Process for FWS:

1. Each blinded assessor will be provided with identical photos to be assessed. The pre-treatment and follow-up photos will be consistent in lighting, subject positioning and focus. Each photo's visit interval, i.e., pre-treatment and follow-up, will NOT be marked. The images placement (right or left) will be randomly ordered for pre-treatment and follow-up images. Images for each subject will be grouped together into one set with all pre-treatment and follow-up images in the same location (right/left) for the subject set.
2. Each blinded assessor will conduct their assessment independently with no input from another blinded assessor.
3. Each blinded assessor reviews the Left photo and assigns a FWS score.
4. Each blinded assessor reviews the Right photo and assigns a FWS score.
5. Enough time should be allowed to do this for each image, so the assessments are not rushed.
6. The change between FWS scores will be calculated during data analysis after assessments are complete.
7. Success will be determined by at least 1-point improvement in FWS by at least two out of three blinded, independent reviewers.

Table 3: Fitzpatrick Wrinkle and Elastosis Scale

Table 3: Fitzpatrick Wrinkle and Elastosis Scale			
Class	**Description**	**Score**	**Description**
I	Fine wrinkles	**1-3**	**Mild:** Fine texture changes with subtly accentuated skin lines.
II	Fine to moderate depth wrinkles, Moderate number of lines	**4-6**	**Moderate:** Distinct papular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia.
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	**7-9**	**Severe:** Multipapular and confluent elastosis (thickened, yellow and pallid) approaching or consistent with cutis rhomboidalis.

7.3 Modified Global Aesthetic Improvement Scale (GAIS)

The Global Aesthetic Improvement Scale (GAIS) is a subjective rating of improvement in treatment results compared to pre-treatment. A modification of the GAIS to include "much worse" and "very much worse" as rating options will be used in this study. The Investigator will grade the overall improvement of treatment area as indicated in Table 4a by comparing the subject's appearance at follow-up visits against a photograph taken prior to procedure. Likewise, the subject will also rate their improvement compared to pre-treatment as shown in Table 4b.

The modified GAIS results will be collected at the 30, 90, and 180-day follow-up visits.

Table 4: Modified Global Aesthetic Improvement Scale Evaluation

Table 4a: Modified Global Aesthetic Improvement Scale Evaluation (GAIS): Investigator	
Rating	**Description**
Very much improved	Optimal cosmetic result from this procedure in this subject
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject
Improved	Obvious improvement in appearance from the initial condition
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition
Much worse	The appearance is much worse than the original condition
Very much worse	The appearance is very much worse than the original condition

Table 4b: Modified Global Aesthetic Improvement Scale Evaluation (GAIS): Subject	
Rating	
Very much improved	□ Optimal cosmetic result.
Much improved	□ Marked improvement in appearance from the initial condition, but not completely optimal.
Improved	□ Obvious improvement in appearance from initial condition.
No change	□ The appearance is essentially the same as the original condition
Worse	□ The appearance is worse than the original condition.
Much worse	□ The appearance is much worse than the original condition.
Very much worse	□ The appearance is very much worse than the original condition.

7.4 Re-epithelization and Down Time

The study investigators and/or Independent Photographic Reviewers (as applicable) will be required to obtain and document re-epithelization and down time defined as per below:

1. **Achievement of Re-epithelization -** determine percentage epidermal recovery per treatment zone at the 1, 6, 10, 30, and 90-day follow-up visits.
2. **Down Time** - date when study subject felt comfortable, willing and able to go in public following study procedure (assessed at the 1, 6, 10, and 30-day follow-up visit).

7.5 Visual Analog Scale (VAS)

The study subjects will be asked to complete an 11-point Visual Analog Scale (VAS) for the following assessments:

1. Level of pain and discomfort associated with study procedure – to be completed by the subjects on the day of the procedure (prior to the procedure and immediately following the procedure), daily between the date of the procedure (reported at home) and the 10 day follow-up visit, and at all follow-up visits.
2. Subject satisfaction with treatment – at the 3 visits. Additionally, the subjects will be asked if they would recommend the treatment to friends and acquaintances (yes, perhaps, or no) and improvements noted (if any).

Scoring for the VAS will consist of making a mark on a 10-cm line demarcated at 1-cm intervals. Each end of the line will be awarded a score of 0 or 10 according to the extreme points of reference pertaining to an individual measure.

7.6 Subject Diary

Study subjects will be asked to complete a daily diary (see Appendix E: Subject Diary) starting from the procedure date (after study procedure, at home) until the 10 day follow-up visit to complete daily 11-point VAS pain assessments and document any complications they have experienced.

7.7 Blinded Identification of 90-Day Images

Assessment of each subject's baseline and 90-day follow-up images viewed simultaneously will be performed by the Independent Photographic Reviewers (IPR) who will be blinded to the study subject's visit (baseline and 3-month follow-up visit). Each IPR will view each subject's randomized baseline and 90-day follow-up images and assess which set of images represent the subject's post-treatment images. Each photograph will have a unique identification number, but the sets of images will not be arranged in any specific order (i.e., randomized order).

Independent Photographic Review Evaluation Process for Masked Assessment:

1. Each blinded assessor will be provided with identical photos to be assessed. The pre-treatment and follow-up photos will be consistent in lighting, subject positioning and focus. Each photo's visit interval, i.e., pre-treatment and follow-up, will NOT be marked. The images placement (right or left) will be randomly ordered for pre-treatment and follow-up images. Images for each subject will be grouped together into one set with all pre-treatment and follow-up images in the same location (right/left) for the subject set.

2. Each blinded assessor will conduct their assessment independently with no input from another blinded assessor.
3. Each blinded assessor compares the Left and Right photo for improvement. Assessors should look through each view and assess change. Enough time should be allowed to do this for each subject, so the assessments are not rushed.
4. The following definition will be used:
    - Change: An improvement that is:
        - Striking, substantial and immediately noticeable, or
        - Readily apparent but modest in nature, or
        - Slight and subtle in nature; may require close examination.
5. The assessor chooses which photo they believe to be the Post treatment photo (i.e., Left photo or Right photo) once all images in the subject set have been reviewed.
6. Post-Analysis Coding of Masked Assessment:
    - If the assessor incorrectly chooses the Post treatment photo, this will be coded as an "Incorrect post selection".
    - If the assessor correctly chooses the Post treatment photo, this will be coded as a "Correct post selection".
7. Success will be determined by correct identification of post treatment follow-up visit photographs by at least two out of three blinded, independent reviewers.

8 ADVERSE EVENTS ASSESSMENT REPORTING

8.1 Adverse Events Evaluation

Safety evaluations for this study include an interview with the study subject at each follow-up visit by the Investigator or Research Coordinator to elicit information about any medical occurrence that meets the definition of Adverse Event. This information will be documented in CRF without regard for cause or relation to device and/or procedure.

In addition, study subjects will be instructed to report all of complications experienced post study procedure to the site personnel as soon as they occur/are observed.

It is the Investigator's responsibility to determine seriousness, severity, and relatedness of the Adverse Event to the device and procedure using the definitions below.

8.2 Adverse Event (AE) and Expected Treatment Effect (ETE) Definition

An **adverse event** (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. An **expected treatment effect** (ETE) is any typical treatment side-effect of the Renuvion Dermal System

lasting up to a typical maximum duration. All ETEs and AEs will be collected during the conduct of this trial.

A preexisting condition (one that is present at the start of the study) will be recorded as an AE only if the frequency, intensity, or the character of the condition worsens during the study period.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances: hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

8.3 Serious Adverse Event (SAE) Definition

Serious Adverse Event (SAE) is an adverse event that:

- Led to a death or
- Led to a serious deterioration in the health of a subject that:
  - Resulted in a life-threatening illness or injury,
  - Resulted in a permanent impairment of a body structure or body function,
  - Required in-patient hospitalization or prolongation of existing hospitalization,
  - Resulted in medical or surgical intervention to prevent impairment to body structure or a body function
  - Led to fetal distress, fetal death or a congenital abnormality or birth defect, or
  - Other serious (important) medical events that may jeopardize the subject and may require medical or surgical intervention to prevent on of the other outcomes.

