# CLINICAL TRIAL PROTOCOL NUMBER: APX-22-04-GR

# A POST-MARKET STUDY IN GREECE OF A MINIMALLY INVASIVE LOWER EYELID TREATMENT UTILIZING THE RENUVION SYSTEM

SPONSOR: APYX MEDICAL

FUNDED BY: APYX MEDICAL

DATE: OCTOBER 2, 2023

DRAFT OR VERSION: 4.0

CONFIDENTIAL – PROPRIETARY INFORMATION

# SPONSOR STATEMENT AND SIGNATURE PAGE

| | |
|---|---|
| Company Name: | Apyx Medical |
| Address: | 5115 Ulmerton Rd.<br>Clearwater, FL 33760 |
| Telephone: | 800.537.2790 |
| Study Device: | Apyx APR System |
| Protocol Title: | A Post-Market Study in Greece of a Minimally Invasive Lower Eyelid Treatment Utilizing the Renuvion System |
| Protocol Number: | APX-22-04-GR |
| Revision / Date: | v.4.0 10022023 |

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") 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:

_____ _____

Emily Hughes — Date
Senior Manager, Clinical Affairs

_____ _____

Kari Larson — Date
Sr. Director, Clinical Affairs

_____ _____

Shawn Roman — Date
Vice-President, R&D

_____ _____

Kim Hanson — Date
Director, Clinical Operations & Medical Affairs

_____ _____

Terrence Sullivan — Date
Vice-President, Quality Assurance & Regulatory Affairs

## 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 3 days after 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 (if any) in this study will be provided to the Study Sponsor. The 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.

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

# 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 |

# PROTOCOL SYNOPSIS

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| Protocol Title: | A Post-Market Study in Greece of a Minimally Invasive Lower Eyelid Treatment Utilizing the Renuvion System |
| Study Device: | The Renuvion Generator (K192867) is indicated for delivery of radiofrequency energy and/or helium plasma to cut, coagulate and ablate soft tissue during open and laparoscopic surgical procedures. The Renuvion APR Handpiece (K191542) is intended to be used with compatible electrosurgical generators for the delivery of radiofrequency energy and/or helium plasma for cutting, coagulation and ablation of soft tissue during open surgical procedures.<br><br>Together, the Renuvion Generator and Handpiece are referred to as the Renuvion APR System. |
| Development Phase: | Post-Market |
| Study Purpose: | To evaluate the use of the Renuvion APR System as a minimally invasive lower eyelid procedure. |
| Brief Study Overview: | This is a prospective, multi-center, non-randomized, single-arm study of up to 16 subjects treated with the Renuvion APR System. Subjects will receive treatment with the Renuvion APR System in the lower periorbital area on both sides of the face.<br><br>At baseline, images will be taken utilizing the site's private practice camera system. Baseline images will be used as comparator images for follow-up images for Independent Photographic Reviewer evaluation and subject/investigator assessments.<br><br>The treatment area will be tumesced with 20 - 25ml of fluid on each side of the periorbital area.<br><br>Study treatment will be performed by the principal investigator only. The treatment of the periorbital area will be accessed from an incision placed in the crease of the lower lid. Two incisions will be placed in both the medial and lateral crease of the lower lid. Treatment will be performed through one incision and the second incision will be used to allow for adequate venting of helium gas. Care will be taken to undermine the tissue and to ensure the incisions communicate with each other to allow adequate venting. An optional third lower lid incision may be made as needed. The treatment plane will be above the orbicularis muscle. The treatment settings will be 60-70% Power, 1 LPM, and 3 Passes. Procedure data and adverse events will be captured.<br><br>Follow-up will occur 1 day, 3 days, 7 days, 30 days, 90 days, and 180 days post-procedure; images will be taken at all visits. Investigator/subjects assessments will be completed at D30, D90, and D180 visits. Subjects may also be seen back for follow-up at the investigator's discretion. |
| Number of Sites Enrolling Participants: | Subjects will be recruited from one study site in Greece. |
| Sample Size: | N = 16 treated subjects; subjects enrolled may be greater than subjects treated. |

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| Subject Population: | Healthy, female and male adult subjects ages 18 – 75 years old who meet the inclusion/exclusion criteria. |
| Inclusion Criteria: | • Male or female subjects, ages 18 – 75 years old.<br>• ASA Physical Status Classification System Class I and Class II subjects.<br>• Complaint of skin laxity or lines in the lower eyelid area.<br>• Understands and accepts the obligation not to undergo any other procedures or treatments in the areas to be treated during study participation.<br>• Absence of physical conditions unacceptable to the investigator.<br>• Females of childbearing potential who are sexually active must be willing to use an approved method of birth control during study participation.<br>• Willing and able to comply with protocol requirements, including study-required images/photos, assessments/measurements, and returning for follow-up visits.<br>• Willing to release rights for the use of study photos, including in publication.<br>• Able to read, understand, sign, and date the informed consent.<br>• Able to communicate with the site via video and/or photographs, in the event of a virtual follow-up visit. |
| Exclusion Criteria: | • Subjects presenting with ASA Physical Status Classification System Classes III or higher.<br>• Festoons in the periorbital area.<br>• Prior cosmetic/aesthetic fillers (hyaluronic acid, poly-l-lactic acid, calcium hydroxylapatite, et.) in the study treatment area within the past 12 months.<br>• Pregnant, lactating, or plans to become pregnant during study participation.<br>• Known hypersensitivity or allergy to tumescent anesthetic (lidocaine/ epinephrine).<br>• Known hypersensitivity or allergy to ibuprofen or other NSAIDS.<br>• Previous surgery in the study treatment area.<br>• Active systemic or local skin disease that may alter wound healing.<br>• Significant or uncontrolled medical condition that in the opinion of the investigator participation in the study may compromise the patient's health.<br>• History of autoimmune disease (excluding Hashimoto's thyroiditis).<br>• Known susceptibility to keloid formation or hypertrophic scarring.<br>• Cancerous or pre-cancerous lesions in the area to be treated.<br>• Possesses a surgically implanted electronic device (i.e., pacemaker).<br>• Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in the past two years.<br>• Participation in any other investigational study within 30 days prior to consent and throughout study participation.<br>• Subject who, in the opinion of the investigator, is not an appropriate candidate for the study. |
| Primary Outcome Measures: | Improvement in the lower eyelid area as determined by a masked, qualitative assessment of photographs at 180-days post-treatment compared to baseline. Improvement will be assessed based on photographs taken at all visits using the site's 2D camera system. |

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| Secondary Outcome Measures: | 1. Improvement in the lower eyelid area as determined by a masked, qualitative assessment of photographs at 90-days post-treatment compared to baseline.<br>2. Analysis of change from baseline to D30, D90, & D180 in Snap-back Test Grade (Bashour[14]).<br>3. Analysis of change from baseline to D30, D90, & D180 in Medial Canthal Laxity Test Grade (Bashour[14]).<br>4. Analysis of change from baseline to D30, D90, & D180 in Lateral Canthal Laxity Test Grace (Bashour[14]).<br>5. The Principal Investigator will complete a GAIS[13] assessing overall aesthetic improvement at day 30, 90, and 180 post-treatment.<br>6. The subject will complete a GAIS[13] assessing overall aesthetic improvement at day 30, 90, and 180 post-treatment.<br>7. The subject will complete a patient satisfaction questionnaire at the 180-day follow-up visit.<br>8. During study treatment, the subject's pain levels will be monitored using the 11-point Numeric Rating Scale (NRS)[20]. The average pain score for the entire region treated will be recorded. Pain scores will be recorded at all follow-up visits. |
| Safety Variables: | ▪ Prior to treatment, the subject's medical history will be reviewed, a urine pregnancy test will be performed (if applicable), and a physical examination will be conducted.<br>▪ Following study treatment and at each subsequent visit, the subject will be queried about adverse events, expected treatment effects, and changes in concomitant medications, and the treatment area will be visually examined. |
| Study Duration: | The duration from when the study opens to enrollment until completion of data analyses is anticipated to be 12 months. |

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# 1. KEY ROLES

Persons, companies, and/or groups serving in key roles in the conduct or oversight of this clinical trial are listed in **Table 1** and **Table 2** below, including sponsor, clinical project manager for the trial, investigator responsible for conducting the trial.

