A Prospective, Multi-Center, Evaluator-Blinded Study Evaluating the Safety and Effectiveness of the Renuvion APR Device to Improve the Appearance of Lax Tissue in the Neck and Submental Region

Clinical Study Protocol

Study Protocol No: **VP-1902**

Revision No.: 9.2

Version Date: December 16, 2020

Sponsor:

Apyx Medical Corporation
5115 Ulmerton Road
Clearwater, FL 33760-4004 USA
Phone: (800) 537-2790
Fax: (800) 323-1640

Table of Contents

List of Tables

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
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
NRS	Numeric Rating Scale
NSAID	Non-steroidal Anti-Inflammatory Drug
PP	Per Protocol
PPS	Per Protocol Set
RF	Radiofrequency
SAE	Serious Adverse Event
SAL	Suction-Assisted Liposuction
UADE	Unanticipated Adverse Device Effect

1 STUDY SYNOPSIS

Study Title	A Prospective, Multi-Center, Evaluator-Blinded Study Evaluating the Safety and Effectiveness of the Renuvion APR Device to Improve the Appearance of Lax Tissue in the Neck and Submental Region
Study Device	Renuvion APR handpiece Note: For marketing reasons that do not affect the safety and effectiveness of the device, we have updated the name from Apyx Plasma/RF to Renuvion APR handpiece. (APR stands for Apyx Plasma/RF).
Study Population	The study population will consist of males and females, 35-65 years of age (inclusive), who desire a procedure to improve the appearance of lax tissue in the neck and submental region and meet the eligibility criteria of the study.
Study Purpose	The purpose of the study is to evaluate the safety and effectiveness of the Renuvion APR Device to improve the appearance of lax tissue in the neck and submental region.
Study Design	This is a prospective, multi-center, multi-phase, evaluator-blinded study of subjects undergoing a procedure to improve the appearance of lax tissue in the neck and submental region. The study will be conducted at up to 8 investigational centers in the United States. All study subjects will be treated with the Renuvion APR handpieces. Follow-up visits will occur 1 day, 7 days, 14 days, 30 days, 90 days, and 180 days post-procedure. **Phase I (n=17)** of this study was conducted and provided to the FDA as an interim safety report of safety data including information related to adverse events followed through resolution for all subjects. Phase I of this study was conducted prior to Revision 9 of this protocol. **Phase II (n=65)** of this study will be conducted as the pivotal study to demonstrate the safety and effectiveness of the Renuvion APR Device to improve the appearance of lax tissue in the neck and submental region. Phase II of the study begins with Revision 9 of this protocol.
Study Endpoints	**Primary Effectiveness Endpoint** is improvement in the appearance of lax tissue in the neck and submental region at 180 days compared to baseline as determined by qualitative 2D photography assessment by blinded Independent Photographic Reviewers. Three experienced, blinded photographic reviewers will perform a qualitative analysis/review of the pre-treatment and post-treatment sets of images of each subject in a blinded and randomized order. Each blinded reviewer will choose which image is the post-treatment image. Success will be correct post-

	treatment image selection by at least 2 of the 3 reviewers. The percentage of subjects with a correct post-treatment image selection will be calculated. The study design and sample size calculation assumes a 75% success rate of subjects with correctly identified 180-day images (i.e. 180-day images correctly identified by 2 out of 3 blinded Independent Photographic Reviewers) and the lower confidence interval greater than the performance goal of 55% (calculated with a one-side alpha of 0.025 and 90% power). **Primary Safety Endpoint** The primary safety endpoint is the level of pain and discomfort after treatment as reported by the subject on a Numeric Rating Scale (NRS) through the 7-day follow-up visit.

Additional Endpoints	• The improvement in the appearance of lax tissue in the neck and submental region at 90 days compared to baseline as determined by qualitative 2D photography assessment by blinded Independent Photographic Reviewers.
	• Subject Modified Global Aesthetic Improvement Scale (GAIS) at 90-day and 180-day FUV.
	• Investigator Modified GAIS at 90-day and 180-day FUV.
	• Subject satisfaction with procedure recorded at the 180-day visit.
	• Quantitative improvement in overall lift of the neck and submental area at 180-days as determined by quantitative assessment based on 2D photography.
	  o The analysis will compare the population of subjects who respond to treatment by achieving at least 20 mm^2 of lift of the submental region. Responders will be determined based on change from baseline of area as measured by 2D photography in standard lighting conditions.
	  o For the quantitative assessment, fixed landmarks on the subject's face will be used to systematically place a horizontal line, including the point where the chin meets the neck and 35 mm beyond. At this point, a vertical line will be placed and the area of submental skin between the two lines will be calculated. An area reduction of more than 20 mm^2 will be considered to be an improvement.
	• Quantitative improvement in submental volume at 180 days as determined by quantitative assessment based on 3D photography.
	• The evaluation of adverse events up to the 180-day visit following treatment.
	• The evaluation of pain scores through the 30-day follow-up visit as reported by the subject on a Numeric Rating Scale (NRS).

Additional Assessments	• TEN Testing for Sensory Nerves • Examination of Facial Motor Nerve • Burn Depth Assessment (Burn Adverse Events Only)
Planned Study Period	Phase I of the study was 12 months from site initiation to the last subject completing their 6-month visit. Study enrollment for Phase II of this study is expected to occur over 6-8 months. Imaging and study assessments will be conducted at each follow-up visit. Total Phase II duration for the study is expected to be approximately 14 months. After all subjects have completed their 180-day visit, the study will be considered complete, the final results will be determined, and a final report will be prepared.

2 STUDY ADMINISTRATIVE STRUCTURE

Study Sponsor: Apyx Medical Corporation (formerly Bovie Medical Corporation)
5115 Ulmerton Road
Clearwater, FL 33760-4004
Phone: (800)537-2790

The investigation will be conducted in compliance with the clinical investigation plan (CIP), GCP, EN ISO 14155, the Declaration of Helsinki, and regulatory authority requirements.

Apyx Medical (hereinafter "Study Sponsor" or "Sponsor") maintains responsibility for the ongoing safety of this clinical trial involving the evaluation of the Renuvion APR system. Study Sponsor will promptly notify all investigators, the responsible IRB(s), and the regulatory authorities of any findings from ongoing trial monitoring activities that could adversely affect the safety of subjects, impact the conduct of the clinical study, or alter the IRB's approval to continue the study, specifically within 5 working days of making an Unanticipated Adverse Device Effect (UADE) determination or 15 working days after first receiving notice of the UADE, within 10 days for Serious Adverse Event reports, and at least annually for routine reports. In the event that participant safety could be directly affected by study results after the study has ended, Study Sponsor will notify all investigators of these results to enable investigators to consider informing participants as soon as possible or at least within one year of study closure.

The following individuals are responsible for the content of the CIP:

Kari Larson, MBA Sr. Director, Clinical Affairs	Date
Shawn Roman VP, R&D	Date
Topaz Kirlew, PhD VP, Regulatory Affairs	Date

2.1 Statement of Compliance

I have thoroughly read and reviewed this clinical investigation plan (CIP) and hereby agree to participate in this clinical trial sponsored by Study Sponsor. I agree to conduct this investigation according to the requirements of the CIP provided by the Study Sponsor and in accordance with Good Clinical Practice (GCP) as required by EN ISO 14155, the Declaration of Helsinki, Investigational Device Exemption (21 CFR Part 812), Protection of Human Subjects (45 CFR Part 46), and other applicable FDA regulations, and regulations of other relevant regulatory authorities and conditions imposed by the reviewing Institutional Review Board (IRB) or Ethics Committee (EC). I agree that no deviation from, or changes to the CIP will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. I agree to ensure that appropriate informed consent is obtained from all subjects prior to inclusion in this study. I also agree to supervise all testing of the device involving human subjects, and to report to the Study Sponsor, within 24 hours, any adverse event that is serious, whether considered treatment-related or not. I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor.

All study data will be entered within three (3) days of the study visit.

I am also aware that I may be inspected by a representative of the relevant regulatory authorities, including the United States Food and Drug Administration, to verify compliance with applicable regulations related to clinical research on human subjects.

My current curriculum vitae and the curriculum vitae of physicians/licensed practitioners at this institution who will participate as co-investigators/sub-investigators in this study will be provided to the Study Sponsor. These curriculum vitae will include the extent and type of our relevant experience with pertinent dates and locations.

All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I certify that I have not been involved in an investigation that was terminated for non-compliance at the insistence of the Study Sponsor, the IRB or EC, or other regulatory authorities. I agree to provide the Study Sponsor sufficient, accurate financial disclosure information. I also agree to update financial disclosure information if any relevant changes occur during the investigation and for one year following the completion of the study.

I understand that this CIP and the trial results are confidential, and I agree not to disclose any such information to any person other than a representative of the Study Sponsor or the relevant competent authorities without the prior written consent of the Study Sponsor.