All SAEs that occur during the study period, whether considered to be related to the investigational product or not, must be reported to the Sponsor within 24 hours of knowledge of the event. IRB reporting requirements may also apply for SAEs.

8.4 Unanticipated Adverse Device Effect (UADEs) Definition

An **unanticipated adverse device effect** (**UADEs)** is defined as any serious adverse effect on health or safety or 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 investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

In addition, any **UADEs** will be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than within 24 hours of knowledge of the event.

All adverse events, anticipated or unanticipated, will be monitored until they are adequately resolved or explained.

8.5 Reporting Requirements

All adverse events (AEs) observed by study subjects, investigators or other study staff from first exposure to the study product through last study follow-up visit will be recorded. If a device-related AE, SAE, or unanticipated serious device related effect is ongoing at the final study visit,

the subject will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator should make every effort to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate, as completely as practical, the nature and/or causality of the AE or SAE. This may include unscheduled follow up visits for AE assessment.

Study subjects will be instructed to report all AEs to the clinical study staff. AE information will be collected throughout the study and recorded on CRFs.

8.6 Severity of Adverse Events

The **severity of adverse events** will be categorized using the following criteria:

- **Mild:** easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. These events generally do not require treatment.
- **Moderate:** sufficiently discomforting to interfere with normal everyday activities. These vents are usually relieved by simple therapeutic measures.
- **Severe:** prevents normal, everyday activities. These events may require systemic drug therapy or other medical treatment.

8.7 Relationship to the Study Device and/or Procedure

The **relationship to the study device and/or procedure** will be determined by the investigator utilizing the following categories:

- **Not Related:** An event for which an alternative explanation is conclusively identified – e.g., concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is highly unlikely.

- **Related:** The adverse event follows a reasonable temporal sequence related to treatment by the device, follows a known or suspected response pattern and a plausible alternative etiology cannot be identified.

- **Undetermined:** The relation of the adverse event has some temporal relationship to the device and/or device procedure, is not clearly due to another condition and the involvement of the study device is unknown.

8.8 Stopping Guidelines / Stopping Rules: Safety

The Sponsor and/or investigator may recommend termination or modification of the study if there is an occurrence of any device- or treatment-related Serious Adverse Event, using the clinical protocol definitions of Serious Adverse Event in **Section 8.3** of this protocol. In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a severe burn (anticipated or unanticipated), a higher than anticipated rate for any component of the safety measures, device failures resulting in Adverse Events, or unexpected SAEs.

9 RISK AND BENEFITS

9.1 Benefits

A possible benefit of using the Renuvion Dermal System is the potential for improvement in wrinkle severity. Additional potential benefits of improving the appearance of wrinkles could include enhanced well-being, with improved satisfaction with the appearance of less facial wrinkles or the perception of a having a more youthful appearance.

9.2 Risks

The following are expected treatment effects (ETE) with the Renuvion Dermal System:

- Pain & tenderness immediately after the procedure, decreasing substantially by 10 days post-procedure; and
- Erythema, swelling, induration (crusting) and/or urticaria (itching) persisting approximately 7-14 days.
- Pin-point bleeding during reepithelialization resolving by 14 days.
- Temporary post-inflammatory hyperpigmentation resolving by 90 days,

Potential risks with the Renuvion Dermal System are similar to those that are encountered for many routine facial soft tissue reductions. These include but are not limited to:

- pain,
- tenderness,
- itching,
- bleeding,
- bruising/hematoma/seroma,
- allergic reaction,
- hypersensitivity to the treatment (resulting in erythema, swelling, induration and/or urticaria),
- temporary or permanent post-inflammatory hyperpigmentation,
- telangiectasias,
- skin overheating/burn,
- hypertrophic scarring
- discoloration/permanent hypopigmentation,
- vessel laceration or occlusion,
- abscess (infection) at treatment site which may result in induration and/or scar formation, and
- prolonged wound healing.

Subjects using drugs that reduce coagulation (aspirin or NSAIDs) may experience increased bruising or bleeding at the treatment site.

Side effects of nerve blocks and tumescent local anesthesia containing lidocaine or epinephrine include:

- Nausea
- Vomiting
- Mild sleepiness

- Confusion
- Convulsions
- Respiratory depression and/or respiratory arrest
- Cardiovascular stimulation or depression
- Cardiac arrest
- Lightheadedness or dizziness
- Nervousness
- Apprehension
- Euphoria
- Tinnitus
- Blurred or double vision
- Sensations of heat, cold or numbness
- Twitching
- Tremors
- Unconsciousness
- Anaphylactic response (hypotension, difficulty breathing, tightness in chest, and/or shortness of breath)

Side effects and subject instructions for medications that are at investigator discretion include:

- **Keflex**

  If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Diarrhea
- Nausea
- Vomiting
- Upset stomach

  This medication may rarely cause a severe intestinal condition due to resistant bacteria. This condition may occur during treatment or weeks to months after treatment has stopped. Do not use anti-diarrhea or opioid medications if you have any of the following symptoms because these products may make them worse. Tell your doctor right away if you develop:

- Persistent diarrhea
- Abdominal or stomach pain/cramping
- Blood/mucus in your stool

  A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Rash

- Itching/swelling
- Severe dizziness
- Trouble breathing

Other things to note:

- Use of this medication for prolonged or repeated periods may result in oral thrush or a new yeast infection. Contact your doctor if you notice white patches in your mouth, a change in vaginal discharge, or other new symptoms.

- **Z-pak**

If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Stomach upset
- Diarrhea/loose stools
- Nausea
- Vomiting
- Abdominal pain

Tell your doctor right away if any of these unlikely but serious side effects occur:

- Hearing changes
- Eye problems
- Difficulty speaking/swallowing
- Muscle weakness
- Signs of liver problems

Get medical help right away if any of these rare but serious side effects occur:

- Fast/irregular heartbeat
- Severe dizziness
- Fainting

This medication may rarely cause a severe intestinal condition due to resistant bacteria. This condition may occur during treatment or weeks to months after treatment has stopped. Do not use anti-diarrhea or opioid medications if you have any of the following symptoms because these products may make them worse. Tell your doctor right away if you develop:

- Persistent diarrhea
- Abdominal or stomach pain/cramping
- Blood/mucus in your stool

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Fever that doesn't go away
- New or worsening lymph node swelling
- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

Other things to note:

- Use of this medication for prolonged or repeated periods may result in oral thrush or a new yeast infection. Contact your doctor if you notice white patches in your mouth, a change in vaginal discharge, or other new symptoms.
- An allergic reaction to this medication may return even if you stop the drug. If you have an allergic reaction, continue to watch for any of the above symptoms for several days after your last dose.

- **Acyclovir**

If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Nausea
- Diarrhea
- Headache
- Vomiting

Tell your doctor right away if any of these unlikely but serious side effects occur:

- Dizziness
- Drowsiness
- Signs of kidney problems
- Mental/mood changes

- Shaky/unsteady movement
- Trouble speaking

This medication may rarely cause a life-threatening disorder that affects the blood cells, kidneys, and other parts of the body. This disorder is more likely to occur if you have conditions related to a weakened immune system. Seek immediate medical attention if any of these rare but serious side effects occur:

- Extreme tiredness
- Slow/fast/irregular heartbeat
- Easy bruising/bleeding
- New fever
- Bloody/dark urine
- Severe stomach/abdominal pain
- Yellowing eyes/skin
- Sudden vision changes
- Loss of consciousness
- Seizures

A very serious allergic reaction to this drug is rare. However, seek immediate medical attention if you notice any symptoms of a serious allergic reaction, including:

- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

- **Valtrex**

If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Nausea
- Stomach pain
- Headache
- Dizziness

Tell your doctor right away if you have any serious side effects, including:

- Mental/mood changes
- Trouble speaking
- Shaky/unsteady movements
- Signs of kidney problems

This medication may rarely cause a life-threatening disorder that affects the blood cells, kidneys, and other parts of the body. This disorder is more likely to occur if you have conditions related to a weakened immune system. Get medical help right away if you have any serious side effects, including:

- Extreme tiredness
- Slow/fast/irregular heartbeat
- Easy bruising/bleeding
- New fever
- Bloody/dark urine
- Severe stomach/abdominal pain
- Yellowing eyes/skin
- Sudden vision changes
- Loss of consciousness
- Seizures

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

- **Diflucan**

If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Nausea

- Diarrhea
- Stomach pain
- Headache
- Dizziness

Get medical help right away if any of these rare but serious side effects occur:

- Fast/irregular heartbeat
- Severe dizziness
- Fainting

This drug may rarely cause serious liver disease. Get medical help right away if you develop any signs of liver disease, including:

- Severe stomach/abdominal pain
- Persistent nausea/vomiting
- Yellowing eyes/skin
- Dark urine
- Unusual tiredness

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

Other things to note:

- If your doctor has directed you to use this product, remember that he or she has judged that the benefit to you is greater than the risk of side effects. Many people using the product do not have serious side effects.
- **Ativan**

If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Drowsiness
- Dizziness

- Loss of coordination
- Headache
- Nausea
- Blurred vision
- Change in sexual interest/ability
- Constipation
- Heartburn
- Change in appetite

Tell your doctor right away if you have any unlikely but serious side effects, including:

- Mental/mood changes
- Slurred speech or difficulty talking
- Vision changes
- Unusual weakness
- Trouble walking
- Memory problems
- Signs of infection

Get medical help right away if you have any rare but very serious side effects, including:

- Yellowing eyes or skin
- Seizures
- Slow/shallow breathing

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

- **Valium**

If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Drowsiness
- Dizziness
- Tiredness
- Blurred vision
- Unsteadiness

Tell your doctor right away if you have any serious side effects, including:

- Mental/mood changes
- Trouble speaking
- Trouble walking
- Muscle weakness
- Shaking
- Trouble urinating
- Yellowing eyes/skin
- Signs of infection

Get medical help right away if you have any very serious side effects, including:

- Slow/shallow breathing

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

- **Norco**

Tell your doctor right away if you have any serious side effects, including:

- Mental/mood changes
- Stomach/abdominal pain

- Difficulty urinating
- Signs of your adrenal glands not working well

Get medical help right away if you have any very serious side effects, including:

- Fainting
- Seizure
- Slow/shallow breathing
- Severe drowsiness/difficulty waking up

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

Other things to note:

- Nausea, vomiting, constipation, lightheadedness, dizziness, or drowsiness may occur. Some of these side effects may decrease after you have been using this medication for a while. If any of these effects persist or worsen, tell your doctor or pharmacist promptly.
- To prevent constipation, eat dietary fiber, drink enough water, and exercise. You may also need to take a laxative. Ask your pharmacist which type of laxative is right for you.
- To reduce the risk of dizziness and lightheadedness, get up slowly when rising from a sitting or lying position.

- **Ultram**

Tell your doctor right away if you have any serious side effects, including:

- Mental/mood changes
- Severe stomach/abdominal pain
- Difficulty urinating
- Signs of your adrenal glands not working well

Get medical help right away if you have any very serious side effects, including:

- Fast/irregular heartbeat

- Severe dizziness
- Fainting
- Seizure

This medication may increase serotonin and rarely cause a very serious condition called serotonin syndrome/toxicity. The risk increases if you are also taking other drugs that increase serotonin, so tell your doctor or pharmacist of all the drugs you take. Get medical help right away if you develop some of the following symptoms:

- Fast heartbeat
- Hallucinations
- Loss of coordination
- Severe dizziness
- Severe nausea/vomiting/diarrhea
- Twitching muscles
- Unexplained fever
- Unusual agitation/restlessness

Tramadol is changed into a strong opioid drug in your body. In some people, this change happens faster and more completely than usual, which increases the risk of very serious side effects. Get medical help right away if you notice any of the following:

- Slow/shallow breathing
- Severe drowsiness/difficulty waking up
- Confusion

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any of the following symptoms:

- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

Other things to note:

- Nausea, vomiting, constipation, sweating, trouble sleeping, dry mouth, fatigue, lightheadedness, dizziness, drowsiness, or headache may occur. Some of these side

effects may decrease after you have been using this medication for a while. If any of these effects persist or worsen, tell your doctor or pharmacist promptly.

- To prevent constipation, eat dietary fiber, drink enough water, and exercise. You may also need to take a laxative. Ask your pharmacist which type of laxative is right for you.
- To reduce the risk of dizziness and lightheadedness, get up slowly when rising from a sitting or lying position.

- **Gabapentin**

If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Drowsiness
- Loss of coordination
- Dizziness

Tell your doctor right away if you have any serious side effects, including:

- Swelling of the hands/ankles/feet

Get medical help right away if you have any very serious side effects, including:

- Slow/shallow breathing

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Fever
- Swollen lymph nodes
- Rash
- Itching/swelling
- Severe dizziness
- Trouble breathing

Other things to note:

- A small number of people who take anticonvulsants for any condition may experience depression, suicidal thoughts/attempts, or other mental/mood problems. Tell your doctor right away if you or your family/caregiver notice any unusual/sudden changes in your mood, thoughts, or behavior including signs of depression, suicidal thoughts/attempts, thoughts about harming yourself.

- **Tylenol with Codeine**

Common side effects of Tylenol with Codeine include:

- nausea,
- vomiting,
- upset stomach,
- constipation,
- headache,
- lightheadedness,
- dizziness,
- drowsiness,
- blurred vision, or
- dry mouth
- Inform your doctor if you experience unlikely but serious side effects of Tylenol with Codeine including mental/mood changes, severe stomach/abdominal pain, or difficulty urinating.

- **NSAIDS**

  The most common side effects are:

  - vomiting,
  - nausea,
  - constipation,
  - diarrhea,
  - reduced appetite,
  - headache,
  - dizziness,
  - rash, and
  - drowsiness.

  NSAIDs also may cause swelling of the arms and legs due to the retention of fluid from their renal effects.

  The most serious side effects are ulcers, bleeding, kidney failure, and, rarely, liver failure.

Individuals allergic to NSAIDs may experience shortness of breath after taking an NSAID and may experience a similar reaction when other NSAIDs are taken.

People with asthma are at higher risk for experiencing serious allergic reactions to NSAIDs.

NSAIDs (except aspirin) may increase the risk of heart attacks, stroke, and related conditions, which can be fatal. This risk may increase with duration of use and in patients who have underlying risk factors for disease of the heart and blood vessels.

NSAIDs, particularly non-selective NSAIDs, cause an increased risk of serious, even fatal, stomach and intestinal adverse reactions such as bleeding, ulcers, and perforation of the stomach or intestines. These events can occur at any time during treatment and without warning symptoms. Elderly patients are at greater risk for these types of reaction.

- **Antihistamines**
    - Less common or rare

- Abdominal or stomach pain
- burning
- chills
- clay-colored stools or dark urine
- cough
- diarrhea
- difficulty swallowing
- dizziness
- fast or irregular heartbeat
- fever
- headache
- hives
- itching
- prickly sensations
- puffiness or swelling of the eyelids or around the eyes, face, lips or tongue
- redness of skin

- seizures
- shortness of breath
- skin rash
- swelling
- tightness in chest
- tingling
- unusual tiredness or weakness
- wheezing

Check with your doctor as soon as possible if any of the following side effects occur:

- Less common or rare
- Sore throat
- unusual bleeding or bruising
- unusual tiredness or weakness
- Symptoms of overdose
- Clumsiness or unsteadiness
- convulsions (seizures)
- drowsiness (severe)
- dryness of mouth, nose, or throat (severe)
- feeling faint
- flushing or redness of face
- hallucinations (seeing, hearing, or feeling things that are not there)
- shortness of breath or troubled breathing
- trouble in sleeping

9.3 Mitigation of Risks

These risks have been mitigated by utilizing qualified clinical Investigators who have training and are experienced in wrinkle reduction procedures and following study treatment procedures. In addition, risks are mitigated by including only those subjects that meet the study eligibility criteria. This study also includes evaluation of study subject satisfaction with this procedure. Given that the anticipated risks have been mitigated to an acceptable level, the benefits of using the Renuvion Dermal System for use in dermal skin resurfacing outweigh the reasonable risks.