## 1.1 INTERNAL RESPONSIBILITIES

**TABLE 1: INTERNAL RESPONSIBILITIES**

| Name | Function | Address |
|---|---|---|
| Apyx Medical | Sponsor | 5115 Ulmerton Road<br>Clearwater, FL |
| Emily Hughes | Sr. Manager, Clinical Affairs | Phone: 731.414.2603<br>Email: Emily.Hughes@apyxmedical.com |
| Kari Larson | Sr. Director, Clinical Affairs | Phone: 801.244.0058<br>Email: Kari.Larson@apyxmedical.com |
| Shawn Roman | VP, R&D and Clinical Affairs | Phone: 904.382.4857<br>Email: Shawn.Roman@apyxmedical.com |
| Kim Hanson | Director, Clinical Operations & Medical Affairs | Phone: 720-480-6584<br>Email: Kim.Hanson@apyxmedical.com |
| Terrence Sullivan | VP, Quality Assurance and Regulatory Affairs | Phone: 508.918.0812<br>Email: Terry.Sullivan@apyxmedical.com |

## 1.2 EXTERNAL RESPONSIBILITIES

The administrative structure for external responsibilities includes, but is not limited to, the participants in **Table 2**.

**TABLE 2: EXTERNAL RESPONSIBILITIES**

| Name | Function | Address |
|---|---|---|
| Dr. Aris Sterodimas | Site Principal Investigator | Address: 264 Mesogeion Ave,<br>Athens, 15562, Greece<br>Phone :+30 210 65 02 936<br>Email: aris@sterodimas.com |
| Castor | EDC | Phone: 628-239-3493<br>Email: anthony.kurda@castoredc.com |
| Technomics Research | Statistical Analysis of Data | Phone: 763-473-6374<br>Email: mharsch@technomicsresearch.com |
| DropBox.com | Secure cloud-based document repository for CRF and images upload | DropBox.com |

# 2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 BACKGROUND INFORMATION & 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 by utilizing 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.

Laxity of the skin is part of the normal aging process, which results in characteristic changes in the skin and underlying connective tissue of the face. Aging is both intrinsic, an inevitable physiological process, and extrinsic, caused by external environmental factors such as air pollution and sun exposure[12]. Aging processes create phenotypic changes in cutaneous cells as well as structural and functional changes in extracellular matrix components such as collagens, elastin, and proteoglycans which provide tensile strength, elasticity, and hydration to the skin[12]. The result of aging is biologic changes to the skin, which include thin, dry skin, fine wrinkles, gradual dermal atrophy, loss of elasticity, and laxity[12]. Specifically, lower eyelid blepharoplasty is a common surgical technique for addressing the undesirable progression of the aging lower eyelids, specifically lower eyelid wrinkles and skin redundancy[19]. This study is utilizing a minimally invasive technique to address the same items of concern.

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. All devices in the product family system 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.

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.

### 2.1.1 Device Name and Indications for Use

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.

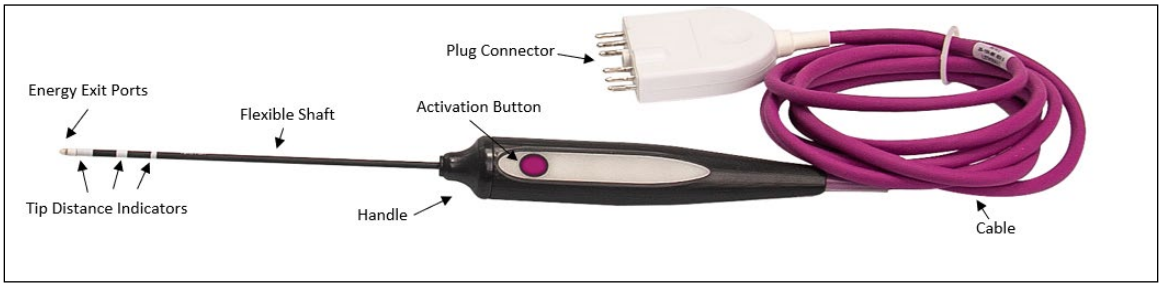


**FIGURE 1: RENUVION APR HANDPIECE**

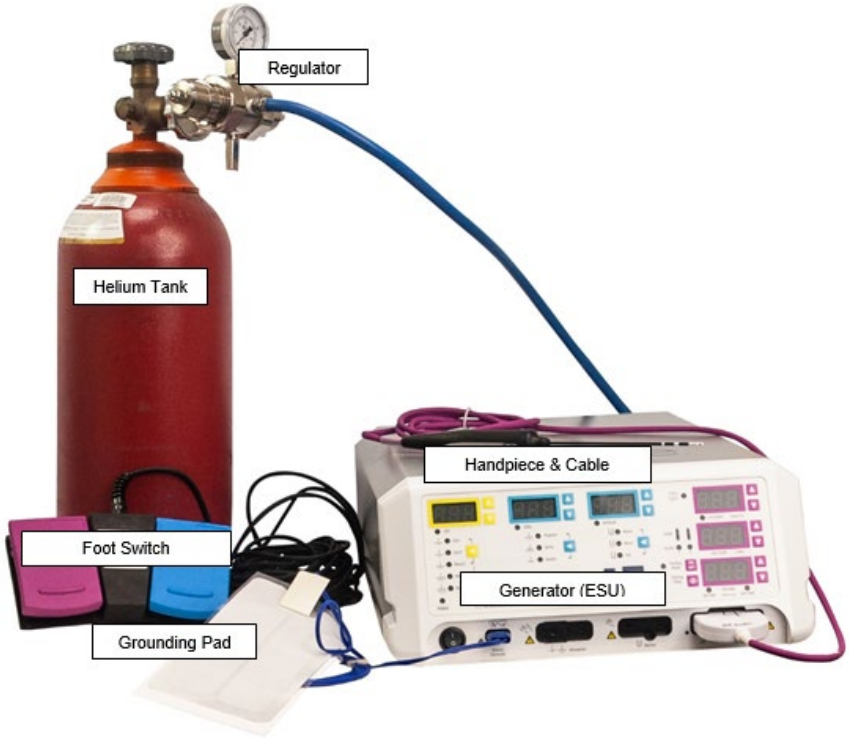


**FIGURE 2: ELECTROSURGICAL UNIT AND HELIUM TANK**

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.