Statement of Compliance accepted by:

Principal Investigator Signature	Principal Investigator Name	Date
Co-/Sub-Investigator Signature	Co-/Sub-Investigator Name	Date
Co-/Sub-Investigator Signature	Co-/Sub-Investigator Name	Date

3 INTRODUCTION

3.1 Study Background and Rationale

Energy has been applied in some form to tissue since the beginning of recorded history. The practice of applying heat to tissue through the use of cauteries was used for thousands of years as an invaluable method of controlling hemorrhage. Continuous improvement of methods for utilizing the beneficial effects of heat on tissue eventually led to the development of the basic concepts of electrosurgery we know today. In October of 1926, Dr. Harvey Cushing used an electrosurgical unit developed by Dr. William T. Bovie to successfully remove a highly vascularized brain tumor from a patient after previous failed attempts. Today, electrosurgical instruments are used in almost every surgical procedure performed worldwide.[1]

Through this long history, the heat effects of the radiofrequency (RF) alternating current used in electrosurgery on cells and tissue have been well established. Normal body temperature is 37°C and, with normal illness, can increase to 40°C without permanent impact or damage to the cells of our body. However, when the temperature of cells in tissue reaches 50°C, cell death occurs in approximately 6 minutes.[2] When the temperature of cells in tissue reaches 60°C, cell death occurs instantaneously.[3] Between the temperatures of 60°C and just below 100°C, two simultaneous processes occur.[1] The first is protein denaturation leading to coagulation which will be discussed in more detail below. The second is desiccation or dehydration as the cells lose water through the thermally damaged cellular wall. As temperatures rise above 100°C, intracellular water turns to steam, and tissue cells begin to vaporize as a result of the massive intracellular expansion that occurs. Finally, at temperatures of 200°C or more, organic molecules are broken down into a process called carbonization. This leaves behind carbon molecules that give a black and/or brown appearance to the tissue.

Understanding these heat effects of RF energy on cells and tissue can allow the predictable changes to be used to accomplish beneficial therapeutic results. Protein denaturation leading to soft tissue coagulation is one of the most versatile and widely utilized tissue effects. Protein denaturation is the process in which hydrothermal bonds (crosslinks) between protein molecules, such as collagen, are instantaneously broken and then quickly reformed as tissue cools. This process leads to the formation of uniform clumps of protein typically called coagulum through a subsequent process known as coagulation. In the process of coagulation, cellular proteins are altered but not destroyed and form protein bonds that create homogenous, gelatinous structures. The resulting tissue effect of coagulation is extremely useful and most commonly used for occluding blood vessels and causing hemostasis.

In addition to causing hemostasis, coagulation results in predictable contraction of soft tissue. Collagen is one of the main proteins found in human skin and connective tissue. The coagulation/denaturation temperature of collagen is conventionally stated to be 66.8°C, although this can vary for different tissue types.[4] Once denatured, collagen rapidly contracts as fibers shrink to one-third of their overall length.[5] This principal of thermally-induced contraction of collagen through denaturation and coagulation of soft tissue is well known in medicine and is used to achieve beneficial results in ophthalmology, orthopedic applications, and the treatment of varicose veins. Once tissue is heated to the appropriate temperature, protein denaturation and collagen contraction occur resulting in a reduction of volume and surface area of the heated tissue.

Noninvasive use of RF devices, lasers, and plasma devices have been used for the reduction of facial wrinkles and rhytides caused by thermal-induced collagen/tissue contraction since the mid-1990s.[6-11]

Recently, the use of thermal-induced collagen/tissue contraction has been expanded to minimally invasive procedures. Laser-assisted lipolysis (LAL) and radiofrequency-assisted lipolysis (RFAL) devices have combined the removal of subcutaneous fat with soft tissue heating to reduce the skin laxity that often results from fat volume removal. These devices are placed in the same subcutaneous tissue plane as a standard suction-assisted lipolysis (SAL) cannula and are used to deliver thermal energy to coagulate the subcutaneous tissue including the underside of the dermis, the fascia, and the septal connective tissue. The coagulation of the subcutaneous tissue results in collagen/tissue contraction that reduces skin laxity.

Apyx Medical Corporation's product family of helium-based plasma technology (Renuvion/J-Plasma family of devices) has FDA clearance for the cutting, coagulation, and ablation of soft tissue. The Renuvion APR Handpiece is a new device designed to be a part of this helium-based plasma technology family. All devices in the product family are a part of a system that consists of an electrosurgical generator unit, a handpiece, and a supply of helium gas. RF energy is delivered to the handpiece by the generator and used to energize an electrode. When helium gas is passed over the energized electrode, a helium plasma is generated which allows heat to be applied to tissue in two different and distinct ways. First, heat is generated by the actual production of the plasma beam itself through the ionization and rapid neutralization of the helium atoms. Second, since plasmas are very good electrical conductors, a portion of the RF energy used to energize the electrode and generate the plasma passes from the electrode to the patient and heats tissue by passing current through the resistance of the tissue, a process known as Joule heating. These two sources of tissue heating give the Renuvion APR device some advantages during use as a surgical tool for the coagulation and contraction of subcutaneous soft tissue.

Apyx Medical Corporation has developed a new product offering to add to the product family of helium-based plasma technology, the Renuvion APR Handpiece, that delivers RF energy in a controlled fashion that results in soft tissue coagulation and contraction within the fibroseptal network (FSN). This helium-based plasma device has technological features that result in an effective method of action for coagulation and contraction of soft tissue. These features and benefits are as follows:

1. The Renuvion APR Handpiece device achieves soft tissue coagulation and contraction by rapidly heating the treatment site to temperatures greater than 85°C for between 0.040 and 0.080 seconds.
2. The tissue surrounding the treatment site remains at much cooler temperatures resulting in rapid cooling after the application of the energy through conductive heat transfer.
3. Focused delivery of energy on immediate heating of the fibroseptal network resulting in immediate soft tissue coagulation and contraction without unnecessarily heating the full thickness of the dermis.
4. 360° tissue treatment without the need for the user to redirect the flow of energy due to electrical energy taking the path of least resistance.
5. Unencumbered delivery of power regardless of the tissue impedance due to the unique power output from the electrosurgical generator.

6. Low current RF energy resulting in minimal depth of thermal effect and prevention of over-treating tissue when performing multiple passes.

3.2 Study Device Description

The Renuvion APR system consists of a handpiece (Figure 1), an electrosurgical unit (ESU, Figure 2), and a supply of helium gas (Figure 2). 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.

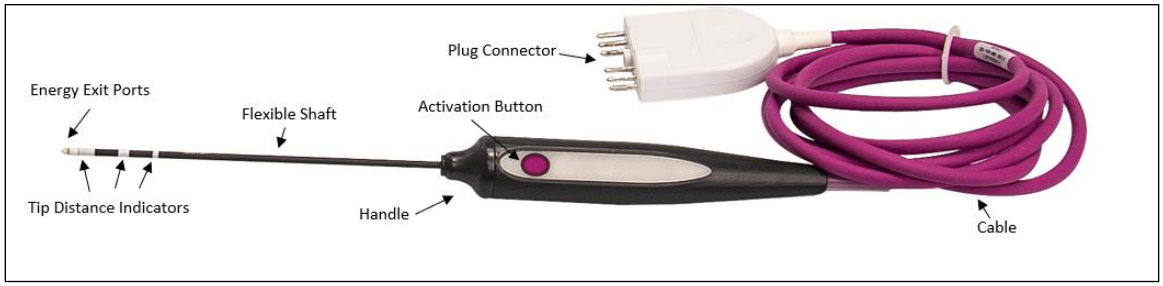

Figure 1: Renuvion APR Handpiece

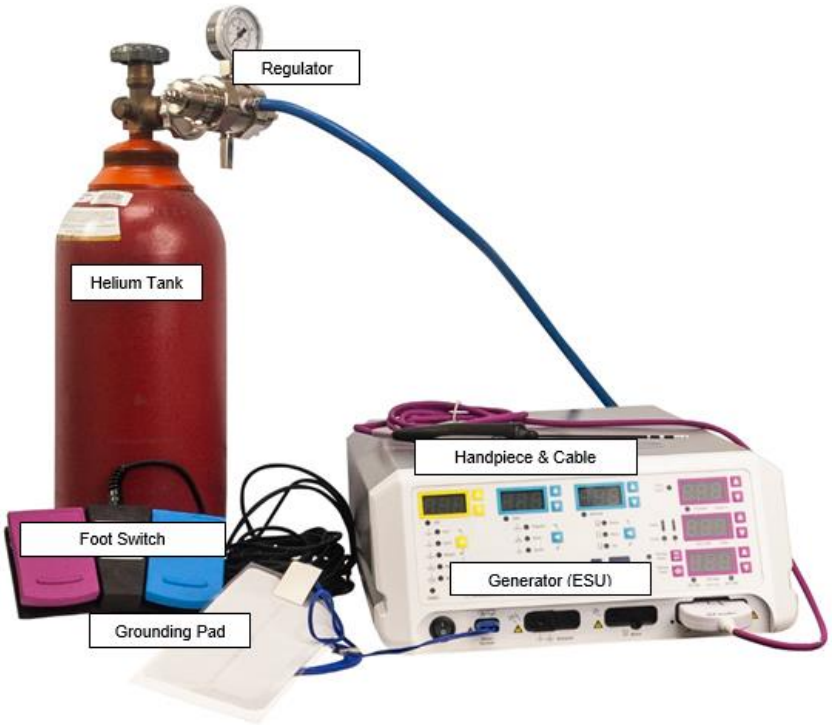

Figure 2: Electrosurgical Unit and Helium Tank

The Apyx Medical Corporation Renuvion/J-Plasma helium plasma family of products has received FDA clearance under 510(k) numbers K090586, K112233, K142975, K151325, K152570, K170188, K170777, K183610, K191542 and K192867 for the cutting, coagulation, and ablation of soft tissue.

