CONtrolled **F**ocal **Fi**brous Band **R**elease **M**ethod Study

(CONFFIRM Study)

Abbreviated Protocol

Protocol Version Number: CP-10472, V6

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Sponsored by: Revelle Aesthetics Inc., (Formerly NC8, Inc.)
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1 PROTOCOL SYNOPSIS

Title	Controlled Focal Fibrous Band Release Method
Short Title	CONFFIRM
IDE No.	G200312
Study Device	Avéli (formerly Deployable Hook)
Intended Use	The intended use of the subject device is to separate tissue (fibrous septa) and provide transillumination for anatomical navigation.
Proposed Indications for Use	Avéli is indicated for temporary reduction in the appearance of cellulite in the buttocks and thigh areas of adult females as supported by clinical data demonstrating benefits through three months of observation.
Study Design	Single arm, multicenter, open label pivotal study
Study Objective	Demonstrate safety and effectiveness of the deployable hook in reducing the appearance of cellulite
Study Duration	1-year participant follow-up
Number of Sites	7 sites in United States and 2 sites in Australia
Enrollment	74 participants, including 6 roll-in patients
Primary Effectiveness Endpoint	Mean change (improvement) from baseline in the Cellulite Severity Scale (CSS) [1] is ≥1 point at 3 months.
Primary Safety Measure	Absence of device related Serious Adverse Events (SAEs) directly attributable to the device at 30 days.

[1] CSS = CSS-A (Number of Evident Depressions) + CSS-B (Average Depth of Depressions) – 1

Secondary Inferential Effectiveness Endpoints	• The CSS score at 3 months. A participant is considered a responder if the 3 month CSS score has improved by at least 1 point from the baseline CSS score. • The GAIS score at 3 months as determined by blinded and independent evaluators. A participant is considered improved if the GAIS assessment is improved (1), much improved (2) or very much improved (3). • The patient satisfaction assessment measured at 3 months. Patient satisfaction is collected using an evenly balanced scale with 5 categories: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied. The general "Satisfied" category is defined as those that indicated they were satisfied or very satisfied with their outcome.

2 STUDY POPULATION

2.1 INCLUSION CRITERIA

Participants eligible for inclusion in this study must fulfill the following criteria:

1. Female age 21 to 55 years
2. Moderate to severe cellulite in the thighs and/or buttocks[2], with a minimum of 5 depressions of moderate (or more severe) depth
3. Cellulite Severity Score (CSS) ≥ 3
4. Will commit to not trying any other cellulite treatments through 12-month follow-up
5. Ability and willingness to provide written informed consent in English
6. Negative urine pregnancy test

2.2 EXCLUSION CRITERIA

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

1. In the last 12 months, underwent a cellulite procedure on the buttocks and/or thighs
2. Previous liposuction on the buttocks and/or thighs
3. Intends to lose greater than 10% of body weight during study follow-up
4. Greater than 10% increase or decrease in body weight within the last six (6) months or any history of weight loss greater than 60 kg/132 lb.
5. Physician assessed severe skin laxity, flaccidity, and/or sagging in targeted regions.
6. Has taken any of the following within 14 days of study procedure:
    a. NSAIDs (aspirin, ibuprofen, naproxen); or,
    b. Vitamin E, herbal teas or dietary supplements (e.g. Gingko Biloba, Willow Bark)
7. Intends to take the following medications within 14 days after procedure
    a. NSAIDs (aspirin, ibuprofen, naproxen); or,
    b. Vitamin E, herbal teas or dietary supplements (e.g. Gingko Biloba, Willow Bark)
8. Known clotting defects, bleeding disorders, or severe anemia (≥ Grade 3, NCI[3])
9. Active dermatologic condition including rash, eczema, psoriasis, or skin cancer in target regions
10. BMI ≥30.0
11. Evidence of an active infection or fever greater than 38°C/100.4°F on day of index procedure.
12. Current or recent smoker, or use of nicotine (within 6 months)
13. History of cardiopathy, hypertension, diabetes or hypoglycemia, or pneumopathy

[2] Participants can be treated unilaterally or bilaterally
[3] ≤ 7.9 g/dL hemoglobin

14. History of peripheral vascular disease, large varicose veins, pedal edema, reduced lower extremity pulses, personal history of connective tissue disease, or family history of Ehlers Danlos disease
15. Planning to get pregnant in next year, or currently pregnant or breastfeeding
16. Has atrophic scars, or a history of atrophic scars or keloids
17. Any participant who is currently participating or considering participation in any other research of an investigational drug or device which may overlap study follow-up
18. Any condition(s) that in the Investigator's opinion, might indicate the participant to be unsuitable for the study, such as co-existing psychiatric illness.
19. Unable to complete data entry into patient health questionnaires due to unwillingness, no computer or internet ready device, or, cannot gain access to internet, or, does not speak English.