### 2.1.2 Preclinical Studies

During the use of the Renuvion system in open surgical procedures involving subdermal tissue coagulation, the tip of the Renuvion handpiece is placed in the subcutaneous tissue plane through the same access ports used during suction assisted lipolysis procedures (liposuction). In this use, it is important to establish that both the external epidermal tissue temperatures and the internal subdermal tissue temperatures remain within safe limits. The following pre-clinical studies were conducted to measure these temperatures on both live porcine skin tissue and ex vivo human skin tissue:

1. **RP-18032301: Evaluation of Porcine Skin Tissue Epidermal Temperature During Subdermal J-Plasma (Renuvion) Application (Non-GLP)**

   This was a pre-clinical study in which the Renuvion system was used to coagulate the subdermal tissue of porcine skin at various treatment parameters in order to measure the maximum temperature on the surface of the epidermis. In this study, the maximum recorded epidermal surface temperatures were 39.1°C and 40.2°C. These temperatures were recorded after performing six consecutive passes of the Renuvion system under the same area of tissue. Six consecutive passes under the same tissue was included in the study to represent a "worst case" scenario. Six passes are not commonly performed clinically. However, even in this "worst case" scenario the epidermal surface temperature remained within safe limits. Pedroso, et.al, reported that because of superficial thermal safety concerns, the skin surface temperature should be maintained below 45°C. This study was subsequently published[1]. The summary of the published study is as follows:

   > *J-Plasma helium was used in porcine, liver, kidney, and muscle tissue at 20%, 50% and 100% power and 1 L/min and 3 L/min gas flow at 1, 5, and 10 second intervals. J-Plasma was then used in ovarian and uterine tissue at maximum power and gas flow settings in intervals of 1, 5, 10 and 30 seconds. Concluded that J-Plasma has predictable thermal spread in a variety of tissue types. Thermal depth of spread increased linearly with increased power setting, gas flow rate, and exposure time. Even at settings that greatly exceeded the manufacturer's recommendation, the depth of thermal spread associated with the J-Plasma device was less than 3 mm (regardless of the type of tissue) and the diameter of lateral spread was 12 mm or less.*

2. **RP-18040201: A Study Evaluating Tissue Contraction, External Tissue Temperature, and Internal Tissue Temperature When Using J-Plasma (Renuvion) on Ex Vivo Abdominoplasty Tissue (non-GLP)**

   This was a pre-clinical study that was performed on ex vivo human tissue collected by a surgeon during previously conducted abdominoplasty procedures. The Renuvion system was used to coagulate the subdermal tissue of the human skin samples at various treatment parameters. During treatment, both the maximum external epidermal tissue temperatures and the maximum internal subdermal tissue temperatures were measured and recorded. The maximum external tissue temperatures ranged from 24.9°C to 37.8°C. This data serves to validate the maximum external tissue temperatures of 39.1°C and 40.2°C reported in RP-18032301 measured in a live porcine model. The maximum internal tissue temperatures ranged from 40°C to 80°C. It is known from the literature that the reported range of temperatures causing collagen shrinkage varies from 60°C to 80°C. Therefore, in order to cause soft tissue coagulation and collagen contraction, the target internal tissue temperature should be within this range. Both the external and internal temperatures remained within safe limits when using the Renuvion system to coagulate the subdermal tissue of human skin samples.

The results of the above summarized pre-clinical testing support the safe and effective use of the Renuvion® system in dermatological and general surgical procedures involving subdermal tissue coagulation.

## 2.2 Potential Risks and Benefits

### 2.2.1 Potential 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. Any other medications prescribed for the procedure or after-procedure by the investigator have their own risks; these risks should be discussed with the subject.

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.

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 as they occur.

#### *2.2.1.1 Minimization of Potential Risks*

These risks are mitigated by utilizing qualified clinical Investigators who have training and are experienced in subdermal Renuvion procedures. In addition, risks are mitigated by including only those subjects that meet the study eligibility criteria.

### 2.2.2 Potential Benefits

A possible benefit of using the Renuvion APR device in the lower eyelid area is the potential for improvement in the appearance of lax tissue in the lower eyelid region utilizing a minimally invasive technique.

# 3. STUDY PURPOSE

The purpose of this study is to evaluate the use of the Renuvion APR System as a minimally invasive lower eyelid procedure.

# 4. STUDY DESIGN AND ENDPOINTS

## 4.1 DESCRIPTION OF THE STUDY DESIGN

This is a prospective, multi-center, non-randomized, single-arm study of up to 16 subjects treated with the Renuvion APR System. Subjects will receive treatment with the Renuvion APR System in the lower periorbital area on both sides of the face.

At baseline, images will be taken utilizing the site's camera system. Baseline images will be used as comparator images for follow-up images for Independent Photographic Reviewer evaluation and subject/investigator assessments.

The treatment area will be tumesced with 20 - 25ml of fluid on each side of the periorbital area.

The treatment of the periorbital area will be accessed from an incision placed in the crease of the lower lid. Two incisions will be placed in both the medial and lateral crease of the lower lid. Treatment will be performed through one incision and the second incision will be used to allow for adequate venting of helium gas. Care will be taken to undermine the tissue and to ensure the incisions communicate with each other to allow adequate venting. An optional third lower lid incision may be made as needed. The treatment plane will be above the orbicularis muscle. The treatment settings will be 60-70% Power, 1 LPM, and 3 Passes. Procedure data and adverse events will be captured.

Follow-up will occur 1 day, 3 days, 7 days, 30 days, 90 days, and 180 days post-procedure; images will be taken at all visits. Investigator/subjects assessments will be completed at D30, D90, and D180 visits. Subjects may also be seen back for follow-up at the investigator's discretion.

## 4.2 DURATION OF STUDY

Recruitment for this study may take approximately four months. Following the treatment visit, subjects will be followed for a total duration of 180-days, after which, data will be analyzed. Therefore, the anticipated total duration of the study is approximately twelve months.

## 4.3 STUDY ENDPOINTS

### 4.3.1 PRIMARY EFFECTIVENESS ENDPOINT

Improvement in the lower eyelid area as determined by a masked, qualitative assessment of photographs at 180-days post-treatment compared to baseline. Improvement based on 2D photographs taken at all visits using the site's photography system.

Three experienced, blinded independent photographic reviewers (IPR) 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.

### 4.3.2 Primary Safety Endpoint

The primary safety endpoint is an analysis of adverse events through the D180 post-treatment visit.

### 4.3.3 Additional Outcome Measures

1. Improvement in the lower eyelid area as determined by a masked, qualitative assessment of photographs at 90-days post-treatment compared to baseline.
2. Analysis of change from baseline to D30, D90, & D180 in Snap-back Test Grade (Bashour[14]).
3. Analysis of change from baseline to D30, D90, & D180 in Medial Canthal Laxity Test Grade (Bashour[14]).
4. Analysis of change from baseline to D30, D90, & D180 in Lateral Canthal Laxity Test Grace (Bashour[14]).
5. The investigator will complete a GAIS[13] assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment.
6. The subject will complete a GAIS[13] assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment.
7. The subject will complete a Patient Satisfaction Questionnaire (PSQ) at the 180-day follow-up visit.
8. During study treatment, the subject's pain levels will be monitored using the 11-point Numeric Rating Scale (NRS)[20]. The average pain score for the entire region treated will be recorded. Pain scores will be recorded at all follow-up visits.

### 4.3.4 Evaluation Tools

The following evaluation tools will be used in this study:

#### 4.3.4.1 2-Dimentional Photography

Two-dimensional (2D) photographic images will be captures utilizing the site's camera system. The same standardized photography views will be used throughout the study. Images will be captured as follows:

- With the subject's entire face freshly washed and clear of eye makeup. Permanent make-up tattoos, if any, will be noted in the Case Report Form.
- With no jewelry (eyebrow rings, nose rings, earrings, necklace, etc.).
- With the subject's eyes open.
- With no expression on the subject's face (smiling, smirking, etc.).
- Aligned to the Frankfurt Plane (see **Appendix C**).

Images will be monitored for quality to ensure standardized images and subject alignment between baseline and follow-up visits. A reshoot may be requested is images are poor photographic quality and/or changes in subject positioning or alignment. 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.

Baseline images may be taken within 30 days prior to study treatment. Subject baseline photos are reviewed by Apyx staff prior to study treatment to ensure proper subject selection.

##### 4.3.4.1.1 Independent Photographic Assessments

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). The Sponsor will prepare and administer the IPR.

#### 4.3.4.1.2 Independent Photographic Review Evaluation Process

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.

Each blinded assessor will conduct their assessment independently with no input from another blinded assessor.

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.

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.