10 STUDY MANAGEMENT/COMPLIANCE/ QUALITY ASSURANCE

10.1 Protocol Deviation Reporting

A protocol deviation is an event in which the investigator or site personnel did not conduct the study in accordance with the protocol or the Clinical Trial Agreement. Prior approval by the Sponsor is expected in situations where the Investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the life or physical well-being of a subject in an emergency. Prior approval is not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g. inadvertent errors, product failure, or inability to perform required procedures due to subject's illness).

All protocol deviations are to be reported to the Sponsor, along with the justification for the deviation, on the Protocol Deviation CRF. Protocol deviations should be reported as soon as possible upon center notification of the deviation.

10.2 Discontinuation of Study Subjects

A subject may discontinue from the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled. An Investigator may also discontinue a subject from the study without the subject's consent, if the Investigator feels it is in the best medical interest of the subject. The date and the reason for study withdrawal will be indicated on the Study Exit CRF. Every effort should be made to contact subjects lost to follow-up, and all such efforts should be documented in the subject's file.

10.3 Supply of Study Materials

Each clinical site will be provided with the investigational devices. A Device Accountability Log will be used to track the receipt, use and return of study devices at each study site. All investigational devices will be returned to study Sponsor after enrollment of all subjects. Study Sponsor will provide appropriate packaging and shipping instructions to the study sites.

10.4 Device Malfunction/Observations

All malfunctions of, or defects of the delivery system will be recorded on the Device Malfunction/Observation Case Report Form and reported to the Sponsor by the investigational sites. This will include situations where the delivery system did not perform as intended; user errors; study device/component being physically defective, including out of the box failure.

10.5 Monitoring

It is the responsibility of the study Sponsor to ensure that proper monitoring of this clinical investigation is conducted. Appropriately trained personnel appointed by the Sponsor will conduct monitoring activities, as needed, and ensure that the investigation is conducted in accordance with the study protocol, the Clinical Trial Agreement, applicable laws and regulations, including ICH GCP, and overseeing IRBs.

Prior to study initiation at each investigational site, approval to enroll subjects will be given by the Sponsor and/or designee.

The Sponsor will determine frequency and timing of interim or periodic monitoring visits for each site based on enrollment rate, volume, study compliance, and findings from previous visits. Each enrolling site will be visited at least annually. Remote monitoring will be conducted to manage study data between site visits. During a monitoring visit, the Monitor will evaluate the site's compliance with regulatory and protocol requirements, verify data recorded on CRFs to available source documents, etc.

In addition, the Monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required.

Data Clarification Forms (DCFs) will be created for identified errors on CRFs that have been submitted to the Sponsor to ensure errors/omissions are corrected. New and previous findings and recommended corrective and preventative actions, if they exist, will be communicated with the study staff during the visit, and will also be addressed in a final letter that will be sent to the Investigator after the visit.

10.6 End of Study

The end of study will be defined as completion of all study visits by all enrolled subjects. If a device-related AE, SAE, or unanticipated serious device-related effect is ongoing at the final study visit, the subject will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up.

Study closure visits may be conducted at all clinical sites in order to review record retention requirements, device disposition requirements, etc., with site personnel. The Sponsor may choose to conduct the closure visit via telephone contact if appropriate.

10.6.1 Premature Termination/Suspension of the Study or a Study Site

The study or parts of the study may be prematurely terminated or suspended by the Sponsor. This discontinuation may be based on a significant number of AEs of a similar nature that warrant such action. Furthermore, the study may be prematurely ended if the regulatory authority or the IRB make a recommendation to terminate or suspend approval for the study, the study site, or the Investigator.

If the study is prematurely terminated or suspended for any reason, the investigator must inform the subjects and assure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the Sponsor will promptly inform the investigators, study sites, the IRB, and regulatory authorities of the termination or suspension of the study, as appropriate

10.7 Audits / Inspections

The Sponsor, their designee, and the reviewing IRB may monitor or audit the study centers. Likewise, regulatory authorities may inspect Sponsor or CRO files or any study center to evaluate the conduct of the study. The Investigator must allow access to the subject files and inspection of their clinical research protocol procedures when requested.

11 STATISTICAL METHODOLOGY

This section describes the statistical analyses foreseen at the time of study planning. For more detail please refer to the Statistical analysis plan.

Any deviations from planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close will be summarized in the Clinical Study Report.

Full details of planned statistical analyses will be outlined in a separate Statistical Analysis Plan (SAP) for the study.

11.1 Determination of Sample Size

The objective of this study is to demonstrate response to treatment with the Renuvion Dermal System. The IPR will assess each subject image and assess using the FWS. The proportion of subjects achieving at least a one-point improvement in 2 out of 3 IPR assessors will be calculated; this is the proportion of treatment successes.

The sample sizes were estimated using PASS 2019[1] with the following inputs:

- A performance goal (PG) of 50% success;
- A one-sample, one-sided t-test against the PG;
- $\alpha = 0.05$;
- Power = 90%;
- Renuvion success proportions (P) of 70%;
- Test is Fisher's Exact Test.

Table 5: Numeric Results for Testing One Proportion using the Exact Test

Table 5: Numeric Results for Testing One Proportion using the Exact Test						
Alternative Hypothesis: One-Sided (H0: P ≤ P0 vs. H1: P > P0)						
Power	**N**	**Performance Goal (PG)**	**Renuvion Proportion**	**Δ = Renuvion - PG**	**Alpha**	**Reject Ho if Successes ≥**
0.90	50	0.5	0.70	0.20	0.05	32

The 50 subjects will be augmented by 10% to 55 subjects to accommodate dropouts and losses to follow-up.

11.2 Performance Goal Rationale

A performance goal of 50% will be used for testing. A performance goal of 50% is clinically relevant to ensure that there are significant benefits of the procedure to outweigh its risk. The lower bound of the confidence interval of the proportion of subject achieving treatment

[1] PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

successes will be compared against this Performance Goal. This primary effectiveness endpoint definition and performance goal have been used in prior clinical studies to support their 510(k) clearances (i.e., eTwo Skin Treatment System, cleared under K141507 on December 8, 2014[2]). Moreover, the expected Renuvion proportion used to determine the study sample size is within the observed results range of the clinical studies conducted to support this indication for other FDA cleared devices (e.g., Picosure Workstation, cleared under K140719 on May 23, 2016[3] and the eTwo Skin Treatment System mentioned above).

11.3 Analysis Sets

The full analysis dataset will be used in our main analyses.

Full Analysis Dataset (Intent-to-Treat Sample, ITT)
Participants enrolled in the study who had baseline photographs taken will be included. Those with missing data items at 90-day visit will be imputed using multiple imputation. The primary efficacy endpoints will use this data set. The primary safety endpoint will also use this data set, but without multiple imputation. The reason is that the analysis method takes into account missing data (see the Analysis section below).

Modified Analysis Datasets (modified Intent-to-Treat Samples, mITT)
Participants enrolled in the study who had baseline data and endpoint data will be included. No imputation will be done for missing endpoints unless there is evidence that the endpoint is missing for cause. The Secondary and Additional endpoints will use these datasets. The reason that there are more than one mITT data set is that the data set is dependent upon the endpoint in questions; only those subjects with baseline and endpoint data *for that endpoint* will be included in the analysis.

Per Protocol Dataset (Per-Protocol Sample, PP)

This will be a subset of the full analysis dataset comprising participants without major protocol deviations. Participants with major protocol deviations will be identified at the data review meeting that takes place before database lock. If the primary effectiveness endpoint is not met, it will be repeated on the PP data set.

11.3 Other Data Issues

11.3.1 Discontinuations and Missing Data

The primary endpoints will be tested or estimated using the full (ITT) sample, with missing endpoints will be multiply imputed. Secondary and Additional endpoints will use the mITT data sets.

11.4 Safety Endpoints

An interim safety report of 30-day safety data including analysis of treatment data, adverse events, and pain scores will be completed.

