CLINICAL TRIAL PROTOCOL NUMBER: APX-22-03

A POST-MARKET STUDY OF A MINIMALLY INVASIVE BREAST LIFT PROCEDURE UTILIZING THE RENUVION APR SYSTEM

SPONSOR: APYX MEDICAL

FUNDED BY: APYX MEDICAL

DATE: SEPTEMBER 23, 2022

VERSION: 2.0

CONFIDENTIAL – PROPRIETARY INFORMATION

SPONSOR STATEMENT AND SIGNATURE PAGE

Company Name:	Apyx Medical
Address:	5115 Ulmerton Rd. Clearwater, FL 33760
Telephone:	800.537.2790
Study Device:	Renuvion APR System
Protocol Title:	A Post-Market Study of a Minimally Invasive Beast Lift Procedure Utilizing the Renuvion APR System
Protocol Number:	APX-22-03
Revision / Date:	v.1.0 21APR2022
Revision / Date:	v.2.0 23SEP2022

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 EC(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 EC'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:

_____ _____

Garrick Fenton
Sr. Manager/Manager, Clinical Affairs — Date

_____ _____

Kari Larson
Sr. Director, Clinical Affairs — Date

_____ _____

Shawn Roman
Vice-President, R&D — Date

_____ _____

Kim Hanson, RN
Vice-President, Medical Affairs — Date

_____ _____

Lisa Graney
Vice-President, Quality Assurance & Regulatory Affairs — Date

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 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 Ethics Committee (EC), 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.

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 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 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
Sub-Investigator Signature	Sub-Investigator Name	Date

Sub-Investigator Signature	Sub-Investigator Name	Date
Sub-Investigator Signature	Sub-Investigator Name	Date
Sub-Investigator Signature	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
EC	Ethics Committee
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

Protocol Title:	A Post-Market Study of a Minimally Invasive Breast Lift Procedure Utilizing the Renuvion APR System
Investigational 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. Together, the Renuvion Generator and Handpiece are referred to as the Renuvion APR System.
Development Phase:	Post-Market
Study Purpose:	To evaluate the use and safety of the Renuvion APR Device for use in a minimally invasive breast lift procedure.
Brief Study Overview:	This is a prospective, non-randomized, single-center, evaluator-blinded study of up to 15 study subjects undergoing a minimally invasive breast lift procedure utilizing the Renuvion APR System. The study will be conducted at a single investigational center in Greece. At baseline, the grade of breast ptosis will be recorded by side (Eyck et al, Rainbow Scale for Assessing Breast Ptosis), breast measurements will be taken, and pre-surgery photographs taken in the frontal, lateral, and oblique views. All study subjects will be treated with the Renuvion APR Device. The treatment area is defined as superior most not to exceed a horizontal line from the superior aspect of the axilla to the midline; inferior most not to cross the junction of the breast with the abdomen (inframammary fold). Lateral border to the outermost curvature of the breast or a vertical line drawn from the preaxillary line to the IMF; medial most to the innermost curvature of the breast up to 1 cm lateral to the sternal midline. The procedure will be in the intradermal and subdermal planes in the full breast area, without penetrating the breast gland. Renuvion APR System settings will be 60-70% Power, 1.5 LPM, and up to 6 retrograde or 3 antegrade/retrograde passes, with a minimum of 2 incision sites. Endermologie is not allowed post-procedure. Post-procedure compression for 2-4 weeks with a standard compression vest for all subjects. Follow-ups will occur at 30, 90, and 180-days post-procedure.
Number of Sites Enrolling Participants:	Subjects will be recruited from a single study site in Greece.
Sample Size:	N = 15 treated subjects; subjects enrolled may be greater than subjects treated.
Subject Population:	Healthy, adult female subjects ages 18 – 75 years old who meet the inclusion/exclusion criteria.

Inclusion Criteria:	• Female subjects, ages 18 – 75 years old. • ASA Physical Status Classification System Class I and Class II subjects. • Breast Ptosis Class II and Class III as per the Eyck et al, Rainbow Scale for Assessing Breast Ptosis[14]. • Breast Cup Size A and Size B[18]. • 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.
Exclusion Criteria:	• Subjects presenting with ASA Physical Status Classification System Classes III or higher. • Breast ptosis Class IV or more as per the Eyck et al, Rainbow Scale for Assessing Breast Ptosis[14]. • Breast Cup Size C, Size D or larger[18]. • Prior surgery or procedure in the breast area (i.e., implants, skin tightening procedures, breast reduction, etc.). • 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. • Previous treatment in the study treatment area. • 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.
Outcome Measures:	1. Independent Photographic Review of before and after images compared to baseline at D90 and baseline compared to D180.