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".
- Success will be determined by correct identification of post-treatment photographs by at least two out of three blinded, independent reviewers.

#### 4.3.4.1.3 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. Instructions will include that each blinded assessor should pay close attention to changes in:

- Lower Eyelid laxity
- Lower Eyelid fine lines and wrinkles
- Overall appearance of the treatment area

*4.3.4.2 Snap-Back Test Grade*

Analysis of change from baseline to D30, D90, and D180 in the Snap-back Test Grade[14]. This test provides relative lower lid laxity. In normal lids, the skin snaps-back to the original position immediately; the longer it takes, the more laxity is present.

To perform the snap-back test, pull the lower lid away and down from globe for several seconds and wait to see how long it returns to the original position without the subject blinking.

Grade 0 – IV (0 = normal, IV = severe laxity:

- Grade 0 – Normal lid that returns to position immediately on release.
- Grade I – Approximately 2-3 seconds to return to original position.
- Grade II – 4-5 seconds to return to original position.
- Grade III - >5 seconds but does return to original position with blinking.
- Grade IV – Never returns to original position and continues to hang down in frank ectropion after the snap-back test.

**FIGURE 3: SNAP-BACK TEST**

*4.3.4.3 Medial Canthal Laxity Test Grade*

Analysis of change from baseline to D30, D90, and D180 in the Medial Canthal Laxity Test[14]. This test provides medial canthal laxity by means of measuring displacement. The greater the distance, the more the laxity.

To perform the medial canthal laxity test, pull the lower lid laterally away from the medial canthus and measure displacement of medial punctum.

Grade 0 – IV (0 = normal, IV = severe laxity:

- Grade 0 – <2mm displacement.
- Grade I – Approximately 2mm displacement.
- Grade II – Approximately 3mm displacement.
- Grade III - >3mm displacement.
- Grade IV – Does not return to baseline after release and blinking

*4.3.4.4 Lateral Canthal Laxity Test Grade*

Analysis of change from baseline to D30, D90, and D180 in the Medial Canthal Laxity Test[14]. This test provides lateral canthal laxity by means of measuring displacement. The greater the distance, the more the laxity.

To perform the lateral canthal laxity test, pull the lower lid medially away from the lateral canthus and measure displacement of lateral canthal corner.

Grade 0 – IV (0 = normal, IV = severe laxity:

- Grade 0 – <2mm displacement.
- Grade I – 2-4mm displacement.
- Grade II – 4-6mm displacement.
- Grade III - >6mm displacement.
- Grade IV – Does not return to baseline after release and blinking

*4.3.4.5 Global Aesthetic Improvement Scale (GAIS)*

The Global Aesthetic Improvement Scale (GAIS) is a scale that rates global aesthetic improvement from the pretreatment appearance[13]. In this study both live observation and photo review are utilized by the physician or a qualified, delegated clinician and subject in order to assign a score. The PGAIS (Physician Global Aesthetic Improvement Scale) must be performed by the principal investigator. Both the PGAIS and SGAIS (Subject Global Aesthetic Improvement Scale) should be completed in two steps:

- Based on a live assessment of the subject while referring to the subject's pre-treatment photographs (subjects should be given a hand mirror for assessment); and
- Based on a comparison of the subject's pre-treatment photographs to the current post-treatment photographs.

The Investigator will grade the overall improvement of treatment area as indicated in **Table 3** 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 4**. The modified GAIS results will be collected at the 30-day, 90-day, and 180-day follow-up visits.

**TABLE 3: 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 4: MODIFIED GLOBAL AESTHETIC IMPROVEMENT SCALE EVALUATION - SUBJECT**

| Rating | |
|---|---|
| Very much improved | ☐ |
| Much improved | ☐ |
| Improved | ☐ |
| No change | ☐ |
| Worse | ☐ |
| Much worse | ☐ |
| Very much worse | ☐ |

#### *4.3.4.6 Subject Satisfaction Survey*

The study subjects will be asked to complete a Subject Satisfaction Survey (**Appendix A**) at the 180-day follow-up visit. The subject should complete this assessment while referring to baseline photos, current photos, and a hand mirror.

#### *4.3.4.7 Numeric Rating Scale (NRS)*

The study subjects will be asked to complete a 11-point Numeric Rating Scale (NRS)[20] for the level of pain and discomfort associated with the study procedure. 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** of this protocol.

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

Numeric Rating Scale will be completed pre-treatment, post-treatment, and at all follow-up visits to capture pain scores.

#### *4.3.4.8 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 and/or procedure causality: not related, related, undetermined

#### *4.3.4.9 ASA Physical Status Classification System*

The ASA Physical Status Classification System has been in use for over 60 years[19]. The purpose of the system is to assess and communicate a patient's pre-anesthesia medical co-morbidities. The classification system alone does not predict the perioperative risks, but used with other factors (e.g., type of surgery, frailty, level of deconditioning), it can be helpful in predicting perioperative risks, see **Table 5**.

**TABLE 5: ASA PS CLASSIFICATION**

| ASA PS Classification | Definition | Adult Examples, Including, but not Limited to: |
|---|---|---|
| ASA I | A normal healthy patient | Healthy, nonsmoking, no or minimal alcohol use. |
| ASA II | A patient with mild systemic disease | Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease. |
| ASA III | A patient with severe systemic disease | Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents. |
| ASA IV | A patient with severe systemic disease that is a constant threat to life | Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis. |
| ASA V | A moribund patient who is not expected to survive without the operation | Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction. |
| ASA VI | A declared braindead patient whose organs | (Intentionally left blank) |

# 5. SUBJECT ENROLLMENT AND WITHDRAWAL

## 5.1 Study Population

The study population will consist of males and females between 18 – 75 years of age who have chosen to participate in this clinical trial as evidenced by execution of the informed consent document and meet eligibility criteria defined in this protocol are eligible for participation in this clinical trial. Subjects will be considered enrolled into the study when they have signed an approved informed consent form. Subjects who are enrolled and do not meet eligibility criteria will be exited as a screen fail without study treatment. A study exit Case Report Form will be completed for all enrolled subjects.

### 5.1.1 Informed Consent

Informed consent will be obtained from all subjects prior to study participation. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to each participant.

Investigators have ethical and legal responsibilities to ensure that the protocol is clearly explained to each subject considered for enrollment in the study. Compliance with this requirement should be documented on a written Informed Consent Form approved by the reviewing IRB. Each Informed Consent Form will include the elements required by FDA regulations in 21 CFR Part 50/EU MDR Article 63.

Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator, or investigator-delegated study personnel, will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The IRB-approved Informed Consent Form will be signed by the study personnel obtaining consent. A copy of the informed consent document will be given to the participants for their records. The investigative site will keep the original on file. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The participants may withdraw consent at any time throughout the course of the trial 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.

### 5.1.2 Pre-treatment Recruiting/Screening

Subjects will be recruited from the study site's patient database and social media advertising. Study site personnel will explain the design and purpose of the study to potential study subjects and a pre-screening questionnaire (**Appendix B**) will be completed. Subjects interested in participating and who qualify based on the pre-screening questionnaire will visit the study site where informed consent will be obtained.

#### *5.1.3.1 Screen Failures*

A screen failure subject is one from whom informed consent is obtained and is documented in writing (i.e., subject signs an Informed Consent Form), but who does not receive a study treatment because of failure to meet all of the eligibility criteria. Screen failure subjects will be included in the total number of subjects enrolled (i.e., all subjects consented), but not counted towards the total subjects treated.

## 5.2 Inclusion Criteria

Subjects must meet all of the following criteria for study enrollment:

- Male or female subjects, ages 18 – 75 years old.
- ASA Physical Status Classification System Class I and Class II subjects.
- Complaint of skin laxity or lines in the lower eyelid area.
- Understands and accepts the obligation not to undergo any other procedures or treatments in the areas to be treated during study participation.
- Absence of physical conditions unacceptable to the investigator.