[2] https://www.accessdata.fda.gov/cdrh_docs/pdf14/K141507.pdf
[3] https://www.accessdata.fda.gov/cdrh_docs/pdf14/K140719.pdf

11.4.1 Primary Safety Endpoint

The primary safety endpoint is the enumeration of each subject's adverse events (AE) up to the 90-day visit after treatment. Each AE will be categorized by cause, severity, seriousness, and relatedness to the procedure, the device, and the therapy.

11.4.2 Secondary Safety Endpoint

The secondary safety endpoint is the evaluation of the change in pain and discomfort after treatment (baseline, within 60 minutes following the procedure) experienced in the period up to the 10-day follow-up visit. Pain or discomfort will be recorded daily by each participant in a diary using an 11-point Visual Analogue Scale (VAS).

11.5 Effectiveness Endpoints

11.5.1 Primary Effectiveness Endpoint

Primary Effectiveness Endpoint

On each subject, the appearance of facial wrinkles and rhytides at baseline and the 90-day images will be assessed by three blinded Independent Photographic Reviewers using the FWS. Each subject will have three change scores; if 2 or more of the 3 change scores are one point or higher, the subject will be considered a success (Y or 1) and if 2 or more of the 3 change scores are less than one point, the subject will be considered a failure (N or 0).

11.6 Additional Endpoints

Other endpoints to be evaluated include:

1. Whether or not (Yes/No) at least 2 out of 3 blinded Independent Photographic Reviewers (IPRs) correctly identify the 90-day image of a subject from the pair of baseline and 90-day images.
2. Magnitude of improvement measured by the mean change in FWS from baseline to 90-day visit as determined by the Investigators.
3. Subject modified GAIS at 90-day FUV.
4. Investigator modified GAIS at 90-day FUV.
5. Subject satisfaction with procedure recorded at the 90-day visit.
6. Achievement of re-epithelialization by facial zone and across all facial zones at the 10 day, 30-day and 90-day follow-up visits as reported by the investigator.
7. Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject.

11.7 Statistical Analysis of Safety Endpoints

All statistical analyses will be described in detail in an accompanying statistical analysis plan (SAP).

Primary Safety Endpoint

Adverse event rates will be estimated using Kaplan-Meier time-to-event analyses. The monthly event rates and their 95% confidence intervals (CIs) will be reported by their type, severity, and relationship to the study procedure, device, and therapy.

Secondary Safety Endpoint

The mean VAS score will be reported at each measurement along with it 95% CI, its SD and its minimum and maximum. The change from baseline will be similarly reported.

11.8 Statistical Analysis of the Effectiveness Endpoint

All statistical analyses will be described in detail in an accompanying statistical analysis plan (SAP).

For the primary effectiveness endpoint, the proportion of successful patients (P) will be tested against the PG. If the lower bound of the 95% confidence interval of the proportion of subject achieving treatment successes is greater than the Performance Goal, the effectiveness endpoint would be met. The statistical test will be a one-sided Fisher's Exact Test at $\alpha = 0.05$. For the effectiveness endpoint to be met, Ho must be rejected.

$$\text{Ho: } P \leq 50\% \quad \text{vs.} \quad \text{Ha: } P > 50\%$$

11.9 Statistical Analysis of Additional Endpoints

These analyses will be described in the accompanying SAP.

11.10 Subgroup Analysis

Subgroup analyses will include modeling (using linear regression analysis) the effect of on age, gender, race/ethnicity, and Fitzpatrick Skin Scale (FSS) on the ΔFWS. (Age *et al* are called "independent variables".) The goal is to determine whether certain types of subjects are more likely to have a better response than other types. If any of the independent variables are significant, the effect size and better responders will be reported. This is examined in greater depth in the SAP.

12 DATA HANDLING AND RECORDKEEPING

12.1 Investigator Records

The Investigator is responsible for the preparation, review, signature, and retention of the records listed below:

- signed Clinical Trial Agreement and Curriculum Vitae
- all correspondence pertaining to the investigation with other investigators, the reviewing IRB, the study Sponsor, the Monitor and FDA,
- investigational device receipt, use and disposition records,
- subject case history records relating to use of the device, including Case Report Forms, medical records, progress notes, nurses' notes, etc.,
- all signed informed consent forms,
- all shipping and disposition records for investigational devices and relevant observations relating to the device, and
- the protocol and documentation of date and reason for any deviation from investigational plan.

Records are subject to FDA inspection and must be retained for a period of at least two years after the latter of two dates:

1. date on which the investigation is terminated or completed, or
2. date that the records are no longer required for purposes of supporting an application to the FDA to market the device.

12.2 Investigator Reports

The Investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 6. These are also subject to the FDA inspection and the retention requirements described above for the Investigator's Records.

Table 6: Required Investigator Reports

Table 6: Required Investigator Reports		
Report	**Submit to**	**Description**
Unanticipated Adverse Device Effect (UADE)	Sponsor and IRB	The Investigator must submit to the Sponsor and reviewing IRB a report of any UADE as soon as possible but not less than 10 working days after the Investigator first learns of the effect.
Withdrawal of IRB Approval	Sponsor	The Investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	Sponsor, Monitor and IRB	The Investigator must submit this report at regular intervals, but not less than once per year to the IRB, Sponsor and Monitor.
Deviation from Protocol in Emergency	Sponsor and IRB	Deviation from the study protocol that is made to protect the life or physical well-being of a subject in an emergency situation must be reported within 5 working days after the emergency occurred.
Deviation from Protocol that affect the scientific soundness of the study plan or the rights, safety or welfare of human subjects	Sponsor	Prior approval by the Sponsor is required when a deviation of this nature is anticipated.
Failure to obtain informed consent	Sponsor and IRB	If a study device was used without obtaining informed consent, the Investigator must notify the Sponsor and IRB within 5 working days of the use of the device.
Final Report	Sponsor and IRB	The Investigator must submit this report to the Sponsor and IRB within 3 months after the termination or completion of the study, or after the Investigator's participation in the study is complete.

12.3 Data Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site Principal Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

Data management and oversight is the responsibility of the Sponsor or Sponsor representative. Responsibilities include, but are not limited to, the following:

- Clinical strategy and oversight
- Clinical study operations
- File management and study documentation
- Site initiation visits and study close-out visits
- Clinical quality assurance
- Statistical support and programming
- Data management, including database development and programming and electronic data capture (EDC) programming, training, and management

Additionally, management and oversight of photographic imaging is the responsibility of Canfield Scientific. Responsibilities include, but are not limited to, the following:

- Providing photographic equipment and supplies as well as installation and training at each investigational site
- Project management of photographic imaging throughout the investigation
- Preparation of the User Manual for use during the study to ensure consistent serial photography is achieved
- Monitoring and quality review of incoming images
- Digital image management and storage
- Management of all independent photographic panel review activities, including sourcing and contracting independent reviewers, facilitating reviews, and transferring the data per an approved Data Transfer Agreement

12.4 Data Capture Methods

Data will be recorded on Paper Data Capture forms, then transcribed into an Electronic Data Capture (EDC) system and saved in that system as an electronic case report form (eCRF).

Photographic images will be captured utilizing the Canfield Scientific Visia-CR system as specified in the Canfield User Manual for the study.

13 PUBLICATION POLICY

The publication policy will be in accordance with the Investigator Agreement with each Principal Investigator or similar agreement.

14 REFERENCES

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15 APPENDICES

Appendix A: Sample Visual Analog Scale (VAS)

Visual Analog Scale (VAS): Study subjects will use the visual numeric scale below to determine the level of pain/discomfort they are experiencing pre-procedure and post-procedure

Appendix B: Sample Modified Global Aesthetic Improvement Scale (GAIS) Evaluation - Investigator

Modified Global Aesthetic Improvement Scale (GAIS) Evaluation - Investigator	
Rating	**Description**
Very much improved	Optimal cosmetic result from this procedure in this subject
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject
Improved	Obvious improvement in appearance from the initial condition
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition
Much worse	The appearance is much worse than the original condition
Very much worse	The appearance is very much worse than the original condition

Appendix C: Sample Modified Global Aesthetic Improvement Scale (GAIS) Evaluation - Subject

Subject Global Aesthetic Improvement Scale (GAIS) Evaluation - Subject	
Rating	
Very much improved	□ Optimal cosmetic result.
Much improved	□ Marked improvement in appearance from the initial condition, but not completely optimal.
Improved	□ Obvious improvement in appearance from initial condition.
No change	□ The appearance is essentially the same as the original condition
Worse	□ The appearance is worse than the original condition.
Much worse	□ The appearance is much worse than the original condition.
Very much worse	□ The appearance is very much worse than the original condition.