4 STUDY DESIGN

4.1 Study Purpose

The purpose of the study is to evaluate the safety and effectiveness of the Renuvion APR device to improve the appearance of lax tissue in the neck and submental region.

4.2 Study Design

This is a prospective, multi-center, evaluator-blinded study of subjects undergoing a procedure to improve the appearance of lax tissue in the neck and submental region. The study will be conducted at up to 8 investigational centers in the United States, with a maximum of 20 study subjects enrolled at each site. All study subjects will be treated with the Renuvion APR device. Follow-up will occur 1 day, 7 days, 14 days, 30 days, 90 days, and 180 days post-procedure.

Subjects will have the informed consent administered prior to performing any study related assessments. Only subjects who sign the informed consent will have the screening assessments performed.

Phase II study enrollment is expected to occur over 6-8 months. Imaging and study assessments will be conducted at each follow-up visit. Total Phase II study duration is expected to be approximately 14 months. After all subjects have completed their 180-day visit, the study will be considered complete, the final results will be determined, and a final report will be prepared.

4.3 Study Objectives and Endpoints

The following endpoints will be assessed in this study.

4.3.1 Primary Effectiveness

The primary effectiveness endpoint is improvement in the appearance of lax tissue in the neck and submental region at 180-days as determined by qualitative 2D photography assessment by blinded Independent Photographic Reviewers.

The primary effectiveness objective is to demonstrate that the proportion of successful subjects exceeds the performance goal (PG).

$$Ho: P \leq PG \quad vs \quad Ha: P > PG$$

Where P is the proportion of successful subjects and PG is the performance goal.

Three experienced, blinded photographic reviewers will perform a qualitative analysis/review of the pre-treatment and post-treatment sets of images of each subject in a blinded and randomized order. Each blinded reviewer will choose which image is the post-treatment image. Success will be correct post-treatment image selection by at least 2 of the 3 reviewers. The percentage of subjects with a correct post-treatment image selection will be calculated.

The study design and sample size calculation assumes a 75% success rate of subjects with correctly identified 180-day images (i.e. 180-day images correctly identified by 2 out of 3 blinded Independent Photographic Reviewers) and the lower confidence interval greater than the performance goal of 55% (calculated with a one-side alpha of 0.025 and 90% power).

4.3.2 Primary Safety

The primary safety endpoint is the level of pain and discomfort after treatment as reported by the subject on a Numeric Rating Scale (NRS) through the 7-day follow-up visit (see **Section 7.5**).

The primary safety objective is to demonstrate that the proportion of subjects with none-to-moderate pain exceeds the performance goal (PG).

$$\text{Ho: } P \leq PG \quad \text{vs} \quad \text{Ha: } P > PG$$

Where P is the proportion of subjects with acceptable pain and PG is the performance goal.

The performance goal is 55%. The null hypothesis test is that Renuvion APR results in fewer than 55% of subjects with maximal pain of "moderate" (NRS pain score of 7 or less) post-procedure and at the 1-day and 7-day follow-up visits (i.e., more than 45% have severe pain). The alternative is that more than 55% of subjects have moderate or less pain (NRS pain score of 7 or less) immediately post-procedure and at the 1-day and 7-day follow-up visits, and fewer than 45% have severe pain.

4.3.3 Additional Endpoints

Other endpoints to be evaluated include:

1. The improvement in the appearance of lax tissue in the neck and submental region at 90 days compared to baseline as determined by qualitative 2D photography assessment by blinded Independent Photographic Reviewers.
2. Subject Modified Global Aesthetic Improvement Scale (GAIS) at 90-day and 180-day FUV.
3. Investigator Modified GAIS at 90-day and 180-day FUV.
4. Subject satisfaction with procedure recorded at the 180-day visit.
5. Quantitative improvement in overall lift of the submental area at 180 days as determined by quantitative assessment based on 2D photography.
    - The analysis will compare the population of subjects who respond to treatment by achieving at least 20 mm^2 of lift of the submental region. Responders will be determined based on change from baseline of area as measured by 2D photography in standard lighting conditions.
    - For the quantitative assessment, fixed landmarks on the subject's face will be used to systematically place a horizontal line, including the point where the chin meets the neck and 35 mm beyond. At this point, a vertical line will be placed and the area of submental skin between the two lines will be calculated. An area reduction of more than 20 mm^2 will be considered to be an improvement.
6. Quantitative improvement in submental volume at 180 days as determined by quantitative assessment based on 3D photography.

7. The evaluation of adverse events up to the 180-day visit following treatment.
8. The evaluation of pain scores through the 30-day follow-up visit as reported by the subject on a Numeric Rating Scale (NRS).

5 INVESTIGATORS SELECTION AND STUDY POPULATION

5.1 Investigator Selection

Participating Investigators will be qualified based on professionals experienced in treatment of skin laxity, such as plastic or cosmetic 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 applicable regulations.

5.2 Study Population

Sections 5.2.1 and 5.2.2 represent the eligibility criteria for this study. Subjects who plan to undergo a procedure for the purpose of improving the appearance of lax tissue in the neck and submental region from each participating investigator's subject population and meet the eligibility criteria as defined within this protocol will be enrolled in the study.

Subjects will be considered enrolled into the study when they have signed an approved informed consent form, meet all study criteria, and have undergone the study procedure.

5.2.1 Inclusion Criteria

Potential subjects must meet all of the following inclusion criteria:

1. Male or female subjects 35-65 years of age (inclusive).
2. Healthy as determined by the investigator examining the subject.
3. Seeking improvement of the appearance of lax tissue in the neck and submental region.
4. Females of childbearing potential who are sexually active must be willing to use an approved method of birth control during study participation.
5. Willing and able to comply with protocol requirements, including obtaining study-required images/photos and assessments, and returning for follow-up visits.
6. Willing to release rights for the use of study photos, including in potential publication.
7. Understands and accepts the obligation not to have significant weight loss or weight gain (≥8 pounds) post the treatment, and for the duration of participation in the study.
8. Willing to abstain from the use of blood thinners (including, but not limited to, Coumadin, NSAIDS, Ibuprofen, vitamin K, other) for 2 weeks (14 days) prior to the procedure.
9. Willing to abstain from smoking, vaping, or the use of e-cigarettes for 1 year prior to and for the entire duration of participation in the study.

10. Willing to abstain from the use of marijuana for 2 weeks prior to and for the duration of participation in the study.
11. Able to communicate with the site via video and/or photographs, in the event of a virtual follow-up visit.
12. Able to read, understand, sign and date the informed consent document (English only).

5.2.2 Exclusion Criteria

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

1. Pregnant or lactating.
2. Pregnancy within 12 months prior to screening.
3. Use within 24 hours preceding surgery of ibuprofen, acetaminophen, any other analgesics, anti-inflammatory products, or any products including herbals and supplements that could interfere with the clinical assessments of this study (other than drugs used for anesthesia).
4. Allergy to tumescent anesthetic (lidocaine/epinephrine).
5. Excessive subcutaneous fat in the treatment area (as determined by the treating investigator).
6. Active systemic or local skin disease that may alter wound healing.
7. Significant or uncontrolled medical condition that, in the opinion of the investigator, participation in the study may compromise the patient's health.
8. Severe solar elastosis.
9. History of autoimmune disease (excluding Hashimoto's thyroiditis).
10. Known hypersensitivity or adverse reaction to anesthetics.
11. Known susceptibility to keloid formation or hypertrophic scarring.
12. Cancerous or pre-cancerous lesions in the area to be treated.
13. History or current diagnosis of cancer of any type (excluding skin cancer).
14. History of uncontrolled cardiovascular disease (i.e. myocardial infarction, hypertension, hypercholesterolemia, peripheral vascular disease, other).
15. History, or current bleeding disorders (i.e. hemophilia or von Willebrand disease), or anticipated treatment with prescription anticoagulants.
16. Possesses a surgically implanted electronic device (i.e. pacemaker).
17. History of AIDs/HIV.
18. Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in the past two years.
19. Chronic hypoxia or dependence on supplemental oxygen.
20. Participation in any other investigational study within 30 days prior to consent.
21. Any surgical or transdermal neck/submental aesthetic procedures or plans to undergo any other aesthetic procedure during study participation. Such procedures include, but are not limited to, submentoplasty, liposuction, ultrasound, cryolipolysis, radiofrequency, and laser.
22. History of or current injury to the head and neck or any area of the body being treated as a part of this study.
23. Presence of more than mild platysmal banding as per the Geister, et al Validated Assessment Scale for Platysmal Bands[24]. (See **Appendix D**).