	2. Bilateral analysis of change to Morphometric breast measurements as per Brown, An Analysis of Ptosis[15] at baseline and day 30, 90, and 180. 3. Bilateral analysis of change to Ptosis Classification per the Eyck et al, Rainbow Scale for Assessing Breast Ptosis[14] at baseline and day 180. 4. The Principal Investigator will complete a PGAIS[16] assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment. 5. The subject will complete a SGAIS[16] assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment. 6. The subject will complete a Patient Satisfaction Questionnaire (PSQ) at the 180-day follow-up visit. 7. The subject will complete a Breast-Q survey at baseline and 180-day follow-up visit.
Safety Measures:	1. Analysis of adverse events through the D180 post-treatment visit. 2. During study treatment, the subject's pain levels will be monitored using the 11-point Numeric Rating Scale (NRS)[17]. The average pain score for the entire region treated will be recorded. Pain scores will be recorded at all follow-up visits.
Study Duration:	The duration from when the study opens to enrollment until completion of data analyses is anticipated to be 12 months.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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 Clearwater, FL
Garrick Fenton	Sr. Manager, Clinical Affairs	Phone: 662.902.9830 Email: Garrick.Fenton@apyxmedical.com
Kari Larson	Sr. Director, Clinical Affairs	Phone: 801.244.0058 Email: Kari.Larson@apyxmedical.com
Shawn Roman	VP, R&D and Clinical Affairs	Phone: 904.382.4857 Email: Shawn.Roman@apyxmedical.com
Kim Hanson	Director, Clinical Operations & Medical Affairs	Phone: 720-480-6584 Email: Kim.Hanson@apyxmedical.com
Lisa Graney	VP, Quality Assurance and Regulatory Affairs	Phone: 813.459.0611 Email: Lisa.Graney@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, Athens, 15562, Greece Phone :+30 210 65 02 936 Emailaris@sterodimas.com
Castor	EDC	Phone: 628-239-3493 Email: anthony.kurda@castoredc.com
Technomics Research	Statistical Analysis of Data	Phone: 763-473-6374 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 caused by thermal-induced collagen/tissue contraction since the mid-1990s.[6-11]

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

Laxity of the skin is part of the normal aging process, which results in characteristic changes in the skin and underlying connective tissue. 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]. Sagging of the breast or breast ptosis is common in women due to normal aging or after weight loss, pregnancy, or breastfeeding[13]. Mastopexy or surgical breast lift seeks to reposition the breast back higher on the chest wall[13]. 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. The Renuvion APR Handpiece is a new device designed to be a part of this helium-based plasma technology family. All devices in the product family 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.

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

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

5. Unencumbered delivery of power regardless of the tissue impedance due to the unique power output from the electrosurgical generator.
6. Low current RF energy resulting in minimal depth of thermal effect and prevention of over-treating tissue when performing multiple passes.

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.

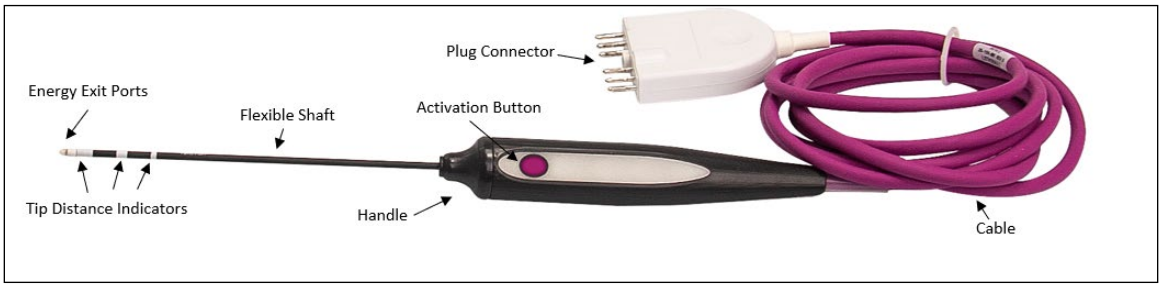


FIGURE 1: RENUVION APR HANDPIECE

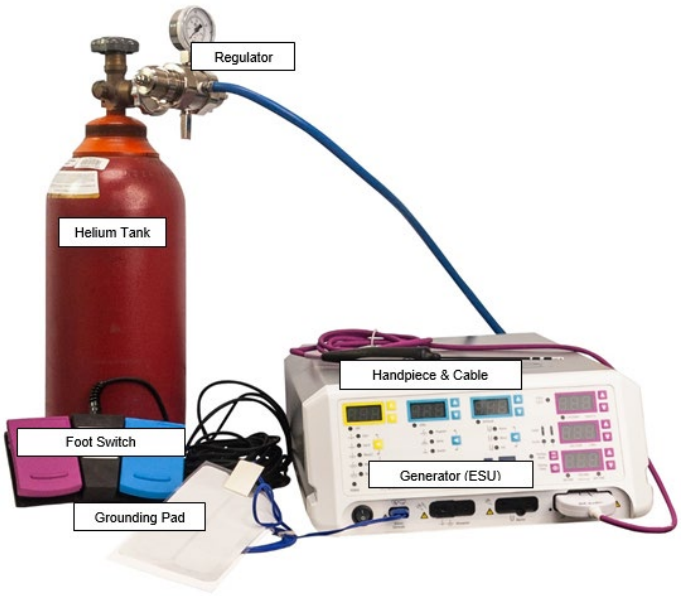


FIGURE 2: ELECTROSURGICAL UNIT AND HELIUM TANK

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

Pre-Clinical Studies to Support Safe Tissue Temperatures during Device Use

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.