Appendix D: Sample Subject Satisfaction Survey

Subject Satisfaction Survey

1. Are you happy with your results of the procedure performed on your face? ☐ Yes ☐ No

2. Would you recommend the procedure performed on your face to a friend? ☐ Yes ☐ No

3. Would you consider having the procedure that was performed on your face performed again? ☐ Yes ☐ No

4. Which, if any, changes do you see in the area treated?

a. Skin Texture Improvement	☐ Yes	☐ No
b. Skin Tone Improvement	☐ Yes	☐ No
c. Skin Pigmentation Improvement	☐ Yes	☐ No
d. Fine Lines & Wrinkles Improvement	☐ Yes	☐ No
e. Skin Pore Size Improvement	☐ Yes	☐ No
f. Skin Feels Better	☐ Yes	☐ No
g. Skin Feels Tighter	☐ Yes	☐ No
h. Skin Appears Tighter	☐ Yes	☐ No
i. Skin Looks more Radiant	☐ Yes	☐ No
j. Skin Appears Brighter	☐ Yes	☐ No
k. Skin Seems more Youthful	☐ Yes	☐ No

l. Other: _____

☐ **NONE**

5. Since your treatment have you felt…

a. An improvement in your social life?
☐ **Completely** ☐ **A great deal** ☐ **Somewhat** ☐ **Not much** ☐ **Not at all** ☐ **It is worse**

b. An improvement in your family life?
☐ **Completely** ☐ **A great deal** ☐ **Somewhat** ☐ **Not much** ☐ **Not at all** ☐ **It is worse**

c. More secure?
☐ **Completely** ☐ **A great deal** ☐ **Somewhat** ☐ **Not much** ☐ **Not at all** ☐ **It is worse**

d. An improvement in how people respect you?
☐ **Completely** ☐ **A great deal** ☐ **Somewhat** ☐ **Not much** ☐ **Not at all** ☐ **It is worse**

e. An improvement in your mood?

☐ Completely ☐ A great deal ☐ Somewhat ☐ Not much ☐ Not at all ☐ It is worse

f. An improvement in your daily quality of life?
☐ Completely ☐ A great deal ☐ Somewhat ☐ Not much ☐ Not at all ☐ It is worse

g. An improvement in your self-esteem?
☐ Completely ☐ A great deal ☐ Somewhat ☐ Not much ☐ Not at all ☐ It is worse

h. More confident?
☐ Completely ☐ A great deal ☐ Somewhat ☐ Not much ☐ Not at all ☐ It is worse

i. An improvement in your sensuality?
☐ Completely ☐ A great deal ☐ Somewhat ☐ Not much ☐ Not at all ☐ It is worse

j. An improvement in your vitality?
☐ Completely ☐ A great deal ☐ Somewhat ☐ Not much ☐ Not at all ☐ It is worse

Appendix E: Sample Study Subject Daily Diary

Apyx Medical Corporation Renuvion Dermal System Study
SUBJECT DAILY DIARY

Site ID	Subject ID	Procedure Date (DD/MMM/YYYY)
☐☐	☐☐☐	☐☐/☐☐☐/☐☐☐☐

Instructions:

Please use this Form to gather any complications on your health condition after study procedure.
Please complete this Form daily for up to 14 days after Procedure until 1st Study Follow-Up Visit (10 Days Follow-up) with the study team.

Use the scale below to determine the level of pain/discomfort that you are experiencing each day in the area treated. Record your pain score each day where 0 means no pain and 10 means the worst pain you can imagine.

Use these Definitions to describe the degree of any complications you are experiencing each day:

Mild: easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities. These events generally do not require treatment.

Moderate: sufficiently discomforting to interfere with normal everyday activities. These events are usually relieved by simple therapeutic measures.

Severe: prevents normal, everyday activities. These events may require systemic drug therapy or other medical treatment.

Expected device related adverse events with the Renuvion Dermal System include:

- Pain immediately after the procedure, decreasing substantially by 10 days post-procedure; and
- Swelling persisting approximately 7-14 days.

Be sure to include all anticipated adverse events in your daily report as well as any unanticipated complications.

Please return this Form at your next study visit.

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 0 (within 60 minutes following procedure)		No □ Yes □		No □ Yes □

DAY 0 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with
0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary.

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 1		No □ Yes □		No □ Yes □

DAY 1 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary.

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 2		No □ Yes □		No □ Yes □

DAY 2 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**

		post study procedure?		
Day 3		No □ Yes □		No □ Yes □

DAY 3 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 4		No □ Yes □		No □ Yes □

DAY 4 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**

		post study procedure?		
Day 5		No □ Yes □		No □ Yes □

DAY 5 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 6		No □ Yes □		No □ Yes □

DAY 6 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 7		No □ Yes □		No □ Yes □

DAY 7 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 8		No □ Yes □		No □ Yes □

DAY 8 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and	**Any Complication**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**

	Subject Initials	**experienced post study procedure?**		
Day 9		No □ Yes □		No □ Yes □

DAY 9 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 10		No □ Yes □		No □ Yes □

DAY 10 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 11		No □ Yes □		No □ Yes □

DAY 11 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 12		No □ Yes □		No □ Yes □

DAY 12 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 13		No □ Yes □		No □ Yes □

DAY 13 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

	Date Logged (dd/mmm/yy) and **Subject Initials**	**Any Complication experienced post study procedure?**	**Description of your complication including the degree (mild, moderate, severe*)**	**Contacted Study Personnel?**
Day 14		No □ Yes □		No □ Yes □

DAY 14 PAIN SCORE

Please indicate the number that represents the current level of pain and discomfort associated with the study procedure you are experiencing on this day, with 0 representing no pain/discomfort and 10 the worst possible pain/discomfort. Refer to the pain scale on page 1 of this patient diary

Score: _____

Appendix F: Renuvion Dermal System Instructions for Use (IFU)

REF
BVX-044-DERM

renuvion®
COSMETIC TECHNOLOGY

Renuvion®
Dermal Handpiece

Read Instructions Before Use	Do Not Reuse; Single Use Device
STERILE EO Sterile, ETO	Do Not Resterilize
Manufacturer	Do Not Use Beyond Expiration Date
MR MR Unsafe	LOT Lot Number
Do Not Use if Packaging is Damaged or Opened	

Instructions For Use

INDICATIONS FOR USE/INTENDED USE
For the non-invasive treatment of facial wrinkles and rhytides in patients with Fitzpatrick skin types I, II or III.

DEVICE DESCRIPTION
The Handpiece is a sterile, single use electrosurgical (monopolar) device intended to be used in conjunction with a compatible electrosurgical generator (BVX-200H or BVX-200P) for the delivery of helium plasma for dermal resurfacing during cosmetic surgical procedures. The handpiece is activated by pressing the activation button on the handpiece or by pressing the purple foot pedal on the footswitch accessory.

MEDICAL PURPOSE / INDICATION
Single use electrosurgical device intended to be used in conjunction with the BVX-200H or BVX-200P electrosurgical generators for the delivery of helium plasma for the noninvasive treatment of facial wrinkles and rhytides in patients with Fitzpatrick skin types I, II or III.

CONTRAINDICATIONS:
The use of the device is contraindicated for the following:

- For use on the neck and chest.
- For use on Fitzpatrick Skin types IV, V and VI.
- For use on subjects with known susceptibility to keloid formation or hypertrophic scarring.
- For use on subjects who are pregnant or lactating.
- For use on subjects with active HSV-1 or diabetes mellitus or history of autoimmune disease.
- For use on subjects with active cut, wound, or infection on the skin of the face.
- For use on subjects with a known adverse reaction to anesthetics.
- For use on subjects with active skin disease of the facial area or known connective tissue disease.
- For use on subjects that have used, within the past 30 days, Accutane or any medication that can cause dermal hypersensitivity.
- Do not treat with subdermal treatments at the same time.