24. Subject requiring removal of adipose tissue prior to index procedure.
25. A family member of the investigator or sponsor; an employee of the investigator or sponsor.
26. 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 sufficient 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

Study subjects will have verification of eligibility criteria, a brief general examination including medical history, and pre-procedure assessments as detailed below 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 the 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 if pre-procedure screening and procedure are not performed on the same day).

The following pre-treatment assessments will be performed:

- 2D/3D photographic images will be captured. The same standardized photography views will be used throughout the study as documented in the image capture document developed for the study. In addition to the standardized photography views, the baseline 2D/3D photographic images will include an image of the subject performing a grimace to allow for determination of subject eligibility related to the platysmal banding exclusion criteria. **Table 1** illustrates study procedures that will occur at each visit.
- Urine pregnancy test (for females of childbearing potential).
- General physical exam including medical history, vital signs, collection of patient demographic information, and BMI.

Medications subject is taking upon entry into the study should also be documented in the Case Report Forms (CRF). Documentation should include medications 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.

Medications at investigator discretion may be provided as follows:

- Optional Pre-Procedure:
    - Antibiotics: Keflex 500mg BID (first dose just prior, within 60 minutes, to procedure) x 7 days. Alternative, Z-pack.

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).

Medications at investigator discretion may be provided as follows:

- Optional for Procedure (given within 90 minutes prior to procedure):
    - Ativan 2mg or Valium 10-20mg
    - Norco 5-10mg, Hydrocodone 5-10mg, or Ultram 200mg

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

During the study procedure, subjects will be treated with the Renuvion APR device according to the product IFUs and procedures described in this section of the protocol. The bilateral treatment area includes the tissue of the neck (to the posterior border of the sternocleidomastoid muscle) and submental area. Treatment will be performed through three (3) incisions (2 periauricular and 1 submental) with each incision large enough to allow for gas egress, see **Figure 1**. Each incision site will be anesthetized with 1% or 2% Lidocaine with Epinephrine (1:100,000) prior to incision being made.

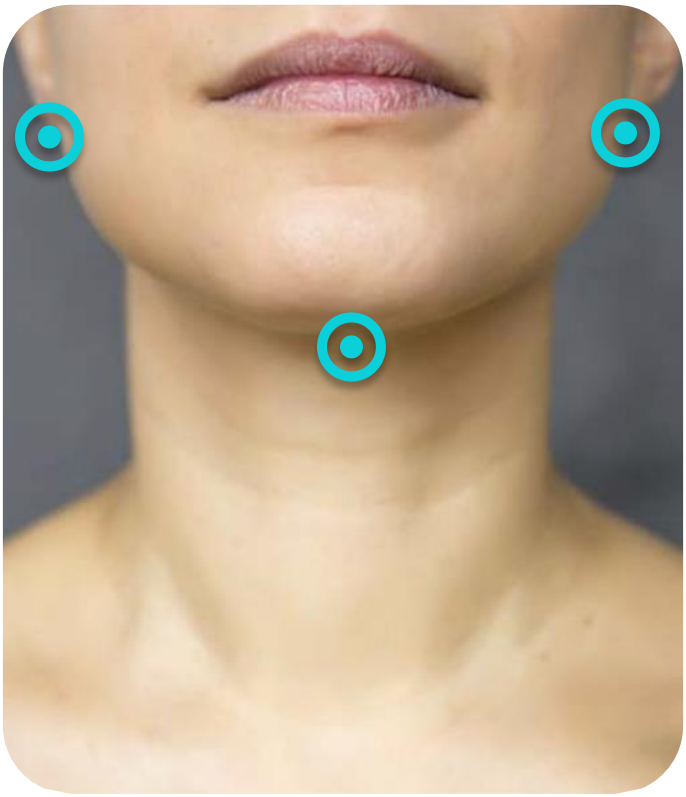

Figure 1: Treatment incisions (2 periauricular and 1 submental).

The treatment area will be infused with standard of care tumescent solution referred to as a Klein solution. The solution consists of 1% or 2% Lidocaine (Plain) to make a 0.2% concentration (double Klein) and Epinephrine 1mg/1ml (1:1,000) and optional Sodium Bicarbonate 8.4% added to Normal Saline or Lactated Ringers. Infuse area with 150-250cc or until the area is taut. To prevent lidocaine toxicity, 35-55mg/kg should not be exceeded[16].

Once infused with Klein solution, undermining of the tissue in the area to be treated will be performed using a cannula 3-4mm in diameter. No energy (i.e. radiofrequency, ultra-sound, or laser energy) or suction will be used during the undermining of the tissue.

After undermining, the Renuvion APR device treatment will be performed using 4-6 treatment passes with settings of 70% power and 1.5 LPM of helium flow with an activation speed of approximately 1-3 cm/s. Prior to performing treatment through each one of the three (3) incisions, the investigator will evaluate activation speed by performing the following steps in the sterile field at a safe distance from the subject:

1. Using a sterile ruler, two parallel lines will be drawn in the sterile field that are 10cm apart.
2. The investigator will place the tip of the device on one of the lines and simulate the activation speed until the tip reaches the second parallel line.
3. While the investigator performs this simulation, an assistant will measure the amount of time it takes for the tip of the device to travel from one line to the other using a stopwatch

or timer. The measured time must be between 3.3 seconds and 10 seconds inclusive to correspond to an activation speed of 1-3 cm/s. The investigator will repeat the simulation until the measured time falls within this range. The final measured simulation time will be recorded in the Procedure CRF for each incision site to provide evaluation of the activation speed at the beginning, middle, and end of the procedure.

6.4 Follow-up Procedures

6.4.1 Immediately Post-Procedure

Following treatment with the Renuvion APR device, surveillance aspiration and manual expression will be performed to evacuate any excess helium gas and/or residual fluid in the treatment area. Surveillance aspiration will be performed using a 10cc locking syringe and a 2.5mm or smaller single hole cannula. Aspiration amount will be limited to 8cc maximum.

Following the procedure, the research staff and the subject will care for the treated areas using the Post-Procedure Care Instructions listed below and the following optional medications at investigator discretion may be provided as follows:

- Optional Post-Procedure
  - Norco 5-10mg, Hydrocodone 5-10mg, or Ultram 200mg
  - Tylenol (OTC) as needed

6.4.2 Post-Procedure Care Instructions

The subject will receive a printed copy of the Take-Home Post-Procedure Care Instructions, see **Appendix C**.

Compression Garment Instructions:
The investigator or directed staff will place a Velcro chin-strap neck compression garment on the subject prior to the subject departing the site. Subjects will be directed to wear the compression garment as follows:

- **Days 0-3:** Wear the neck compression garment for 22 hours per day, removing only for showering/bathing.
- **Days 4-21:** Wear the neck compression garment at night.

Additional Instructions:
Subjects will be instructed to:

- Complete Subject Diary daily through your 14-Day Follow-up Visit.
- Report any treatment effects by noting them in the Subject Diary.
- Call the investigator or study staff if you have a complication outside of the Expected Treatment Effects listed in the Subject Diary.
- Bring your Subject Diary in with you to each visit, through the 14-Day Follow-up Visit when you will turn the Subject Diary into study staff.
- Continue to keep your study doctor and/or study staff aware of any new complications you may experience beyond the 14-Day Follow-up Visit.

6.4.2. Follow-up Visits & Subject Contact outside of Follow-up Visits

Subjects will be asked to return to the study site at the following times post-procedure:

- 1 (+2) day
- 7 (±1) days
- 14 (±3) days
- 30 (±7) days
- 90 (±10) days
- 180 (±15) days

Post-procedure assessments and 2D/3D photographic imaging will be performed during the follow-up visits. The same standardized photography views will be used throughout the study as documented in the image capture document developed for the study. **Table 1** illustrates study procedures that will occur at each visit.

Due to the challenges of COVID-19, if a subject is unable to return to the office for an in-person visit, follow-up visits will be conducted virtually. If a visit is completed virtually, missing assessments such as photographs will be documented as a protocol deviation specifically noting COVID-19. Outside of photographs, study investigators and study staff will ensure all other assessments related to each follow-up visit are completed virtually if the visit is done virtually. For virtual visits, the investigator and/or study staff completing the visit and assessments will be identified on the case report form; as well, the manner in which the visit was completed will also be marked on the Case Report Form (i.e. video call, phone call, etc.). Virtual visits should be done via video call if possible, to ensure subject identity. If a telephone call must be done, the investigator and/or study staff must positively identify the subject prior to conducting the virtual visit by requesting the subject to state their address and date of birth. Subjects will be strongly encouraged to come in (albeit safely) for their D180 visit; this visit is vitally important as this is the primary endpoint and photographic images are needed for many of the assessments. Only investigators and study staff who have been trained and delegated to conduct virtual visits as indicated on the delegation log may conduct virtual study visits.