- Females of childbearing potential who are sexually active must be willing to use an approved method of birth control during study participation.
- Willing and able to comply with protocol requirements, including study-required images/photos, assessments/measurements, and returning for follow-up visits.
- Willing to release rights for the use of study photos, including in publication.
- Able to read, understand, sign, and date the informed consent.
- Able to communicate with the site via video and/or photographs, in the event of a virtual follow-up visit.

## 5.3 Exclusion Criteria

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

- Subjects presenting with ASA Physical Status Classification System Classes III or higher.
- Previous surgery in the periorbital area.
- Festoons in the periorbital area.
- Pregnant, lactating, or plans to become pregnant during study participation.
- Known hypersensitivity or allergy to tumescent anesthetic (lidocaine/ epinephrine).
- Known hypersensitivity or allergy to ibuprofen or other NSAIDS.
- Active systemic or local skin disease that may alter wound healing.
- Significant or uncontrolled medical condition that in the opinion of the investigator participation in the study may compromise the patient's health.
- History of autoimmune disease (excluding Hashimoto's thyroiditis).
- Known susceptibility to keloid formation or hypertrophic scarring.
- Cancerous or pre-cancerous lesions in the area to be treated.
- Possesses a surgically implanted electronic device (i.e., pacemaker).
- Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in the past two years.
- Participation in any other investigational study within 30 days prior to consent and throughout study participation.
- Subject who, in the opinion of the investigator, is not an appropriate candidate for the study.

## 5.4 Strategies for Recruitment and Retention

Subjects will receive compensation for completion of the Day 1, Day 3, Day 7, Day 14, Day 30, Day 90, and Day 180 visits. Subject stipend amounts will be outlined in the site specific ICF and approved by the IRB prior to subject enrollment.

## 5.5 Participant Withdrawal or Termination

### 5.5.1 Reasons for Withdrawal or Termination

All subjects have the right to withdraw at any point during the study without prejudice. The investigator can discontinue any subject, at any time, if medically necessary. Subjects must be discontinued from the investigation by the investigator at any time for any of the following reasons:

- Withdrawal of informed consent.
- Pregnancy (no further study-related procedures will be performed).
- Any AEs for which treatment continuation would constitute an unacceptably high risk for the subject.

The reason for subject's withdrawal should be documented on the appropriate study specific CRF.

### 5.5.2 Handling of Withdrawals or Termination

The subject must undergo the recommended follow-up assessments specified for the last study visit unless contraindicated due to a medical condition. Withdrawn subjects will not be replaced.

Subjects who are discontinued from the study due to an AE(s) will be treated according to standard clinical practice and will be followed-up until the final study visit/safety visit as described in **Section 7**. All pertinent information concerning the AE will be documented on the appropriate study specific CRF.

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.

## 5.6 Premature Termination or Suspension of the Study or a Study Site

The study or a study site can be prematurely terminated or suspended by the sponsor. Reasons for termination of the study or a study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory.
- The risks and benefits of continuing the study have been reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs constitutes a potential health hazard to the subjects.
- New scientific data do not justify a continuation of the study.
- The investigator or study site exhibit serious and/or persistent non-adherence to the protocol, the Declaration of Helsinki, EN ISO 14155, and/or applicable regulatory requirements.
- The sponsor decides to terminate the study at any time for any other reason.

Furthermore, the study may be prematurely ended if the regulatory authority or the IRB has decided 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 well as provide reasons for the action.

# 6. STUDY DEVICE

FDA-cleared devices shipped for use in clinical investigations conform to the applicable general safety and performance requirements (GSPR) apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution is taken to protect the health and safety of the subjects. This includes, where appropriate, technical, and biological safety testing and pre-clinical evaluation as well as provisions in the field of occupational safety and accident prevention and taking into consideration the state of the art. Apyx Medical will provide devices for use in this clinical investigation.

## 6.1 Packaging & Storage

The sponsor will provide appropriate packaging and storage instructions to the study sites.

### 6.2 ACCOUNTABILITY

The investigator, or designee, must maintain an inventory record using the site-specific Device Disposition Form of study devices received, used for treatment, and returned to the Sponsor to ensure that the investigational device will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. There will be 100% accountability for all clinical study devices. The clinical study site shall maintain all devices received for clinical trial use in a locked, limited access cabinet or room until the end of the study unless they are returned to Apyx while the study is being conducted, such as at the end of study treatments.

### 6.3 DEVICE MALFUNCTION/OBSERVATION

All malfunctions of, or defects of the delivery system will be 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.

## 7. STUDY PROCEDURES AND SCHEDULE

### 7.1 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, see **Table 6**. 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:

- Subject ASA will be determined.
- Brief medical history and physical examination per the Investigator's standard of care.
- Urine pregnancy test (for females of childbearing potential).
- Baseline imaging using the site's 2D photography system.
- Snap-back Test Grade.
- Medial Canthal Laxity Test Grade.
- Lateral Canthal laxity Test Grade.

Medications the subject is taking upon entry into the study should also be documented in the Case Report Forms (CRF). All concomitant prescription medications taken during study participation will be recorded on the appropriate study specific CRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported on the CRF and entered on the eCRF are concomitant prescription medications, over-the-counter medications, and non-prescription 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.

## 7.2 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), see **Table 6**. Medications at investigator discretion may be provided. The treatment area will be tumesced with 20 - 25ml of fluid on each side of the periorbital area.

The treatment of the periorbital area will be accessed from an incision placed in the crease of the lower lid. Two incisions will be placed in both the medial and lateral crease of the lower lid. Treatment will be performed through one incision and the second incision will be used to allow for adequate venting of helium gas. Care will be taken to undermine the tissue and to ensure the incisions communicate with each other to allow adequate venting. An optional third lower lid incision may be made as needed. The treatment plane will be above the orbicularis muscle. The treatment settings will be 60-70% Power, 1 LPM, and 3 Passes. Procedure data and adverse events will be captured.

## 7.3 Follow-up Procedures

### 7.3.1 Immediately Post-Procedure

Following the procedure, the research staff and the subject will care for the treated areas using the Post-Procedure Care Instructions per the Investigator's standard clinical practice.

### 7.3.2 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 day
- 3(±1) days
- 7 (±3) days
- 30 (±7) days
- 90 (±10) days
- 180 (±15) days

Post-procedure assessments and 2D photographic imaging will be performed during the follow-up visits, see **Table 6**. The same standardized photography views will be used throughout the study as documented in the image capture document developed for the study.

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 recorded (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 regular intervals. If the subject is unreachable by the preferred method of contact, another method of contact may be attempted.

**TABLE 6: STUDY REQUIRED PROCEDURES**

| | Baseline/ Pre-Procedure Screening[1] | Procedure (Day 0) | 1 Day | 3 Days | 7 Days | 30 Days | 90 Days | 180 Days |
|---|---|---|---|---|---|---|---|---|
| | | | 1 day | 2-4 days | 4-10 days | 23-37 days | 80-100 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 |
| Visia Photographic Images[3] | X[6] | X[6] | | X | X | X | X | X |
| Numeric Rating Scale (11-point NRS) | | X[4] | X | X | X | X | X | X |
| Study Procedure | | X | | | | | | |
| Adverse Event Assessment | | X | X | X | X | X | X | X |
| Laxity Assessments | X | | | | | X | X | X |
| Modified Global Aesthetic Improvement Scale (GAIS)[5] | | | | | | X | 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).

[3]Digital photographs will be taken and labeled according to Photography Instructions. Standard positioning and lighting will be used for all photographs.

[4] NRS pain score will be captured prior to study treatment and immediately (within 60 minutes) after procedure.