WARNINGS:

- Treatment speed is an important factor contributing to the safety and efficacy of the device. Treatment speed should be quick and consistent over the entire treatment area. Special care should be taken not to dwell in one treatment location. Over treatment may result in unwanted burns.
- Power settings above 40% power have not been evaluated for safety and efficacy of the device for the non-invasive treatment of facial wrinkles and rhytides.
- The peer reviewed, published literature relating to adverse events for dermal resurfacing procedures reports an increase in incidence rates for areas of thin tissue and areas with reduced blood supply. Special care should be taken when treating such areas.
- This medical device cannot be effectively cleaned and/or sterilized by the user and therefore cannot be safely reused. It is intended for single use only. Any attempt by the user to clean and resterilize this device may result in bio-incompatibility, infection, or other risks of device failure to the patient.
- Subjects using drugs that reduce coagulation (such as aspirin, NSAIDs or marijuana) may experience increased bruising or bleeding at the treatment site.
- Over treatment may result in unwanted burns.
- DO NOT use magnification that restricts your field of vision to visually monitor the facial results while the dermal resurfacing procedure is in progress. Concentrating on activities other than the helium plasma application per the recommended application pattern may have adverse effects. See recommended application patterns under Instructions for Use. Spot skin effects can be magnified along with increased lateral spread if the distal end of handpiece contacts the skin.
- The procedures should only be performed by persons with adequate training, product in-service and education. Personnel should fully understand the nature and use of gas delivered energy before performing electrosurgical procedures, to avoid the risks of shock and burn hazards to both the patient and the operator and damage to the handpiece.
  - DO NOT use electrosurgery in the presence of flammable anesthetics or other flammable gases, near flammable fluids or objects, or in the presence of oxidizing agents, as a fire could result.
  - DO NOT place the handpiece near or in contact with flammable materials (such as gauze or surgical drapes). If the handpiece is activated or hot from use, it may cause a fire.
  - When not using the handpiece, place it in a clean, dry location away from the patient. Inadvertent contact with the patient may result in burns.
  - Do not connect wet accessories to the BVX-200H or BVX-200P electrosurgical generator.

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CAUTIONS:

R_x ONLY

Federal Law (USA) restricts this device to sale by or on the order of a physician. For a listing of indications, contraindications, precautions, and warnings, please refer to this document.

- Examine the shipping carton, packaging, sterile barrier, cable and handpiece for any signs of transit damage. If there are any shortages, breakage or apparent damage, do not use the handpiece. Return the handpiece to Apyx™ Medical Corporation.
- For patients with cardiac devices such as AICD, pacemakers and defibrillators or other active implants, a possible hazard exists because of interference with the device. In case of doubt, seek approved qualified advice.
- For use of this device on patients with implanted devices, refer to the implanted device IFU.
- Jewelry and all piercing should be removed from the patient prior to the procedure.
- Any metal objects near the target treatment area should be removed prior to the procedure.
- Over treatment to the targeted area or combined therapies using other technologies may cause unwanted burns, skin contour irregularities, scarring, pigmentation changes and increased healing time.
- Inadvertent activation can result if either the activation button on the handpiece or the foot pedal is pressed when the handpiece is not in use and is attached to the generator. Take care to properly position the handpiece in a holster or an area clear of obstructions to keep pressure off of the activation button.
- Place any monitoring electrodes being used as far away as possible from the handpiece. Avoid needle monitoring electrodes.
- If the device is dropped prior to use or between uses, discard the device and continue the treatment with a new device.

CLINICAL SIDE EFFECTS / RISKS:

Providers should be aware that use of the device for its intended Indications for Use may still result in the following side effects:

- Pain or tenderness in the treatment area.
- Erythema may be present for many weeks following treatment. As with laser dermatological treatments, this is a normal side effect.
- Hypo- and hyper-pigmentation. There is a risk of pigmentation changes which may be temporary or permanent following treatment. It is likely that the risk of pigmentation changes increases with the severity of the treatment applied.
- Unwanted scarring. As with other methods of skin treatment there is a risk of both temporary and permanent scarring of the treatment area. Subjects who form keloid scars are particularly at risk (see Contraindications).
- Milia may occur as a result of follicular re-epithelialization and may be compounded by the use of occlusive moisturizers.
- Acne may result following treatment particularly in subjects with a history of acne.
- Re-activation of dormant infections. A dormant infection such as herpetic sores may become active following treatment and prophylaxis should be administered.
- Risk of Infection: The treatment site may be subject to an opportunistic infection. Precautions should be taken to prevent infection and promote healing.
- Dry eyes or corneal abrasions
- Lagophthalmos
- Conjunctivitis
- Bleeding, bruising, hematoma, and/or seroma formation
- Telangiectasias
- Systemic events such as flu-like symptoms (fever, headache, myalgia, neuralgia, nausea, malaise)

INSTRUCTIONS FOR USE:

Set Up

1. For proper generator and helium gas tank setup and safety instructions, refer to the instructions supplied with the appropriate generator manual.
2. Use aseptic techniques to open the package of the handpiece, remove the tip protector, inspect the handpiece for damage and pass the contents onto the sterile field.
3. Remove twist ties from the cable.
4. Before connecting the handpiece or any other adaptors or accessories to the generator:
   - 4.1. Ensure the generator is off.

     WARNING: Failure to do so may result in an injury or electrical shock to the patient or operating room personnel.
   - 4.2. Inspect all devices for damage and do not use if damage is found.
   - 4.3. Ensure all electrical connections are clean and dry.
5. Properly position the return electrode pad on the patient and connect it to the plug receptacle on the front of the generator (see IFU for the return electrode pad).

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6. Connect the cable plug of the handpiece into the generator and ensure that it is fully seated in the device plug receptacle. The cable plug is designed to fit in only one direction.
7. Use aseptic techniques to open the package of the standoffs and pass the contents onto the sterile field. Apply a standoff to the shaft of the handpiece and ensure proper placement on the shaft (see figures below). The periorbital standoff is designed to facilitate treatment of the periorbital area including along the lash line.

Standoff in Proper Location on the Shaft

Periorbital Standoff in Proper Location on Shaft

8. An optional footswitch accessory, BVX-JPDPS, can be attached to the rear of the generator and used to activate the handpiece.
9. Turn on the generator. After sensing that a handpiece is connected, the generator sets to the default power and gas flow settings to 20% Power and 4.0 L/min.
10. Before activating the handpiece on the patient, confirm the following
    - 10.1. The cable on the handpiece is positioned in a way to avoid contact with the patient or other cables and is not kinked.
    - 10.2. The standoff is firmly attached to the shaft of the handpiece and in the proper position.
    - 10.3. The handpiece and generator are functioning as intended.

      WARNING: Failure of inspection may result in electric shock.

    - 10.4. The generator has been set to the appropriate power and flow settings for the facial zone to be treated per the study protocol.
    - 10.5. As with all dermal resurfacing procedures, proper sedation and anesthesia should be used to manage discomfort. Depending on the treatment consider the following anesthesia options: general, regional block, IV sedation, oral sedation and topical anesthetic.

Device Operation

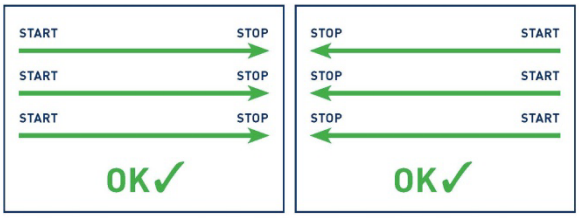
1. Activate the handpiece in a controlled location by pressing the handpiece activation button to check for helium plasma generation before proceeding with treatment. If a plasma stream is not visible at the tip, use the following technique to initiate the plasma:
    - 1.1. Activate on a metal object in the sterile field (for example a surgical instrument) at a distance of 1-2 mm between the handpiece tip and the metal object. If needed, increase the power level to successfully generate the initial activation (Note: Do not forget to decrease the power level again before starting the treatment).
2. After the initial activation check, press the activation button on the handpiece or purple foot pedal on the footswitch accessory to activate the handpiece.
3. Release the activation button on the handpiece or purple foot pedal on the footswitch accessory to deactivate the handpiece.