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.

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

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 (Ethics Committee) 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 breast lift procedures and Renuvion procedures. In addition, risks are mitigated by including only those subjects that meet the study eligibility criteria. This study also includes evaluation of study subject satisfaction with the procedure.

2.2.2 Potential Benefits

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

3. STUDY PURPOSE

The purpose of this study is to evaluate the use of the Renuvion APR device as a minimally invasive lax breast procedure.

4. STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This study is a prospective, single-center, non-randomized clinical trial. Up to 15 subjects will be enrolled and treated if they meet the inclusion/exclusion criteria and provide written informed consent. Investigator will assess baseline ptosis scale and volume assessment prior to treatment to confirm subject eligibility.

Subjects meeting all entrance criteria and confirmed eligible for study treatment will be enrolled. All Subjects will be treated using the Renuvion APR System by the study investigator. Standardized images will be taken prior to treatment and during each follow-up visits. Baseline assessments and pre-treatment images should be obtained within 30 days of the study treatment.

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 OUTCOME MEASURES

1. Independent Photographic Review of before and after images compared to baseline at D90 and baseline compared to D180.
2. Bilateral analysis of change to Morphometric breast measurements as per Brown, An Analysis of Ptosis[15] at baseline and at day 30, 90, and 180 post-treatment.
3. Bilateral analysis of change to Ptosis Classification per the Eyck et al, Rainbow Scale for Assessing Breast Ptosis[14] at baseline and at day 180 post-treatment.
4. The Principal Investigator will complete a PGAIS[16] assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment.
5. The subject will complete a SGAIS[16] assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment.
6. The subject will complete a Patient Satisfaction Questionnaire (PSQ) at the 180-day follow-up visit.
7. The subject will complete a Beast-Q survey at baseline and 180-day follow-up visit.

4.3.2 SAFETY ENDPOINTS

1. Analysis of adverse events through the D180 post-treatment visit.
2. During study treatment, the subject's pain levels will be monitored using the 11-point Numeric Rating Scale (NRS)[17]. The average pain score for the entire region treated will be recorded. Pain scores will be recorded at all follow-up visits.

4.3.3 Evaluation Tools

The following evaluation tools will be used in this study:

4.3.3.1 2-Dimensional Photography

Two-dimensional (2D) photographic images will be captured utilizing the site's current photography system. The same standardized photography views will be used throughout the study. Images will be monitored for quality to ensure standardized images and subject alignment between baseline and follow-up visits. Study staff should review photos with particular care during each visit to ensure consistent alignment.

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 and adequate image capture.

4.3.3.1.1 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).

4.3.3.1.2 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.

4.3.3.1.3 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 and to provide sample images for scoring and discussion of the scoring by IPR assessors. Instructions will include that each blinded assessor should pay close attention to changes in overall appearance of lift in the treatment area.

4.3.3.2 Global Aesthetic Improvement Scale (GAIS)

The Global Aesthetic Improvement Scale (GAIS) is a 5-point scale that rates global aesthetic improvement from the pretreatment appearance[16]. 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 CGAIS must be performed by the principal investigator, sub-investigator or qualified clinician delegated by the principal investigator. Both the CGAIS and SGAIS 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 GAIS results will be collected at the 30-day, 90-day and 180-day follow-up visits.

TABLE 3: 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: GLOBAL AESTHETIC IMPROVEMENT SCALE EVALUATION - SUBJECT

Rating	
Very much improved	□
Much improved	□
Improved	□
No change	□
Worse	□
Much worse	□
Very much worse	□

4.3.3.3 Patient Satisfaction Survey (PSQ)

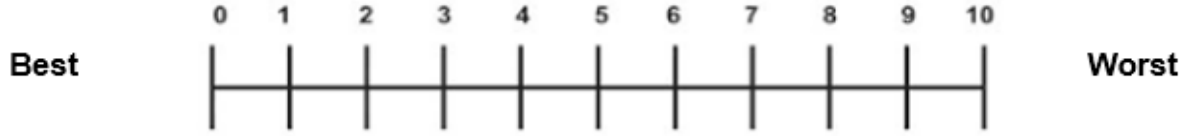
The study subjects will be asked to complete a Patient Satisfaction Survey, see **Appendix A**, at the 180-day follow-up visit.