Subjects may be seen for an unscheduled appointment at any time at investigator's discretion. Study staff will contact (phone, text, email, video call at subject's preference) all subjects with ongoing Adverse Events at the following time points, as applicable:

- 21 (±5) days
- 45 (±5) days
- 60 (±5) days
- 75 (±5) days
- 105 (±5) days
- 120 (±5) days
- 135 (±5) days
- 150 (±5) days
- 165 (±5) days

If the subject is unreachable by the preferred method of contact, another method of contact may be attempted. Three attempts will be made to contact the subject before considering the subject contact visit missed and protocol deviation recorded.

Table 1. Study required procedures

	Baseline/ Pre-Procedure Screening[1]	**Procedure (Day 0)**	**1 Day** 1-3 days	**7 Days** 6-8 days	**14 Days** 11-17 days	**30 Days** 23-37 days	**90 Days** 80-100 days	**180 Days** 165-195 days
Informed Consent	X							
Assess Inclusion/Exclusion Criteria	X							
Urine Pregnancy Test[2]	X	X						
Medical History	X							
General Physical Exam	X							
Review Medications	X	X	X	X	X	X	X	X
2D/3D Photographic Images[3]	X[6]	X[8]		X	X	X	X	X
Numeric Rating Scale (11-point NRS) [4]		X[7]	X	X	X	X	X	X
Study Procedure		X						
Adverse Event Assessment		X	X	X	X	X	X	X
TEN Testing of Sensory Nerves		X	X	X	X	X	As Needed	As Needed
Examination of Facial Motor Nerves		X	X	X	X	X	As Needed	As Needed
Burn Depth Assessment		As Needed	As Needed	As Needed	As Needed	As Needed	As Needed	As Needed
Modified Global Aesthetic Improvement Scale (GAIS) [5]							X	X
Subject Diary		X			X			
Subject Satisfaction Survey								X

[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 will be taken and labeled according to Photography Instructions. 2D images will be extracted from 3D imaging. Both 2D and 3D images will be used for quantitative assessments. Standard positioning and lighting will be used for all photographs.
[4] To be completed by the study subject on a day of the procedure (prior to the procedure and immediately following the procedure) and at all follow-up visits.
[5] To be completed by Investigator and study subject at day 90 and day 180 follow-up visits.
[6] Grimace image taken in addition to standard images at Baseline only.
[7] NRS pain score will be captured prior to study treatment and immediately (within 60 minutes) after procedure.
[8] Pre-procedure images may be taken if Baseline/Screening images are not considered acceptable by the quality review team, however if the Baseline/Screening image is acceptable by the quality review team, no additional pre-procedure image needs to be taken.

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 Numeric Rating Scale and Modified Global Aesthetic Improvement Scale (GAIS) Evaluations at follow-up visits. Subjects will complete a Satisfaction Survey at the 180-day follow-up visit.

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 2-Dimentional and 3-Dimensional Photography

Two-dimensional (2D) photographic images will be extracted from three-dimensional (3D) images which are captured utilizing the Canfield Scientific, Inc. Vectra M4 Plus 3D imaging system. The same standardized photography views will be used throughout the study as documented in the Image Capture document developed by Canfield for the study. Images will be monitored for quality to ensure standardized images and subject alignment between baseline and follow-up visits. If the Canfield image monitoring team notes differences in head position/tilt or noncompliance with study requirements (headband, tank top, no makeup, no facial expressions, no jewelry), a reshoot will be requested and noted in the Photography Result Report provided by Canfield. Study staff should review photos with particular care during each visit to ensure consistent alignment to prevent having to bring the subject back for a reshoot. If a reshoot is required, the reshoot should be taken within the visit window. Study staff should review Photography Result Reports (provided within 48 hours of image upload) for all images taken to check for reshoot requests.

7.1.1 Independent Photographic Assessments (Primary Effectiveness Endpoint)

Three experienced, blinded photographic reviewers will perform a qualitative analysis/review of the pre-treatment and post-treatment sets of images of each subject in a blinded and randomized order. Each blinded reviewer will choose which image is the post-treatment image. Success will be correct post-treatment image selection by at least 2 out of 3 reviewers. The percentage of subjects with a correct post-treatment image selection will be calculated.

Assessment of each subject's baseline and 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 follow-up visit). Each IPR will view each subject's randomized pre-treatment and post-treatment 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). Canfield will prepare and administer the IPR.

7.1.1.1 Independent Photographic Review Evaluation Process:

1. Each blinded assessor will be provided with identical photos to be assessed. The pre-treatment and post-treatment photos will be consistent in lighting, subject positioning, and focus. Each photo's visit interval, i.e., pre-treatment and post-treatment, will NOT be marked. The images placement (right or left) will be randomly ordered for pre-treatment and post-treatment images. Images for each subject will be grouped together into one set with all pre-treatment and post-treatment 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 change that may be striking (substantial and immediately noticeable), readily apparent but modest in nature, or slight and subtle in nature that may require close examination. 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 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.
5. Post-Analysis Coding of Masked Assessment:
    - If the assessor incorrectly chooses the post-treatment photo, this will be coded as an "Incorrect post-treatment selection".
    - If the assessor correctly chooses the post-treatment photo, this will be coded as a "Correct post-treatment selection".
6. Success will be determined by correct identification of post-treatment photographs by at least two out of three blinded, independent reviewers.

7.1.1.2 Independent Photographic Review Training Process:

IPR assessors will participate in a training session prior to completing the IPR. The purpose of the training is to provide guidance to the IPR assessors on the methods for reviewing the study images and to provide sample images from the Phase I safety study for scoring and discussion of the scoring by IPR assessors. Instructions will include that each blinded assessor should pay close attention to changes in:

- Fullness of neck
- Neck lines
- Neck muscle definition
- Jawline definition
- Submental laxity
- Mandibular angle
- Jowling
- Marionette lines
- Overall appearance of the treatment area

IPR assessors will complete a 10-subject mock IPR using images from the Phase I safety study to determine comprehension of the training or need for additional training. The IPR training presentation, 10-subject mock IPR, and mock IPR response instructions/response form are provided as three separate stand-alone documents.

7.1.2 Quantitative Assessment of Lift (Additional Endpoint)

The right profile view of extracted 2D images will be analyzed by Canfield software using marks at the lateral canthus of the eye, anterior nostril margin, and the chin attachment point of the neck to allow for the analysis of submental area as shown in red in the image below, see **Figure 2**. The analysis will compare the population of subjects who respond to treatment by achieving at least 20 mm^2 of lift of the submental region. Responders will be determined based on change from baseline of area as measured by 2D photography in standard lighting conditions. An area reduction of more than 20 mm^2 will be considered to be an improvement.

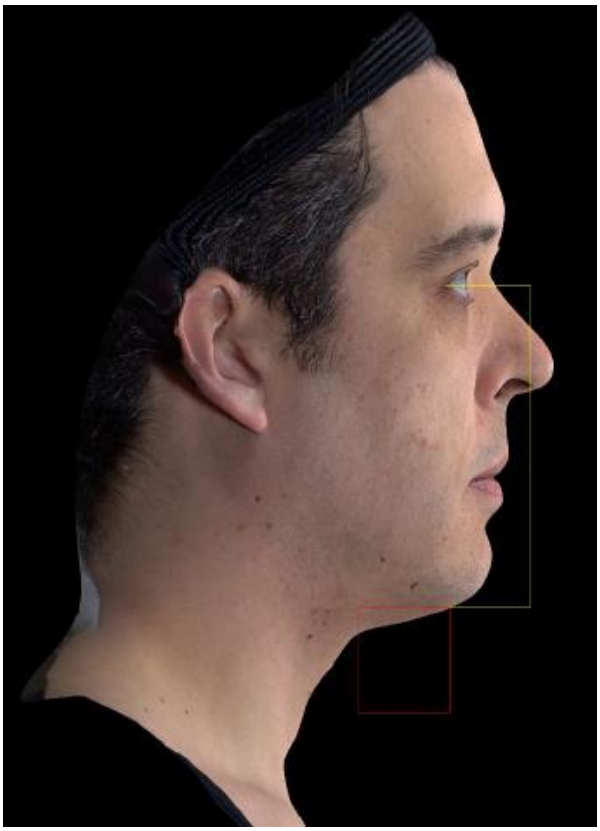

Figure 2: Quantitative Assessment of Submental Area

7.1.3 Quantitative Assessment of Volume (Additional Endpoint)

A series of anatomically defined landmarks on the baseline 3D image will define the submental area of interest for the volume difference measurement, see **Figure 3**. The landmarks will be transposed based on surface tracking to the corresponding follow-up image. The Canfield analysis software will reference the landmarks and create a volume difference model within the area of interest and report measurements of positive, negative, and total volume change.