[5] To be completed by Investigator and study subject at day 30, 90, and 180 follow-up visits.

[6] 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.

## 7.4 Subject Randomization and Treatment Group Assignment

No randomization. Subjects will receive treatment with the Renuvion APR System in the lower eyelid area on both sides of the face.

## 7.3 Study Schedule

### 7.3.1 Screening

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify all preliminary/screening inclusion/exclusion criteria are met.
- Perform screening photography (may be used as baseline images).

### 7.3.2 Baseline Assessment

- Obtain protocol-required baseline measures (Laxity Tests).
- Document medical history.
- Obtain pregnancy screen (if applicable).
- Perform baseline photography if screening images were not acceptable.
- Document concurrent medications.

### 7.3.3 Treatment Visit

- Greater than 30 days between baseline and treatment visits will require that the subject be re-screened to confirm enrollment eligibility.
- Obtain pregnancy screen (if applicable) prior to study treatment.
- Perform study treatment.
- Provide standard of care post-treatment instructions.

### 7.3.4 Follow-up

Subjects will be asked to return to the clinic for follow-up visits at 1, 3, 7-, 30-, 90-, and 180-days post-treatment, see **Table 6**. At all visits, subjects will be assessed for safety and pain, standardized images will be taken, adverse events and protocol deviations will be assessed. At D30, 90, and 180 visits, study outcome measures (GAIS, Laxity Tests) will be completed. At the 180-day follow-up appointment in addition to the above referenced assessments, the subject will complete a Patient Satisfaction Questionnaire.

### 7.3.5 Unscheduled Visit

Any unscheduled visit or examine should be documented in the subject's medical record and adverse event form (if applicable) stating the reason for the visit and any actions taken. The Sponsor should be notified of the unscheduled visit.

### 7.3.6 End of Study (Completion)

All subjects who have signed an Informed Consent Form will be considered enrolled in the study. Subjects who complete the study duration will be considered to have completed the 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.

# 8. ASSESSMENT OF SAFETY

## 8.1 Specifications of Safety Parameters

### 8.1.1 Definition of an Expected Treatment Effect (ETE) and an Adverse Event (AE)

An expected treatment effect is defined as any typical treatment side-effect of the Renuvion APR System of mild to moderate severity and lasting up to a typical maximum duration. An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered device-related by the investigator.

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.

All ETEs and AEs will be collected during the conduct of this trial.

### 8.1.2 Definition of Serious Adverse Event (SAE)

Each adverse event should be assessed for its seriousness. The definition below should be used for this assessment. Please note that the term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experienced by the subject. (Please refer to **Section 8.2.1** for severity definitions.)

An adverse event should be classified as serious if it meets any of the following criteria:

a. Death
   Death was an outcome of the adverse event.
b. Life-threatening
   The subject was at substantial risk of dying at the time of the adverse event or use or continued use of the device.
c. Hospitalization (initial or prolonged)
   Admission to the hospital or prolongation of hospitalization was a result of the adverse event.
d. Disability or Permanent Damage
   The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
e. Congenital Anomaly/Birth Defect
   Exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
f. Required Intervention to Prevent Permanent Impairment or Damage (Devices)
   Medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
g. Other Serious (Important Medical Events)
   The event does not fit the other outcomes, but the event may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

### 8.1.3 Definition of Unanticipated Adverse Device Effects (Events)

An unanticipated adverse device effect 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 application (including

supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

## 8.2 Classification of an Event

### 8.2.1 Severity of Event

Each adverse event should be assessed for its severity, or the intensity of an event experienced by the subject, using the following classifications:

- **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.

### 8.2.2 Relationship to the Study Device and Procedure

The relationship to the study device and/or procedure and non-related events 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 and/or study procedure is unknown.

## 8.3 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during a study visit or upon review by a study monitor. All ETEs and AEs will be captured on the appropriate CRF. Information to be collected includes event description, date of onset, clinician's assessment of seriousness and severity, relationship to study device/treatment (assessed only by those with the training and authority to make a determination), actions taken, and date of event resolution. All AEs occurring while on study must be documented appropriately regardless of relationship. All ETEs/AEs assessed as "not yet resolved" must continue to be followed via telephone contact, email or clinic visit every 7 days or sooner as per the physician's direction until event resolution or stabilization.

A pre-existing condition should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of the problem that has not been attributed to natural history. Changes in the severity of an event will be documented to allow for a determination if the event should be re-categorized from an ETE to AE.

Safety evaluations for this study include an interview with the study subject at each follow-up visit by the Investigator or delegated study staff 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. 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 in this protocol.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of ETEs/AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

## 8.4 Reporting Procedures

### 8.4.1 Adverse Event Reporting

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**.

Any new medical problem, or an exacerbation of an existing condition, reported from the time the informed consent form is signed must be followed until the last study visit after the last study treatment or until event resolution.

### 8.4.2 Serious Adverse Event Reporting

Serious adverse events must be reported to the Sponsor as soon as possible, preferably within 24 hours but in no event later than 72 hours. Any AE considered serious by the PI or Sub-investigator, or which meets the definition of an SAE included in **Definition of Serious Adverse Event** must be documented on an SAE CRF.

The Sponsor will conduct an investigation. If the Sponsor determines that the investigation presents an unreasonable risk to subjects, all investigations or parts of the investigation presenting that risk will be terminated as soon as

possible. The investigator must report serious adverse events to the reviewing IRB/FDA according to the FDA regulations.

### 8.4.3 Unanticipated Adverse Device Effect Reporting

If an unanticipated adverse device effect occurs, the study investigator shall complete the appropriate study specific CRF and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in **Apyx Medical Study Contact List**. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

### 8.4.4 Reporting of Pregnancy

Each pregnancy that starts during the subject's study participation must be reported by the investigator to the Sponsor within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on an Adverse Event form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the device or treatment. Each pregnancy must be reported as a non-serious AE if the subject has received at least one study treatment. The following criteria should be followed:

- If a subject becomes pregnant after the Baseline visit and all study treatments have been completed, the subject should continue to be followed for the duration of the pregnancy.
- If a subject becomes pregnant after the Baseline visit but before any study treatments, the subject should be exited from the study.
- If a subject becomes pregnant after the Baseline visit but before all study treatments have been completed, additional study treatments should be discontinued, and the subject should continue to be followed for the duration of the pregnancy.

### 8.4.5 Reporting of Deaths

The investigator must notify the Sponsor as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of a subject's death, regardless of whether the death is related or unrelated to the investigational device. The investigator should attempt to determine, as conclusively as possible, whether the death is related to the device. The cause of death and the investigator's discussion regarding whether or not the death was device-related should be described in a written report. The investigator mush report death to the reviewing IRB according to the IRB regulations at the study site.

## 8.5 Study Halting Rules

This clinical trial will be halted if subjects' safety is questioned based on a reporting of severe, device-related AEs at an excessive frequency. 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 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. The study sponsor will notify all investigators to immediately halt any

continuing enrollment activities and not enroll any additional study participants. The study sponsor will inform the IRB/FDA of the temporary halt and the disposition of the study.

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 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. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). A study-specific Monitoring Plan will further define responsibilities and details related to clinical site monitoring.

# 10. STATISTICAL METHODOLOGY

## 10.1 Statistical and Analytical Plans

For the purposes of this post-market study, descriptive statistics will be performed. For a given parameter, data will be summarized for each time point for which data for that parameter are available. Categorical variables will be summarized as frequencies and percentages in each category. Continuous and ordinal variables will be summarized as numbers of subjects, means, standard deviations, medians, and ranges.

An interim review and analysis of all study data through Day 90 will be completed once all subjects have passed the Day 90 visit window.

## 10.2 Sample Size

The study will include up to 16 treated subjects from a single center in Greece.