4.3.3.4 Breast-Q

The study subjects will be asked to complete a Breast-Q, see **Appendix B**, at the Baseline (pre-procedure) and 180-day follow-up visits. The Breast-Q Version 2.0 Augmentation Module Pre- and Postoperative Scales have been provided for use under license from Memorial Sloan Kettering Cancer Center. Subjects will complete the Psychosocial Well-Being and Sexual Well-Being questionnaires.

4.3.3.5 Numeric Rating Scale (NRS)

The study subjects will be asked to complete a 11-point Numeric Rating Scale (NRS) for the level of pain and discomfort associated with the study procedure[17] – to be completed by the subjects on the day of the procedure prior to the procedure, following the procedure, and at all follow-up visits. The average pain score for the entire region treated will be recorded. Directions to subject will be: "Please rate the average pain you are experiencing in the treatment area on a scale of 0-10, with 0 being 'Best/No Pain' and 10 being the 'Worst Possible Pain'."



Pain will be defined in this study as the average pain reported in the treatment area using the following categories: None (Score of 0), Mild (Score of 1-5), Moderate (Score of 6-7), and Severe (Score of 8-10). Classifications of NRS pain scores have been documented in literature[18]. 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. The NRS will be completed pre-treatment, post-treatment, daily in the subject diary, and at all follow-up visits to capture pain scores.

4.3.3.6 Adverse Event Reporting

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

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

4.3.3.7 Ptosis Classification

The Rainbow Scale[14] for breast ptosis is validated for photographic review of the anterior-posterior view, the lateral view, and the oblique view, see **Figure 3**, **Figure 4**, and **Figure 5**, using the following grades at baseline at D180:

- **Grade I (no breast ptosis)**: thoraco-mammary angle >90°, no visible breast ptosis.
- **Grade II (mild breast ptosis)**: thoraco-mammary angle <90 °, but nipple lies still above the level of the inframammary fold.
- **Grade III (moderate breast ptosis)**: the nipple lies at the level of the inframammary fold, above the inferior breast contour.
- **Grade IV (severe breast ptosis)**: the nipples below the level of the inframammary fold but remains above the inferior breast contour.
- **Grade V (extreme breast ptosis)**: the nipple lies below the level of the inframammary fold and at the inferior breast contour.

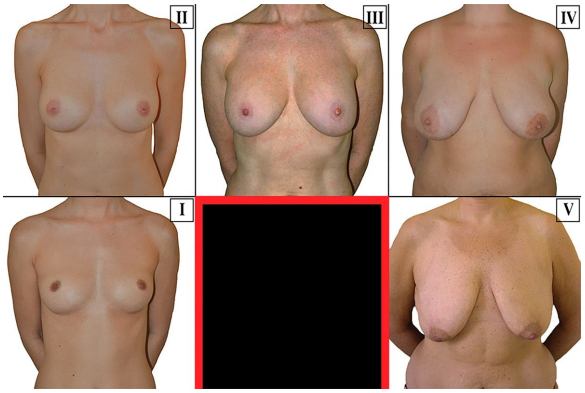


FIGURE 3: RAINBOW SCALE FOR ANTERIOR-POSTERIOR ASSESSMENT

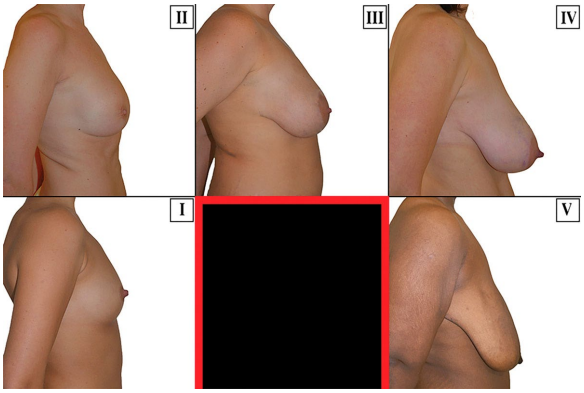


FIGURE 4: RAINBOW SCALE FOR LATERAL ASSESSMENT

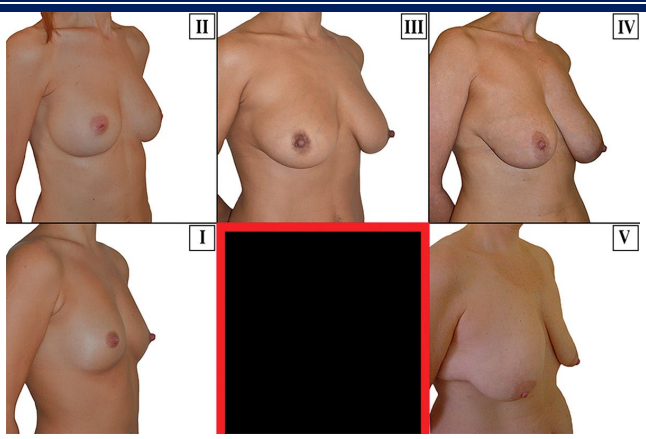


FIGURE 5: RAINBOW SCALE FOR OBLIQUE ASSESSMENT

4.3.3.8 Morphometric Breast Measurements

Morphometric measurements of breast[16] will be conducted at baseline and 30 Days, 90 Days, and 180 Days post procedure as shown in **Figure 8**. Points of measurement will include:

- Suprasternal notch to nipple distance (*SNN-N*): measurements taken at the mid nipple diameter on both sides.
- Inframammary crease to nipple distance (*IMC-N*): measurement taken from the base of the breast to the base of the nipple.
- Midclavicular line to nipple distance (*MCL-N*): measurement taken from the mid clavicle to the mid nipple.
- Nipple to nipple distance (*N-N*): measurements taken at the mid nipple diameter on both sides.
- *SSN-IMC*: vertical distance from the suprasternal notch to the inframammary crease.
- *SSN-base*: vertical distance from the suprasternal notch to the lowest point on the base.
- *PROJ*: maximum point of breast projection measured perpendicular to the chest wall.
- *NAC:* nipple-areola complex diameter.

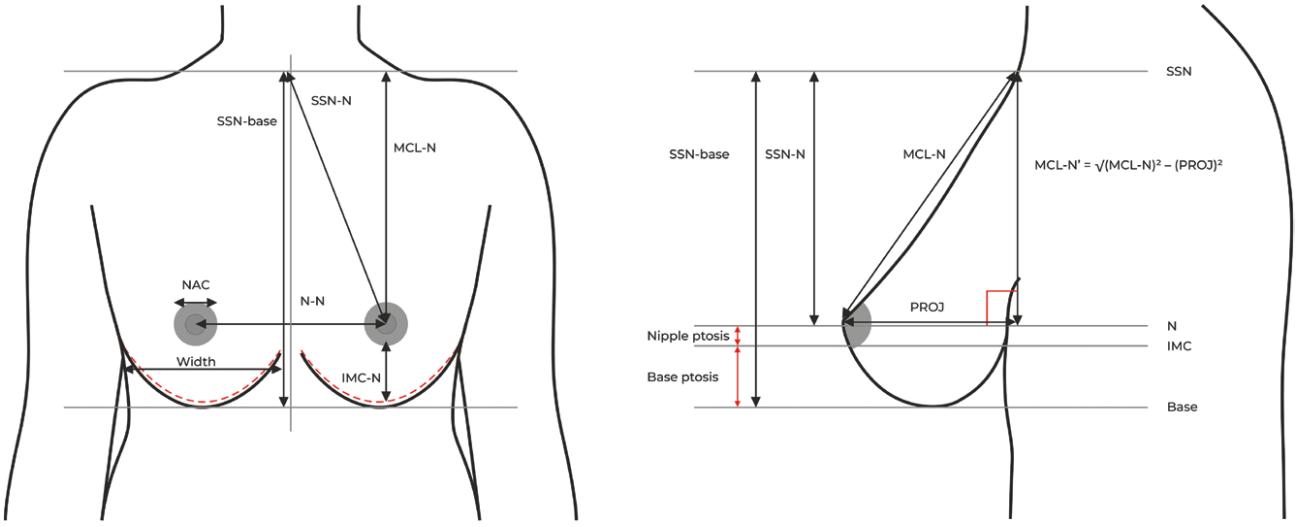


FIGURE 6: MORPHOMETRIC MEASUREMENTS

4.3.3.9 ASA Physical Status Classification System

The ASA Physical Status Classification System has been in use for over 60 years. 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)

4.3.3.10 Standardized Bra Cup Measurement

A hemicircumference measurement[18] will be taken at Baseline to evaluate Inclusion/Exclusion criteria. The hemicircumference (HC) is measured across the maximum projection of the breast from the medial inflection point to the lateral inflection point where the breast creates a crease in the skin when the breast is displaced or pushed medially or laterally[18]. Breast cup size will be determined from the national cohort average HC[18]:

- Cup A – up to 17.8cm
- Cup B – up to 20.0cm
- Cup C – up to 21.5cm
- Cup D+ - over 21.6cm.

5. SUBJECT ENROLLMENT AND WITHDRAWAL

5.1 Study Population

The study population will consist of females between 18 and 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 EC. Each Informed Consent Form will include the elements required by FDA regulations in 21 CFR Part 50.

Consent forms will be EC-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 EC-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.

5.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study device, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study procedure.