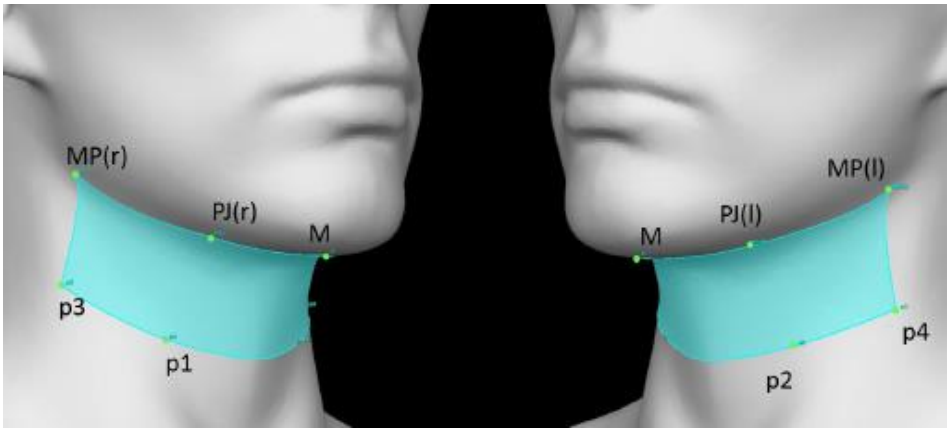

Figure 3: Quantitative Assessment of Submental Volume

7.2 Modified Global Aesthetic Improvement Scale (GAIS) (Additional Endpoint)

The Modified Global Aesthetic Improvement Scale (GAIS) is a subjective rating of improvement in treatment results compared to pre-treatment. The Investigator will grade the overall improvement of treatment area as indicated in **Table 2** 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 3**.

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

Table 2. Modified Global Aesthetic Improvement Scale Evaluation - Investigator

Table 2: Modified Global Aesthetic Improvement Scale 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

Table 3. Modified Global Aesthetic Improvement Scale Evaluation - Subject

Table 3: Modified Global Aesthetic Improvement Scale Evaluation - Subject	
Rating	
Very much improved	☐
Much improved	☐
Improved	☐
No change	☐
Worse	☐
Much worse	☐
Very much worse	☐

7.3 Subject Satisfaction Survey (Additional Endpoint)

The study subjects will be asked to complete Subject Satisfaction Surveys (see **Appendix A**) at the 180-day follow-up visit.

7.4 Subject Diary

Study subjects will be asked to complete a daily diary (see **Appendix B**) starting from the procedure date (after study procedure, at home) until the 14-day follow-up visit to complete daily 11-point NRS pain assessments and document any complications they have experienced.

7.5 Numeric Rating Scale (NRS) (Primary Safety Endpoint)

The study subjects will be asked to complete a 11-point Numeric Rating Scale (NRS) for the level of pain and discomfort associated with the study procedure – to be completed by the subjects on the day of the procedure prior to the procedure, following the procedure, and at all follow-up visits. The average pain score for the entire region treated will be recorded. Directions to subject will be: "*Please rate the average pain you are experiencing in the treatment area on a scale of 0-10, with 0 being 'Best/No Pain' and 10 being the 'Worst Possible Pain'*."

Pain will be defined in this study as the average pain reported in the treatment area using the following categories: None (Score of 0), Mild (Score of 1-5), Moderate (Score of 6-7), and Severe (Score of 8-10). Classifications of NRS pain scores have been documented in literature[20]. Moderate and severe pain/discomfort are considered Adverse Events (AE). Severe subject reported pain does not necessarily correlate to a "severe" adverse event classification. Events will be classified by investigator based on clinical evaluation, the effect to daily activities, and mitigation needed as per **Section 8.6** of this protocol.

Subjects experiencing pain adverse events will be considered resolved when their pain score is documented as returning to a 0 score.

7.6 Adverse Event Reporting

The definitions of Adverse Events (AEs) and the subtypes are provided in **Section 8** of the study protocol. Adverse events will be classified by the investigator as to:

- Anticipated vs unanticipated
- Serious vs not serious
- Expected Treatment Effect (ETE) vs Adverse Event (AE)
- Severity: mild, moderate, severe
- Device causality: not related, related, undetermined
- Procedure causality: not related, related, undetermined.

7.7 TEN Testing of Sensory Nerves

Compares sensation in injured/non-injured areas in response to light-moving touch where 10/10 is normal and 0/10 is no sensation. TEN Testing will be performed as follows:

- Light moving touch (examiner's finger) is applied to the area to be tested as well as to an area of normal sensation (such as arm).
- The subject is asked to rate the best level of sensation they feel in the test area.

- Ten is normal sensation, diminished sensation is rated on a scale of 0-10, with 0 being no sensation, 5 being half of normal, 10 being full sensation.

Subjects experiencing sensory nerve adverse events will be considered resolved when their TEN Testing score is documented as returning to a 10/10 score.

7.8 Examination of Facial Motor Nerves

Observe:

1. Face at rest for any facial asymmetry not apparent at baseline.
2. Any facial tics, asymmetry of eye blinking or eye closure
3. During smiling

In Palsy:

1. Blink: The eyelid on the affected side closes just a trace later than the opposite eyelid.
2. Nasolabial folds: The weaker one is flatter.
3. Mouth: The affected side droops and participates manifestly less in speaking.

Subjects experiencing motor nerve adverse events will be considered resolved when their motor nerve assessment returns to baseline observations by study investigator.

7.9 Burn Depth Assessment (Burn Adverse Events Only)

Burn depth assessment may be difficult, **Table 4** aids in accurate estimation of burn depth, should a burn adverse event be reported. Suspicion of deep partial thickness or full thickness burns warrants notification of study Sponsor.

Table 4. Burn Depth Assessment

Depth	**Cause**	**Surface/color**	**Pain sensation**
Superficial	Sun, flash, minor scald	Dry, minor blisters, erythema, brisk capillary return	Painful
Superficial Partial thickness - (superficial dermal)	Scald	Moist, reddened with broken blisters, brisk capillary return	Painful
Deep Partial thickness - (deep dermal)	Scald, minor flame contact	Moist white slough, red mottled, sluggish capillary return	Painless
Full thickness	Flame, severe scald or flame contact	Dry, charred whitish. Absent capillary return	Painless

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 in the Informed Consent Form, post-procedure take-home instructions, and verbally by study staff to report all complications experienced post study procedure to the site personnel as soon as they occur/are observed. Study staff will ensure that monitoring and management of all adverse events is prioritized. To ensure this, study staff will contact (phone, text, email, video call at subject's preference) all subjects with ongoing Adverse Events at the following time points, as applicable:

- 21 (±5) days
- 45 (±5) days
- 60 (±5) days
- 75 (±5) days
- 105 (±5) days
- 120 (±5) days
- 135 (±5) days
- 150 (±5) days
- 165 (±5) days

Three attempts will be made to contact the subject before considering the subject contact visit missed and protocol deviation recorded. If subjects are unable to be contacted via their preferred method of contact, another method of contact may be utilized.

Subjects may be asked to come into the site at any time to assess adverse events.

Study investigators are provided liberty to mitigate adverse events as deemed necessary per IHC GCP Guidelines E6(R2)4.3.2 which states "During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events related to the trial".

Adverse event resolution dates will be determined by investigator using either in-person or remote (phone, video call, text, email, etc.) examinations or communication with the subject. To ensure the most accurate reporting of adverse event durations, investigators are instructed not to wait until scheduled office follow-up visits to assess resolution.

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) 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.

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, or
  - Led to fetal distress, fetal death or a congenital abnormality or birth defect.

All SAEs that occur during the study period, whether considered to be related to the study device 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) and Expected Treatment Effects (ETEs) 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, ETE, 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 in the ICF, post-treatment take home instructions, and verbally by study staff to report all AEs to the clinical study staff. AE information will be collected throughout the duration of the study and recorded on CRFs. Subjects experiencing ongoing adverse events will be contacted as per **Section 8.1**.

8.6 Severity of Adverse Events

The **severity of adverse events** will be categorized by investigator based on clinical evaluation, the effect to daily activities, and mitigation needed 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 events 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 investigators should differentiate between device and procedure related AEs by classifying events directly attributable to the device itself as "device related" and events that occur from the procedure, irrespective of the device, as "procedure related". Since the study device delivers helium-based plasma energy to the tissue, events directly attributable to the application of energy to the tissue (i.e. burns) or the use of helium (i.e. gas buildup) should be classified as device related. Events that are known to occur in subdermal procedures utilizing tumescent anesthesia and/or undermining of soft tissue (i.e. edema[17,18], hematoma[18,19], nerve injury[19], pain/tenderness[17]) without the use of the study device should be classified as procedure related.

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 and/or study procedure, 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 study 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. Enrollment and treatment would be suspended during root cause investigation to determine the cause of the respective AE.

9 RISK AND BENEFITS

9.1 Benefits

A possible benefit of using the Renuvion APR device is the potential for improvement in the appearance of lax tissue in the neck and submental region.

9.2 Risks

This treatment modality was designed to inherently minimize the risk to the subject. However, treatment with energy-based modalities (laser, radiofrequency, and plasma devices) produce subsequent heating of the soft tissue that could involve the following commonly Expected Treatment Effects (ETEs): discomfort/pain, edema, erythema, ecchymosis, hypoesthesia, temporary sensory nerve injury (touch sensitivity, itching, temporary numbness/tingling), transient migratory firmness, and temporary and/or transient crepitus.