# 11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/ DOCUMENTS

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, study specific CRFs, progress notes, electronic data, computer printouts, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons.

# 12. QUALITY ASSURANCE AND QUALITY CONTROL

Quality Assurance and Quality Control procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution via data queries.

Following written SOPs, the clinical study monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

# 13. ETHICS/PROTECTION OF HUMAN SUBJECTS

## 13.1 ETHICAL STANDARD

This clinical study will be conducted in accordance with the Protection of Human Subjects Regulations, including Subpart B Informed Consent of Human Subjects (21 CFR Part 50); the Institutional Review Board Regulations (21 CFR Part 56); the Financial Disclosure by Clinical Investigators Regulations (21 CFR Part 54); and the Investigational Device Exemptions Regulations (21 CRF Part 812), and the ICH E6.

## 13.2 INSTITUTIONAL REVIEW BOARD

Prior to initiation of any study procedures, the protocol, informed consent, and recruitment materials, and all participant materials will be submitted to a duly constituted IRB for view and approval. In addition, any amendments to the protocol or Informed Consent Form will be reviewed and approved by the IRB. The Sponsor must receive a letter documenting IRB approval at the clinical site prior to the initiation of the study.

The investigator is responsible for providing the appropriate reports to its reviewing IRB during the course of the clinical study. These reports will include:

- Informing the IRB of the study progress periodically as required, but at least annually;
- Reporting any unanticipated adverse device effects within 10 working days of first learning of the event;
- Reporting any deviations from the clinical protocol to protect the life or well-being of a subject in the case of an emergency within five working days after the emergency occurred;
- Reporting the use of the device without obtaining informed consent from a subject within five working days of the event; and
- Providing any other reports requested by the IRB.

The IRB must be notified of study completion within 30 days of the final visit of the last subject and should be provided with a summary of the results of the study by the investigator.

## 13.3 PARTICIPANT AND DATA CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without prior written permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or its representatives) will be allowed full access to inspect the records. 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.

All investigational devices and/or other materials collected will be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Subjects should be identified only by initials and unique subject numbers on study specific CRFs. If necessary, their full names may be made known to a regulatory agency or other authorized officials. Information to be stored on the computer will be identified by subject ID and will be password protected.

# 14. DATA HANDLING AND RECORD KEEPING

## 14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

During each subject's visit to the clinic, study data will be documented by study personnel on study-specific Case Report Forms (CRFs) prior to entry into an Electronic Data Capture (EDC) system. Subject demographic information, procedural data, adverse events, device observations, and study required assessments will be documented on the CRFs by delegated site personnel. Study subjects will complete Numeric Rating Scale, Laxity Grades, and Modified Global Aesthetic Improvement Scale (GAIS) Evaluations at protocol specified follow-up visits. Subjects will complete a Satisfaction Survey at the 180-day follow-up visit. In addition, study personnel will record progress notes to document all significant observations, and any contact with a subject by telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. In this clinical trial, study specific CRFs may serve as source documents.

For transmission to the Sponsor, information from the study progress notes and other source documents will be promptly transcribed to study specific CRF to the EDC with the CRF attached for remote monitoring of the data. Transcription of study data onto study specific CRFs and entry into the EDC should be completed within 3 days of the study visit.

Copies of the electronic CRF (eCRF) serving as source documents must be maintained for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Any changes to information in the study progress notes, other source documents, and CRFs will be initialed and dated in ink on the day the change is made by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator and/or delegated staff.

Photographic images will be captured utilizing the site's camera system as per instructions provided in this protocol. Images will be uploaded by the site to Box.com.

Data management and oversight is the responsibility of the Sponsor, details are provided in a study specific Data Management Plan. 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.
- Management and oversight of photographic imaging.

Responsibilities may be delegated to applicable vendors.

## 14.2 Investigator Records and Reports

### 14.2.1 Investigator Records

Prior to participation in the investigation, the investigator must provide the following documentation to the Sponsor:

- Investigator Agreement, signed by the investigator, which lists any physicians who will be involved in conducting the investigation under the direction of the primary investigator.
- A copy of the principal investigator's, sub-investigator's, other delegated study clinicians' curriculum vitae.
- A letter signed by the chairperson of the IRB overseeing the conduct of this study indicating that the IRB has reviewed and approved this investigational plan.
- A copy of the IRB-approved Informed Consent Form.

During the study, investigators are required to maintain on file the following accurate, complete, and current records relating to this study as described in 21 CFR §812.140. A summary of these records is listed below:

- Executed Clinical Trial Agreement.
- Signed Financial Disclosure.
- All correspondence and required reports, which pertain to the study, including IRB approvals and correspondence.
- Shipping documents and Device Disposition Log which records of receipt, use, or disposition of study devices, including the type and quantity of devices; the dates of receipt; the identifying product numbers; the names of all persons who received, used, or disposed of each device; and why and how many units of the device have been returned to the Sponsor, repaired, or otherwise disposed.
- Records of each subject's case history and exposure to the device.
- Signed and dated consent forms.
- Relevant observations, including records concerning adverse events, condition of each subject upon entering and results of diagnostic tests.
- Study-specific CRFs and corrections to the forms.

- Protocol and amendments with signed Statement of Compliance.
- IRB-approved subject recruiting materials.
- Investigator curriculum vitae and medical license.
- Monitoring reports and correspondence.
- Study logs including Site Training Log, Site Visit Log, Site Delegation Log, and Subject Enrollment Log.

### 14.2.2 Investigator Reports

Investigators are required to prepare and submit to the Sponsor the following complete, accurate, and timely reports on this investigation when are required. These reports, which are listed below, are required by 21 CFR §812.150; additional reports may be requested by the Sponsor:

- The investigator will notify the Sponsor of a subject death occurring during the investigation, as soon as possible, preferably within 24 hours of learning of the subject's death, but in no event later than 48 hours. The investigator will notify the reviewing IRB of a subject death as specified by the IRB.
- The investigator will notify the Sponsor of any unanticipated adverse device effects within 48 hours after learning of the effect. The investigator will notify its reviewing IRB of any unanticipated adverse device effects, as soon as possible, but no later than 10 working days after learning of the effect.
- The investigator will notify the Sponsor of the withdrawal of IRB approval, as soon as possible, but no later than five working days after learning of the withdrawal.
- The investigator will provide current progress reports to the Sponsor and reviewing IRB at regular intervals and at least on an annual basis.
- The investigator will notify the Sponsor and reviewing IRB of any deviation from the investigational plan to protect the life and physical well-being of a subject in an emergency, as soon as possible, but no later than five working days after the emergency occurred.
- The investigator will notify the Sponsor and reviewing IRB that an informed consent was not obtained from a subject, as soon as possible, but no later than five working days after such an occurrence.
- The investigator will provide a final summary report to the Sponsor and reviewing IRB within three months after termination or completion of the study.
- The investigator will provide any other information upon the request of an IRB, FDA, or the Sponsor.

## 14.3 Study Records Retention

The investigator is responsible for retaining the necessary records, including a copy of the protocol, device labeling, study-specific CRFs, medical records, original reports of test results, all study-related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

FDA regulations require all investigators participating in investigational device studies to maintain detailed clinical records during the investigation and for a period of at least two years after the latter of the following two dates:

1. The date on which the investigation is terminated or complete; or
2. The date the records are no longer required for purposes of supporting a premarket approval application.

The investigator must not dispose of any records relevant to this study without either:

1. Obtaining written permission from the Sponsor; or
2. Providing an opportunity for the Sponsor to collect such records.

The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and the FDA.

### 14.4 Protocol Deviations

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. This study should be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of a subject requires a protocol deviation, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). If the deviation from the protocol is necessary to protect the physical well-being of a subject in an emergency, such protocol deviations must be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than five working days after the emergency occurred.