5.1.2 Pre-treatment Recruiting/Screening

Subjects will be recruited from the study site's patient database and screened. Study site personnel will explain the design and purpose of the study to potential study subjects. Subjects interested in participating and who may qualify 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:

- Female subjects, ages 18 – 75 years old.
- ASA Physical Status Classification System Class I and Class II subjects.
- Breast Ptosis Class II and Class III as per the Eyck et al, Rainbow Scale for Assessing Breast Ptosis[14].
- Breast Cup Size A and Size B[18].
- 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.
- Breast ptosis Class IV or more as per the Eyck et al, Rainbow Scale for Assessing Breast Ptosis[14].
- Breast Cup Size C, Size D or larger[18].
- Prior surgery or procedure in the breast area (i.e. implants, skin tightening procedures, breast reduction, etc.).
- 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.
- Previous treatment in the study treatment area.
- 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 30, 90, and 180-day visits. The small stipend will be outlined in the site specific ICF and approved by the EC 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 EC 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 EC, and regulatory authorities of the termination or suspension of the study, as well as provide reasons for the action.

6. STUDY DEVICE

EU Marked 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 investigational 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. 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). Breast ultrasound must be obtained prior to study procedure for females under 40 years old. Breast ultrasound and mammogram must be obtained prior to study procedure for females 40 years old and above.

Table 6 illustrates study procedures that will occur at each visit.

The following pre-treatment assessments will be performed:

- ASA Physical Status
- 2D photographic images will be captured.
- Urine pregnancy test (for females of childbearing potential).
- Breast ultrasound and mammogram (for females 40 years old and above).
- Brief medical history and physical exam per the Investigator's stand of care.
- Breast cup measurement[18].
- Morphometric breast measurements.
- Breast-Q.
- Ptosis Classification.

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.

Pre-procedure preparations will be performed as per the investigator's standard practice of care.

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).

All study subjects will be treated with the Renuvion APR Device. The treatment area is defined as superior most not to exceed a horizontal line from the superior aspect of the axilla to the midline; inferior most not to cross the junction of the breast with the abdomen (inframammary fold). Lateral border to the outermost curvature of the breast or a vertical line drawn from the preaxillary line to the IMF; medial most to the innermost curvature of the breast of to 1 cm lateral to the sternal midline. The procedure will be in the intradermal and subdermal planes in the upper breast area, without penetrating the breast gland.

After undermining, the Renuvion APR device treatment will be performed using up to 6 retrograde or 3 antegrade/retrograde treatment passes with settings of 60- 70% power and 1.5 LPM of helium flow with an activation speed of approximately 1-3 cm/s. A minimum of 2 incision sites will be used for the treatment that are well-hidden in the areola border (approximately 3 and 9 o'clock positions) and pre-axillary fold or in the inframammary fold on the lateral and medial sides of each breast. The study procedure will be in the intradermal and subdermal planes in the upper breast area, without penetrating the breast gland while using a crosshatching pattern.

During the procedure, fat transfer and any other procedure outside of the study specified procedure is not allowed.

7.3 Follow-up Procedures

7.3.1 Immediately Post-Procedure

Endermologie is not allowed post-procedure for the duration of the study. All subjects will be required to wear standard compression vest for 2-4 weeks. Taping is allowed post-procedure at investigator's discretion.

7.3.2 Post-Procedure Care Instructions

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.

7.3.3 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:

- 30 (±7) days,
- 90 (±10) days, and
- 180 (±15) days.

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

Due to the challenges of COVID-19, if a subject is unable to return to the office for an in-person visit, follow-up visits will be conducted virtually. If a visit is completed virtually, missing assessments such as photographs will be documented as a protocol deviation specifically noting COVID-19. Outside of photographs, study investigators and study staff will ensure all other assessments related to each follow-up visit are completed virtually if the visit is done virtually. For virtual visits, the investigator and/or study staff completing the visit and assessments will be identified on the case report form; as well, the manner in which the visit was completed will also be 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.

TABLE 6: STUDY REQUIRED PROCEDURES

	Baseline/ Pre-Procedure Screening[1]	Procedure (Day 0)	30 Days 23-37 days	90 Days 80-100 days	180 Days 165-195 days
Informed Consent	X				
Assess Inclusion/Exclusion Criteria	X	As Needed			
Urine Pregnancy Test[2]	X	X			
Medical History	X				
General Physical Exam	X				
Ultrasound and Mammogram[7]	X				
Review Medications	X	X	X	X	X
2D Photographic Images[3]	X	X	X	X	X
Ptosis Classification	X				X
Morphometric breast measurements	X		X	X	X
Breast-Q	X				X
Numeric Rating Scale (11-point NRS) [4]		X[5]	X	X	X
Study Procedure		X			
Adverse Event Assessment		X	X	X	X
Global Aesthetic Improvement Scale (GAIS)[6]			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 if screening and procedure are not performed on the same day).

[3] 2D-digital photographs will be taken and labeled according to Photography Instructions. Standard positioning and lighting will be used for all photographs.

[4] To be completed by the study subject on a day of the procedure (prior to the procedure and immediately following the procedure) and at all follow-up visits.

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

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

[7] Prior to any breast procedure, ultrasound required for female patients below age 40; ultrasound and mammogram required for female patients aged 40 and above.