In addition to commonly expected treatment effects, treatment with the Renuvion APR device could involve the following risks: helium embolism into the surgical site due to inadvertent introduction into the venous or arterial blood supply system, unintended burns (deep or superficial), pneumothorax, temporary or permanent motor nerve injury, ischemia, fibrosis, infection, gas buildup, bleeding, hematoma, seroma, subcutaneous induration, pigmentation changes, increased healing time, unsatisfactory scarring, asymmetry and/or unacceptable cosmetic result.

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

A grounding pad is used to ground/neutralize the electrical current. Subjects undergoing radiofrequency treatment will be kept away from contact with metal parts which are grounded, or which have appreciable capacitance to earth.

Risks associated with tumescent anesthesia (lidocaine and epinephrine) include blurred vision, mental/mood changes, drowsiness, dizziness, unusually slow heartbeat, rash, itching, swelling, anxiety, apprehensiveness, restlessness, tremor, weakness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties.

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.

- **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.

- **Hydrocodone**

  Tell your doctor right away if you have any serious side effects, including:
  - Stomach/abdominal pain
  - Mental/mood changes
  - Difficult/painful urination

  Get medical help right away if you have any very serious side effects, including:
  - Eye pain/swelling/redness
  - Vision changes
  - Slow/shallow/irregular breathing
  - Severe drowsiness/difficulty waking up
  - Seizure

- **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 (Ultram) 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.

- **Tylenol**

  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:
This drug usually has no side effects. If you have any unusual effects, contact your doctor or pharmacist promptly.

Any unexpected or unforeseen complications will be managed by the investigator throughout the conduct of the study. Unforeseen or unexpected side effects not listed above will be reported to the sponsor and regulatory representatives (IRB) as they occur.

9.3 Mitigation of Risks

These risks are mitigated by utilizing qualified clinical Investigators who have training and are experienced in (1) procedures to improve the appearance of lax tissue in the neck and submental region and (2) 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 the anticipated acceptable risk, the risk-benefit assessment of the use of the Renuvion APR device to improve the appearance of lax tissue in the neck and submental region appears to offer a substantial clinical benefit at a reasonable risk.

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 at least 3 times by contact method of their choice. Sites may choose to send a registered letter as a last attempt to contact. All such efforts should be documented in the subject's file. Subjects will be deemed "Lost-to-Follow-up" if they have not returned within six weeks after the last follow-up target date.

10.3 Supply of Study materials

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

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 the 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 based on enrollment rate, volume, study compliance, and findings from previous visits. The site will be visited at least annually. 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.

A study closure visit may be conducted at the study site 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 or 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 center. 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.

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 primary effectiveness objective and endpoint, primary safety objective and endpoint, additional endpoints, and planned statistical analyses will be outlined in a separate Statistical Analysis Plan (SAP) for the study. Please referred to **Section 8** of the SAP for detailed information on handling missing data, sensitivity analyses of missing data, and poolability.

11.1 Determination of Sample Size

11.1.1 Primary Effectiveness Hypothesis Test

The primary effectiveness objective of this study is to demonstrate response to treatment with the Renuvion APR handpiece. The 3 IPRs will assess each subject's pre-treatment and post-treatment images in blinded random order and independently record which image they believe is the "post-treatment" image. The proportion of subjects achieving at least 2 out of 3 correct IPR assessments will be calculated; this is the proportion of treatment successes.

The sample sizes were estimated using PASS 2019[21] with the following parameters (See **Table 5**):

- A performance goal (PG) of 55% success.
- A one-sample, one-sided binomial exact test against the PG.
- $\alpha = 0.025$.
- Power = 90%
- Plasma/RF success proportions (P) of 75%
- The test is the binomial 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 APR Proportion**	**Δ = Renuvion APR - PG**	**Alpha**	**Reject Ho if Successes ≥**
0.90752	60	0.55	0.75	0.2	0.025	41

*using the Normal approximation, which should be acceptable given the moderate probabilities.

In Phase II, a total of 65 subjects will be treated to accommodate dropouts and losses to follow-up.

11.1.2 Primary Safety Hypothesis Test

The sample size was also calculated for the primary safety hypothesis. Coincidentally, the parameters were identical to those for the primary effectiveness hypothesis, so the sample size was an identical test.

11.2 Performance Goal Rationale

11.2.1 Primary Effectiveness Hypothesis

A Performance Goal (PG) of 55% will be used for testing. A PG of 55% 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 successes will be compared against this Performance Goal. This primary effectiveness endpoint definition and performance goal is more conservative and supported by the results of the Ulthera System study that was conducted to support equivalent indications cleared under K121700. Moreover, this PG is supported by the hypothesis and results of the clinical studies conducted to support the following cleared devices and studies published in clinicaltrial.gov as summarized in **Table 6**.

Table 6: Performance Goal Support

Trial	Sample size	Successes	Success rate	Exact (Clopper-Pearson)[22] 95% lower CI
Ulthera K121700.	70	43	61%	51%
Ulthera K134032	54	37	68%	57%
SofWave NCT04146584	112	56	50%	42%
Evolve System NCT04124419	20	14	70%	49%
COMBINED (weighted)	**256**	**150**	**58%**	**48%**
COMBINED (unweighted)	**256**	**150**	**63%**	**50%**

11.2.2 Primary Safety Hypothesis

A PG of 55% was also established for the primary safety hypothesis test. There were two parts to establishing the PG:

1. Determining which values on an 11-point NRS scale correspond to mild pain and which to moderate.
2. Determining what percentage of subjects with no-to-moderate pain through 7-days is minimally acceptable for a cosmetic procedure.

The first part was answered by Boonstra et al (2016)[20], who showed that on a 11-point NRS, cut-off points of 5 for mild pain and 7 for moderate pain were appropriate. The second part was answered by Broughton et al (2006)[23], who estimated that approximately 55% of subjects reported no-to-moderate pain during the first week post-procedure.

The Broughton estimate was taken from Table 3 of the journal article (see **Table 7)**, which tabulated the percentages of patients reporting pain levels following liposuction by time following the procedure and number of treatment areas. Using the data for subjects receiving treatment in 1-2 areas, we found that 53.4% of subjects reported no higher than moderate pain during the first week post-procedure:

Table 7: Exert of Table 3 Broughton article

Table 3: 1-2 Areas Liposuctioned Discomfort Level by Final Report (per Subject)					
	None	Mild	Moderate	Severe*	TOTAL
1 day	0.023	0.023			
2-3 days		0.093	0.047		
4-7 days		0.209	0.139	0.047	
TOTAL	0.023	0.325	0.186	0.047	.534
> 7 days*	0.023	0.093	0.093	0.209	0.418

* Gray cells not used in calculations.

Therefore, we set our PG at 55%. The null hypothesis test is that Renuvion APR results in fewer than 55% of subjects with maximal pain of "moderate" (NRS pain score of 7 or less) during the first week post-procedure (i.e., more than 45% have severe pain). The alternative is that more than 55% have moderate or less pain (NRS pain score of 7 or less) immediately post-procedure and at the 1-day and 7-day follow-up visits, and fewer than 45% have severe pain.

11.3 Statistical Analysis

These analyses will be performed as follows. The primary effectiveness and primary safety objectives will include hypothesis tests which will be analyzed with Fisher's exact test. All analyses of additional endpoints will be descriptive; standard descriptive statistics will be reported:

- Continuous variables (e.g. age) will be reported as the mean, number of observations, standard deviation, minimum, maximum, and 95% confidence interval (CI) of the mean.
- Categorical variables (e.g. sex) will be reported as the percentage and number of observations in each category and the 95% CI of the percentage.
- Time-to-event variables (e.g. time since last dose of anticoagulant drug) will be reported by the number at risk, the event rates over time and their 95% confidence intervals (CIs). Kaplan-Meier time-to-event analysis will be used to make the estimates.
- Count variables (e.g. number of hospitalizations in the last year) will be reported by the frequency and percentage in each count category, and the 95% CI of each. Poisson regression or negative binomial regression will be used to make the estimates; the method will depend on data dispersion.

Please refer to **Section 9.4** of the SAP for a detailed description of all analyses.

11.4 Subgroup Analysis

Differences in outcomes in age, sex, ethnicity, and body mass index will be explored if the number of study participants in each category is adequate to make such analysis feasible. Please refer to **Section 9.5** of the SAP.

12 DATA HANDLING AND RECORDKEEPING

12.1 Investigator Records

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

- Signed Clinical Trial Agreement and Curriculum Vitae.
- All correspondence pertaining to the investigation with the reviewing IRB, the study Sponsor, and the Monitor.
- 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 study devices and relevant observations relating to the use of the device.
- Relevant observations, including records concerning adverse events, condition of each subject upon entering and results of diagnostic tests.
- The protocol, amendments, and documentation of date and reason for any deviation from investigational plan.

12.2 Investigator Reports

The Investigator is responsible for the preparation, review, signature, and submission of the reports listed in **Table 8**. These are also subject to the FDA inspection and the retention requirements described above for the Investigator's Records.

Table 8: 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 affects 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 the Sponsor.

Responsibilities may be delegated to applicable vendors.

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 Vectra M4 Plus 3D Imaging 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. No information on individual subjects will be revealed in any publications or presentations.