   NOTICE: *Do not unplug the handpiece from the generator while it is active.*

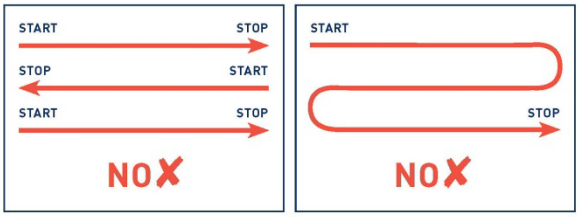
   WARNING: Inadvertent activation or movement of the handpiece outside the field of vision may result in injury to the patient or surgical team.

4. Move the tip of the handpiece to the treatment site.

5. Place the entire distal surface of the standoff in gentle contact with the tissue to be treated. The handpiece should be perpendicular to the tissue. Do not apply pressure to the tissue with the standoff. Applying pressure can cause the tissue to protrude into the distal end of the standoff and decrease the distance of the handpiece tip from the tissue during treatment.
6. Move the tip of the device quickly and consistently over the entire treatment area. Do not dwell in one treatment location. During the first treatment pass, proper treatment speed will result in a white frosting of the treated tissue. If the treated tissue turns color from a white frosting to a light brown, application speed should be increased to avoid overtreatment. During the second treatment pass, proper treatment speed will result in a white blanching of the treated tissue. If the treated tissue turns color from the white blanching to a light brown, application speed should be increased to avoid overtreatment.
7. Apply helium plasma to the treatment site in one of the patterns shown below:



The following plasma application patterns are NOT recommended:



NOTICES:

- *Pressing the blue Coag pedal on the footswitch accessory will display an F18 fault on the generator. Releasing the blue Coag pedal will return the generator to normal operation.*
- *Immediately after activation, the external surfaces of the handpiece shaft can remain hot and may cause burns upon contact. Allow a few seconds for the handpiece to cool down.*
- *Prior to increasing the intensity, check the adherence of the return electrode pad and its connections. Apparent low output or failure of the handpiece to function correctly at the normal operating settings may indicate faulty application of the return electrode pad or poor contact in its connections.*

TROUBLESHOOTING – FAULT INDICATORS & RECOMMENDED ACTIONS

The following generator fault codes describe the faults and recommended actions to take to resolve the faults. These fault codes are displayed on the generator's digital display. The faults are the result of a handpiece fault situation.

Codes	Description	Troubleshooting
F8	Simultaneous activation from a foot pedal and handpiece activation button.	Confirm that activation button and foot pedal are not activated simultaneously.
F9	Activation attempt with an invalid handpiece connected to the generator.	Turn off and then turn on the generator again. Change to a Renuvion handpiece. If problem persists, contact customer service.
F10	Renuvion handpiece activation attempt without gas being connected to the generator.	Confirm that regulator hose is connected to the generator. Confirm that helium tank valve is open. Confirm that helium tank is not empty.
F13	Gas flow fault caused by a restriction or blockage of the gas pathway.	Confirm that handpiece cable is not kinked or that tip exit is not obstructed. If problem persists, contact customer service.
F14	The connected Renuvion handpiece is expired.	Handpiece will expire 2 hours after first activation. If two hours has not expired, turn off and then turn on the generator again. If the problem persists, a replacement handpiece is required.
F18	Activation attempt sensed from the blue Coag foot pedal of the footswitch accessory	The blue Coag foot pedal is not used with this handpiece. If problem persists after blue Coag foot pedal is deactivated, (and the generator has been turned off and then on again) contact customer service.

AFTER PROCEDURE

Disconnect the cable plug from the generator. Discard the handpiece in accordance with the user's institutional sharps/biohazard/medical waste disposal procedures and policy and in accordance with local regulatory requirements.

WARNING: Do not reprocess or resterilize the handpiece.

TREATMENT EXPECTATIONS

- Side effects from the controlled thermal injury could range from flaking, browning of the skin, peeling, temporary exudate condition, discomfort and swelling.
- Erythema may persist for many weeks.
- The outcome is dependent on strictly observing the recommendations on treatment technique and post-treatment care as well as treatment contraindications.
- Full re-epithelialization may occur within 10-14 days.
- Pain or tenderness will be experienced in the treatment area.

Technical Description

General Description:

- Employs helium plasma stream for dermal resurfacing during cosmetic procedure
- Activation by button on the handpiece or by purple foot pedal on the footswitch accessory
- Energy source: External BVX-200H or BVX-200P electrosurgical generator is required

Specifications

- Rated Output Voltage: 4.0kVpeak
- Duty Cycle: Thirty minute total duty cycle of 10s ON and 3s OFF at 40% power level and 4.0 L/m

Environmental Information

Patient Population

- Male or female 30 years of age or older
- Patient with a Fitzpatrick Skin Scale of I, II or III

Site of Use and Site Conditions

- Site of Use: Facial skin including the forehead, nose, cheeks, and perioral and periorbital zones
- Site Condition: Aseptic

Intended User Profile

Education:

- Trained Licensed Physician
- Complete product inservice by qualified person

Knowledge:

- Read and understand the information in the supplied IFU
- Understands the use of compressed gases and / or plasma in procedures
- Understands electrosurgery and electrosurgical techniques
- Understands surgical-related hygiene and understands the management of possible complications as a result of risks listed above
- Understands post treatment patient care

Permissible Impairments:

- Mild reading/vision impairment or corrected vision to 20/20
- Single-hand operation

Intended Conditions for Use

Environment:

- Doctor's Office, Surgery Center, Hospital, or similar environment
- Intended for professional use only
- Indoor or contained area use

Disposal Information

Dispose of used handpiece as a biohazard medical waste in Sharps container.
Do not reprocess or resterilize the handpiece or return electrode pad.

Limited Express Warranty

IF PRIOR TO THE PRODUCT EXPIRATION DATE, THE STERILIZED handpiece IS FOUND TO BE INOPERABLE DURING NORMAL AND PROPER USE IN ACCORDANCE WITH APPLICABLE INSTRUCTIONS, THE COMPANY WILL REPLACE THE PRODUCT AT NO CHARGE. APYX MEDICAL CORPORATION MAKES NO OTHER WARRANTIES WITH RESPECT TO THE PRODUCTS AND EXPRESSLY DISCLAIMS ALL OTHER WARRANTIES, EXPRESSLY OR IMPLIED, AS TO MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER MATTER. IN NO EVENT SHALL THE COMPANY BE LIABLE FOR ANY CONSEQUENTIAL DAMAGES.

The Limited Express Warranty does not extend to a product where the user has compromised the sterile integrity of the package or the products used after the product expiration date. A sterile package that has been compromised should not be used.

Customer Service
Please call Customer Service +1 727 384 2323 (USA)

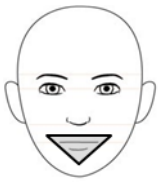
Apyx MEDICAL

Apyx Medical Corporation
5115 Ulmerton Road
Clearwater, Florida 33760 USA

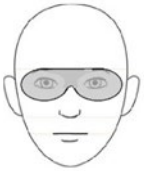
MC-15-450-001 Draft Rev 0
YYYY-MM-DD

Appendix G: Facial Zones

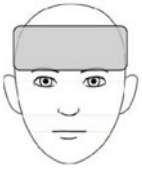
Zone 1 – Perioral



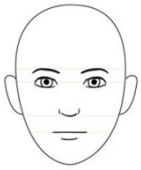
Zone 2 – Periorbital



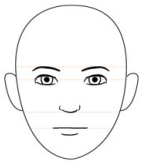
Zone 3 – Forehead



Zone 4 – Nose



Zone 5 – Cheeks



Zone 6 – Jawline/Mandibular Border