In the event of a significant deviation from the protocol due to an accident or mistake, the investigator or designee must contact the Sponsor at the earliest possible time to discuss the deviation and its impact on the study and subject continuation in the study. All protocol deviations and justification for the deviation will be documented on the applicable Case Report Form.

### 14.5 Publication and Data Sharing Policy

The data produced by this Apyx Medical-sponsored study is the sole property of Apyx Medical. Thereby, abstracts, publications and presentations of this data must be pre-approved by Apyx in writing (e-mail approval is acceptable). The Sponsor must also be provided with the opportunity to review all investigator-prepared abstracts, publications, or presentations. A period of thirty (30) days for presentational materials and abstracts and forty-five (45) days for manuscripts will be required for review and comment by Sponsor's Clinical and Medical Affairs Department. These requirements acknowledge Sponsor's responsibility to evaluate such publications for their accuracy, to ascertain whether Confidential Information is being inappropriately released, to provide the Principal Investigator with information which may not yet have been available to him/her, and to provide input from co-authors regarding content and conclusions of the publication or presentation. If requested in writing by the Sponsor, the Institution will withhold publication to protect the potential patentability of any invention described therein and/or made available to fulfill regulatory requirements.

Notwithstanding the foregoing, Institution agrees that if the Study is part of a multi-center study, the first publication of the results of the Study shall be made in conjunction with the results from the investigators at the other study centers as a multi-center publication.

The sponsor ensures that the study is registered, and study results are disclosed in at least one public clinical study registry, in accordance with national/international regulations and other requirements. Study registration may include a list of the study sites, as applicable.

## 15. STUDY ADMINISTRATION

### 15.1 Study Investigators

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.

### 15.2 Amendment Policy

The investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB, except if the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency. Such protocol deviations must be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than five working days after the emergency occurred.

Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed by the investigator(s) and the Sponsor. If agreement is reached regarding the need for an amendment, the Sponsor will write it. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for "administrative amendments", investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; the scientific soundness of the investigational plan or protocol; and the right, safety or welfare of the human subjects involved in the investigation. When, in judgment of the chairman of the IRB, the investigators and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written Informed Consent Form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before continued participation.

## 16. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

# 17. LITERATURE REFERENCES

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# APPENDIX A: PATIENT SATISFACTION QUESTIONNAIRE

*Please have the subject complete this assessment while referring to their image in the mirror and current post-treatment photos compared to baseline photos. Provide the subject with a mirror.*

*Using a mirror and reviewing your post-treatment photos, compare how your treatment area currently looks compared to your pre-treatment photos.*

1. Do you notice any improvement in how your lower eyelid area?
   - ☐ YES →
     - ☐ Improvement in wrinkles
     - ☐ Less sagging skin
     - ☐ Smoother skin texture
     - ☐ Other: _____
   - ☐ NO

2. How would you characterize your satisfaction with the treatment?
   - ☐ Very Satisfied
   - ☐ Satisfied
   - ☐ Slightly Satisfied
   - ☐ Neither Satisfied or Dissatisfied
   - ☐ Slightly Dissatisfied
   - ☐ Dissatisfied
   - ☐ Very Dissatisfied

3. Would you recommend this treatment to your friends and family members *(check one)*?
   - ☐ YES ☐ NO

***Thank you for completing this questionnaire.***

Subject Initials: _____ Date: _____ (DD/MON/YYYY)

# APPENDIX B: PRE-SCREENING QUESTIONNAIRE

This questionnaire may be emailed to potential subjects and/or asked over a telephone conversation. Answers to the following questions will only be used to determine if preliminary criteria for the clinical study is met. Subjects meeting the preliminary criteria and remain interested in participating in the study, will be scheduled to attend an in-office appointment to further determine your eligibility. Answers to the questions below may be collected with but will not be associated with your personal information.

Subject Initials (use dash if no middle initial): ___ ___ ___

What is your age? _____

Are you looking to improve the appearance of lower eyelid (under eye) laxity? ☐ Yes ☐ No

Have you ever had any cosmetic procedures performed on your eye area? ☐ Yes ☐ No

Are you willing to return to the clinic for all follow-up visits for 6 months after your procedure? ☐ Yes ☐ No

Are you willing to have pictures taken of your face and are you willing to allow the study sponsor, Apyx Medical, to use these photographs for study purposes? ☐ Yes ☐ No

Are you taking any blood thinning medications? ☐ Yes ☐ No

Are you currently pregnant or lactating, have you been pregnant within the past 12 months, or planning to become pregnant in the next 6 months? ☐ Yes ☐ No

Do you have or have you ever had cancer of any type and, if so, what type? ☐ Yes ☐ No

If yes, what type(s)? _____

Do you have an autoimmune disease? ☐ Yes ☐ No

Are you sensitive or allergic to anesthesia of any kind? ☐ Yes ☐ No

Do you have or have you ever had a bleeding disorder? ☐ Yes ☐ No

Have you ever participated in a clinical study? ☐ Yes ☐ No

If so, when? _____

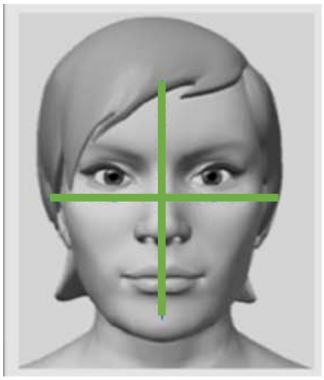
# APPENDIX C: FRANKFURT PLANE POSITIONING

## Patient Positioning: Frankfurt Plane, Front

The subject's face should fill the screen.

The vertical cross hair should align with the center of the nose.

The horizontal cross hair should align with the Frankfurt horizontal line*.



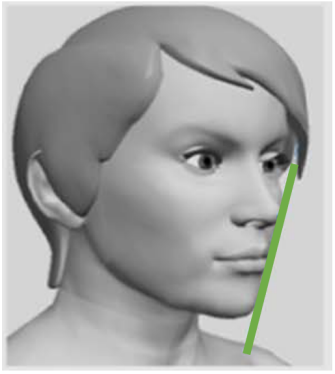
Frankfurt Plane: The horizontal line drawn from the upper edge of the inner ear canal to the inferior point of the orbital rim.

## Patient Positioning: Frankfurt Plane, 45°

The subject's face should fill the screen.

The tip of the subject's nose should align with edge of cheek.

The camera should stay in line with the Frankfurt horizontal line*.

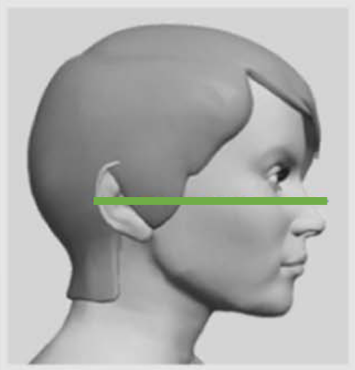


Frankfurt Plane: The horizontal line drawn fromthe upper edge of the inner ear canal to the inferior point of the orbital rim.

# Patient Positioning: Frankfurt Plane

The subject's face should fill the screen.

The camera should be positioned in line with the Frankfurt horizontal line*.



Frankfurt Plane: The horizontal line drawn from the upper edge of the inner ear canal to the inferior point of the orbital rim.

# APPENDIX D: PROTOCOL REVISIONS LOG

**TABLE 7: PROTOCOL REVISIONS LOG**

| VERSION | DATE | SIGNIFICANT REVISIONS |
|---|---|---|
| 1.0 | 02172022 | Initial Release |
| 2.0 | September 27, 2022 | Revise the subject number to 15 |
| 3.0 | 020152023 | 20% power to 60-70% power. |
| 4.0 | 10022023 | Revise subject number to 16 |
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