7.4 Subject Randomization and Treatment Group Assignment

Subjects are not randomized in this study. They will all be treated using the same treatment approach (see Section 5.1 for Study Treatment details).

7.5 Study Schedule

7.5.1 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).

7.5.2 Baseline Assessment

- Obtain protocol-required baseline measures
- Document medical history.
- Obtain pregnancy screen (if applicable).
- Obtain ultrasound and mammogram, as applicable.
- Perform baseline photography if screening images were not acceptable.
- Document concurrent medications.
- Obtain height and weight.

7.5.3 Procedure 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 post-treatment instructions.

7.5.4 Follow-up

Subjects will be asked to return to the clinic for in-person follow-up visits at 30, 90, and 180-days post-treatment. At all visits, subjects will be assessed for safety and efficacy, standardized images will be taken, adverse events and protocol deviations will be assessed. At 30, 90, and 180-days post procedure study outcome measures (GAIS, and Morphometric breast measurements) 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 and Breast-Q.

7.5.5 Safety Assessments

Assess for adverse events immediately post-treatment and at all follow-up visits.

7.5.6 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.

7.5.7 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 or Zoom 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 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.

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 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 Investigational Device

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 30 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.

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.

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 investigate. 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 EC according to the EU 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 EC 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 ECs 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 EC according to the EC 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 EC/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 **Section 8** of this protocol. In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a severe burn (anticipated or unanticipated), a higher than anticipated rate for any component of the safety measures, device failures resulting in Adverse Events, or unexpected SAEs. Enrollment and treatment would be suspended during root cause investigation to determine the cause of the respective AE.

9. 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). Details of clinical site monitoring are documented in the Study-specific Monitoring Plan (SMP), a separate document which documents in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level ofdetail monitoring will be performed, and the distribution of monitoring reports.

10. STATISTICAL METHODOLOGY

10.1 Statistical and Analytical Plans

For the purposes of this study, descriptive statistics will be performed.

10.2 Sample Size

The study will include up to 15 treated subjects from a single EU site.

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 and in compliance with the Declaration of Helsinki, Council for International Organizations of Medical Science (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), and EU MDR for protection of human subjects.

13.2 Ethics Committee Review Board

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

The investigator is responsible for providing the appropriate reports to its reviewing EC and as required by EU MDR during the course of the clinical study. These reports will include:

- Informing the EC 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 EC.

The EC 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 and 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.

Data management and oversight is the responsibility of the Sponsor. 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 EC overseeing the conduct of this study indicating that the EC has reviewed and approved this investigational plan.
- A copy of the EC-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 EC 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.
- 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 EC of a subject death as specified by the EC.
- 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 EC 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 EC 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 EC at regular intervals and at least on an annual basis.
- The investigator will notify the Sponsor and reviewing EC 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 EC 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 EC within three months after termination or completion of the study.
- The investigator will provide any other information upon the request of an EC, EMA, 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 EC 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 breast ptosis, 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, EC 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 EC, 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 EC 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 EC identified with this responsibility. Except for “administrative amendments”, investigators must await EC 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 EC, 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