REFERENCES

1. Feldman LS, Fuchshuber PR, Jones DB. The SAGES Manual on the Fundamental Use of Surgical Energy (FUSE). Springer Science+Business Media, LLC. 2012.
2. Goldberg SN, Gazelle GS, Halpern EF, Rittman WJ, Mueller PR, Rosenthal DI. Radiofrequency tissue ablation: importance of local temperature along the electrode tip exposure in determining lesion shape and size. Acad Radiol. 1996;3:212-8.
3. Thomsen S. Pathologic analysis of photothermal and photomechanical effects of laser-tissue interactions. Photochem Photobiol. 1991;53:825-35.
4. Ross EV, McKinlay JR, Anderson RR. Why does carbon dioxide resurfacing work? A review. Arch Dermatol 1999;135(4):444-454.
5. Gardner ES, Reinisch L, Stricklin GP, Ellis DL. In vitro changes in non-facial human skin following CO2 laser resurfacing: a comparison study. Lasers Surg Med 1996;19(4):379-387.
6. Doshi SN, Alster TS. Combination radiofrequency and diode laser for treatment of facial rhytides and skin laxity. Cosmet Laser Ther 2005;7:11-15.
7. Fatemi A, Weiss MA, Weiss RA. Short-term histologic effects of nonablative resurfacing: results with a dynamically cooled millisecond-domain 1320nm Nd:YAG laser. Dermatol Surg 2002;28(2):172-176.
8. Mayoral FA. Skin tightening with a combined unipolar and bipolar radiofrequency device. J Drugs Dermatol 2007;6(2):212-215.
9. Alster TS, Doshi SN, Hpping SB. Combination surgical lifting with ablative laser skin resurfacing of facial skin: a retrospective analysis. Dermatol Surg 2004;30(9):1191-1195.
10. Zelickson B, Kist D, Bernstein E, Brown DB, Ksenzenko S, Burns J, Kilmer S, Mehregan D, Pope K. Histological and ultrastructural evaluation of the effects of a radiofrequency-based nonablative dermal remodeling device: a pilot study. Arch Dermatol 2004;140:204-209.
11. Hsu T, Kaminer M. The use of nonablative radiofrequency technology to tighten the lower face and neck. Semin Cutan Med Surg 2003;22:115-123.
12. Paul M, Blugerman G, Kreindel M, Muholland RS. Three-dimensional radiofrequency tissue tightening: a proposed mechanism and applications for body contouring. Aesthetic Plast Surg. 2011;35(1):87-95.
13. Hurwitz D, Smith D. Treatment of overweight patients by radiofrequency-assisted liposuction (RFAL) for aesthetic reshaping and skin tightening. Aesthetic Plast Surg. 2012;36(1):62-71.
14. Duncan DI. Nonexcisional Tissue Tightening: Creating Skin Surface Area Reduction During Abdominal Liposuction by Adding Radiofrequency Heating. Aesthetic Surgery Journal. 2013;33(8):1154-1166.
15. Ulthera White Paper. Lower Face, Submentum, and Neck. Publicly available on www.ultherapy.com by Ulthera Inc.
16. Boeni, R. Safety of Tumescent Liposuction under Local Anesthetsia in a Series of 4,380 Patients. Dermatology. 2011;222:278-281.
17. Venkataram J. Tumescent Liposuction: A Review. J Cutan Aesthet Surg. 2008 Jul-Dec; 1(2): 49-57.
18. Boeni, R. Safety of Tumescent Liposuction under Local Anesthetsia in a Series of 4,380 Patients. Dermatology. 2011;222:278-281.
19. Hurwitz DJ. The Liposuction and Body Contouring. Reconstructive Surgery & Anaplastology. 2016;5:3.
20. Boonstra et. al. Cut-off Points for Mild, Moderate, and Severe Pain on the Numeric Rating Scale for Pain in Patients with Chronic Musculoskeletal Pain: Variability and Influence of Sex and Catastrophizing. Frontiers in Psychology, Vol 7, Article 1468, September 2016.
21. PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.
22. Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika. 26 (4): 404–413. doi:10.1093/biomet/26.4.404
23. Broughton G II, Horton B, Kipschitz A, et al. Lifestyle Outcomes, Satisfaction, and Attitudes of Patients after Liposuction: A Dallas Experience. Plast. Reconstr. Surg. 2006; 117: 1738-1749.
24. Geister, et. al. Validated Assessment Scale for Platysmal Bands. Dermatol Surg 2013; 39:1217-1225. DOI: 10.1111/dsu.12240.

APPENDIX A: SAMPLE SUBJECT SATISFACTION SURVEY

Subject Satisfaction Survey

1. Are you happy with the results of the procedure performed?

   ☐ **YES** ☐ **NO**

2. What types of changes to you notice from the results of the procedure performed?

   (Check all that apply)

   - ☐ More jawline definition
   - ☐ Reduction in jowls
   - ☐ Improvement in skin texture in the treatment area
   - ☐ Reduction in the area under the chin
   - ☐ Reduction of lines & wrinkles in the treatment area
   - ☐ Other changes noticed *(please list):*

     _____

3. Would you recommend the procedure performed to a friend?

   ☐ **YES** ☐ **NO**

4. Would you consider having the same type of procedure performed on another part of your body? ☐ **YES** ☐ **NO**

5. On a scale from 1-10 (1 is the worst, 10 is the best), what is your overall satisfaction with the procedure and the results of the procedure performed?

   1 2 3 4 5 6 7 8 9 10

   Worst (circle ONE number) Best

APPENDIX B: SAMPLE STUDY SUBJECT DAILY DIARY

To be completed by study staff:

Site ID #	Subject ID	Subject Initials	Procedure Date
☐☐	☐☐☐	☐☐☐	☐☐/☐☐/☐☐☐☐
		First/Middle/Last	*Day* / *Month* / *Year*

Instructions to subjects:
Please use this form to record any complications after your study procedure. Be sure to complete an entry every day until your 14-day follow-up visit. Please bring this form to your 14-day follow-up visit.

Day X	*Date:*

Please rate the average pain you are experiencing in the treatment area on a scale of 0-10, with 0 being 'Best/No Pain' and 10 being the 'Worst Possible Pain'. Please check one box.

	0	1	2	3	4	5	6	7	8	9	10
Pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check all boxes that apply to record any expected treatment effects that you are experiencing.

Expected Treatment Effect	*Are you experiencing this event?*	*Is this causing an impact to your daily activities such as work, sleep, driving, appetite, etc.?*
Swelling	☐ **YES** ☐ **NO**	☐ **YES** ☐ **NO**
Redness of the skin	☐ **YES** ☐ **NO**	☐ **YES** ☐ **NO**
Bruising	☐ **YES** ☐ **NO**	☐ **YES** ☐ **NO**
Touch sensitivity, numbness/ tingling, itching	☐ **YES** ☐ **NO**	☐ **YES** ☐ **NO**
Firm areas under the skin	☐ **YES** ☐ **NO**	☐ **YES** ☐ **NO**
Crackling sound or popping feeling under the skin	☐ **YES** ☐ **NO**	☐ **YES** ☐ **NO**

Are there any other complications you are experiencing?	☐ **YES*** ☐ **NO** ***If "YES", please call your study doctor to discuss.***

Are you wearing your compression garment 22 hours/day for Days 0 – 3 and at night for Days 4-21 as directed by the Post-Procedure Care Instructions?	☐ **YES** ☐ **NO**

APPENDIX C: SUBJECT TAKE HOME POST-PROCEDURE CARE INSTRUCTIONS

Compression Garment Instructions:
It is important to wear the compression garment following your study procedure as directed by these instructions. This is an important part of the healing process.

- **Days 0-3:** Wear the neck compression garment for 22 hours per day, removing only for showering/bathing.
- **Days 4-21:** Wear the neck compression garment at night.

Additional Instructions:

- Complete Subject Diary daily through your 14-Day Follow-up Visit.
- Report any treatment effects by noting them in the Subject Diary.
- Call the investigator or study staff if you have a complication outside of the Expected Treatment Effects listed in the Subject Diary.
- Bring your Subject Diary in with you to each visit, through the 14-Day Follow-up Visit when you will turn the Subject Diary into study staff.
- Continue to keep your study doctor and/or study staff aware of any new complications you may experience beyond the 14-Day Follow-up Visit.

Follow-up Visits & Subject Contact outside of Follow-up Visits

You will be asked to return to the study site at the following times post-procedure:

- 1 (+2) day
- 7 (±1) days
- 14 (±3) days
- 30 (±7) days
- 90 (±10) days
- 180 (±15) days

Your study doctor may ask you to come into the office if you are experiencing a complication. As well, study staff will contact you if you have an ongoing Expected Treatment Effect or complication at the following time points, as applicable:

- 21 (±5) days
- 45 (±5) days
- 60 (±5) days
- 75 (±5) days
- 105 (±5) days
- 120 (±5) days
- 135 (±5) days
- 150 (±5) days
- 165 (±5) days

APPENDIX D: VALIDATED ASSESSMENT SCALE FOR PLATYSMAL BANDS[24]