1. Feldman LS, Fuchshuber PR, Jones DB. The SAGES Manual on the Fundamental Use of Surgical Energy (FUSE). Springer Science+Business Media, LLC. 2012.
2. Goldberg SN, Gazelle GS, Halpern EF, Rittman WJ, Mueller PR, Rosenthal DI. Radiofrequency tissue ablation: importance of local temperature along the electrode tip exposure in determining lesion shape and size. Acad Radiol. 1996;3:212-8.
3. Thomsen S. Pathologic analysis of photothermal and photomechanical effects of laser-tissue interactions. Photochem Photobiol. 1991;53:825-35.
4. Ross EV, McKinlay JR, Anderson RR. Why does carbon dioxide resurfacing work? A review. Arch Dermatol 1999;135(4):444-454.
5. Gardner ES, Reinisch L, Stricklin GP, Ellis DL. In vitro changes in non-facial human skin following CO2 laser resurfacing: a comparison study. Lasers Surg Med 1996;19(4):379-387.
6. Doshi SN, Alster TS. Combination radiofrequency and diode laser for treatment of facial rhytides and skin laxity. Cosmet Laser Ther 2005;7:11-15.
7. Fatemi A, Weiss MA, Weiss RA. Short-term histologic effects of nonablative resurfacing: results with a dynamically cooled millisecond-domain 1320nm Nd:YAG laser. Dermatol Surg 2002;28(2):172-176.
8. Mayoral FA. Skin tightening with a combined unipolar and bipolar radiofrequency device. J Drugs Dermatol 2007;6(2):212-215.
9. Alster TS, Doshi SN, Hpping SB. Combination surgical lifting with ablative laser skin resurfacing of facial skin: a retrospective analysis. Dermatol Surg 2004;30(9):1191-1195.
10. Zelickson B, Kist D, Bernstein E, Brown DB, Ksenzenko S, Burns J, Kilmer S, Mehregan D, Pope K. Histological and ultrastructural evaluation of the effects of a radiofrequency-based nonablative dermal remodeling device: a pilot study. Arch Dermatol 2004;140:204-209.
11. Hsu T, Kaminer M. The use of nonablative radiofrequency technology to tighten the lower face and neck. Semin Cutan Med Surg 2003;22:115-123.
12. Zhang S, Duan E. Fighting against Skin Aging: The Way from Bench to Bedside. *Cell Transplant*. 2018;27(5):729-738. doi:10.1177/0963689717725755
13. Ramanadham SR, Rose Johnson A. Breast Lift with and without Implant: A Synopsis and Primer for the Plastic Surgeon. Plast Reconstr Surg Glob Open. 2020 Oct 28;8(10):e3057. doi: 10.1097/GOX.0000000000003057. PMID: 33173660; PMCID: PMC7647657.
14. Eyck BM, van Dongen JA, Athanassopoulos T, Bastos Martins J, Stevens HP. The Rainbow Scale for Assessing Breast Ptosis: Validation of Three Different Views. Aesthet Surg J. 2016 Oct;36(9):1010-6. doi: 10.1093/asj/sjw129. Epub 2016 Aug 2. PMID: 27485092.
15. Brown T. An Analysis of Ptosis following Subfascial Breast Augmentation: Calculations That Explain Dogma. Plast Reconstr Surg. 2021 Nov 1;148(5):993-1004. doi: 10.1097/PRS.0000000000008477. PMID: 34529594.
16. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg. 2003 Jun;29(6):588-95. doi: 10.1046/j.1524-4725.2003.29150.x. PMID: 12786700.
17. Pain: clinical manual for nursing practice Pain: clinical manual for nursing practice Margo McCaffery Alexander Beebe Mosby Yearbook UK £17.25 0 7234 1992 2. Nurs Stand. 1994 Dec 7;9(11):55. doi: 10.7748/ns.9.11.55.s69. PMID: 27527475.
18. Bengtson BP, Glicksman CA. The Standardization of Bra Cup Measurements: Redefining Bra Sizing Language. Clin Plast Surg. 2015 Oct;42(4):405-11. doi: 10.1016/j.cps.2015.06.002. Epub 2015 Aug 13. PMID: 26408432.

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 the laxity or sagginess of your breasts?
   - ☐ YES →
     - ☐ Less sagging breasts
     - ☐ Breasts look higher on the chest
     - ☐ Nipple placement is improved
     - ☐ Breasts appear more youthful
     - ☐ Other: _____
   - ☐ NO

2. How would you characterize your satisfaction with the treatment?
   - ☐ Very Satisfied
   - ☐ Satisfied
   - ☐ Slightly Satisfied
   - ☐ Neither Satisfied nor 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-1: BREAST Q™ - AUGMENTATION MODULE (PRE- AND POSTOPERATIVE) VERSION 2.0: PSYCHOSOCIAL WELL-BEING

With your breasts in mind, in the past week, how often have you felt:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Confident in a social setting?	1	2	3	4	5
b.	Good about yourself?	1	2	3	4	5
c.	Confident in your clothes?	1	2	3	4	5
d.	Of equal worth to other women?	1	2	3	4	5
e.	Attractive?	1	2	3	4	5
f.	Accepting of your body?	1	2	3	4	5
g.	Self-assured?	1	2	3	4	5
h.	Confident about your body?	1	2	3	4	5
i.	Self-confident?	1	2	3	4	5

APPENDIX B-2: BREAST Q™ - AUGMENTATION MODULE (PRE- AND POSTOPERATIVE) VERSION 2.0: SEXUAL WELL-BEING

Thinking of your sexuality, how often do you generally feel:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
j.	Sexually attractive in your clothes?	1	2	3	4	5
k.	Comfortable/at ease during sexual activity?	1	2	3	4	5
l.	Confident sexually?	1	2	3	4	5
m.	Sexy when unclothed?	1	2	3	4	5
n.	Confident sexually about how your breasts look when unclothed?	1	2	3	4	5

Note to Investigators: This scale can be used independently of the other scales. The following statement can be added to the stem to provide an opportunity for the patient to decline completing this scale. 'The following questions ask about your sexual well-being. If you are uncomfortable answering these questions or do not feel that they apply to you, please check the box and skip the questions that follow.'

APPENDIX C: PROTOCOL REVISION LOG

TABLE 7: PROTOCOL REVISION LOG

VERSION	DATE	SIGNIFICANT REVISIONS
1.0	21APR2022	Initial release for EC Submission
2.0	23SEP2022	• Breast ultrasound must be obtained prior to study procedure for females under 40 years old. Breast ultrasound and mammogram must be obtained prior to study procedure for females 40 years old and above.