3 STUDY PROCEDURES

3.1 SCHEDULE OF EVENTS

The summary of required visits and testing is provided in **Table 1.**

Table 1 Schedule of Events

Protocol Requirements	Screening / Baseline	Pre-Procedure	Procedure	24-hours	7 Days	1 Month[4]	3 Months[5]	6 Months	12 months
		Day 0	Day 0	18-48 hours Remote	± 3 days Remote or Clinic	+ 2 weeks Clinic	-2 weeks-+ 4 weeks Clinic	± 4 weeks Clinic	± 4 weeks Clinic
Informed Consent[6]	X								
Demographics	X								
Inclusion/Exclusion Criteria	X	X							
Medical and surgical history	X								
BMI	X					X	X	X	X
Participant Reported Questionnaires[7]:									
Procedure Goals	X						X	X	X
Recovery[8]				X	If indicated	If indicated	If indicated	If indicated	If indicated
Discomfort and Soreness, Pain VAS[9]			X[10]	X	X	X	X	If indicated	If indicated
QOL and Satisfaction							X	X	X
Participant Symptom Diary[11]				X	X	X			

[4] 30 days is also referred to as 1-month visit
[5] For purposes of scheduling, the protocol definition of a month is 30 days. Week refers to 7 days.
[6] Prior to any study specific procedures; participant may need to be re-consented if protocol is amended.
[7] Participants should complete via their private ePRO login with the exception of Pain VAS at procedure and Discomfort, Soreness Pain VAS questionnaires if indicated after 3M visit.
[8] Administered until participant returns to normal activities.
[9] Daily completion of Discomfort, Soreness and Pain VAS through 7 days post-procedure.
[10] Only VAS Numeric Pain Distress Scale administered during and after the procedure (before discharge).
[11] Participants to complete weekly, four (4) times through 28 days post-procedure.

Protocol Requirements	**Screening / Baseline**	**Pre-Procedure**	**Procedure**	**24-hours**	**7 Days**	**1 Month[4]**	**3 Months[5]**	**6 Months**	**12 months**
		Day 0	**Day 0**	**18-48 hours Remote**	**± 3 days Remote or Clinic**	**+ 2 weeks Clinic**	**-2 weeks-+ 4 weeks Clinic**	**± 4 weeks Clinic**	**± 4 weeks Clinic**
Physical Exam[12]	X								
Standard Photography	If done				If Clinic[13]				
Study Photography		X[14]				X	X	X	X
Marking the insertion sites and depressions to be treated		X							
Pregnancy test[15]		X							
Vitals		X							
Deployable Hook Procedure			X						
Con. Medications/ Treatments	Captured and Updated From -30 days to Study Exit								
Adverse Event[16] Assessment			Monitored throughout study						
Study Exit									X[17]
Independent Evaluators									
CSS A and B							X	X	X
Blinded 'After' Assessment							X	X	X
GAIS							X	X	X

[12] Includes physical examination on target areas for severity assessments in laxity and depressions, and exclusionary abnormalities. In follow-up, this activity is covered under AE assessment.

[13] If visit done at clinic, photos per the clinic standard of care should be captured

[14] Must be done before and after markings and always before the procedure

[15] Required only for fertile, pre-menopausal women.

[16] Adverse Event collection starts when the Deployable Hook procedure is initiated. At each visit, ongoing AEs should be assessed along with participant interview/examination for potential new AEs

[17] At completion of 1 year, or earlier if participant withdrawn

4 QUESTIONNAIRE CATEGORIES

The set of participant questionnaires developed for this study address a range of clinically important issues (**Table 2**) including behavioral/perception impact, procedure and recovery experience, along with cellulite treatment results satisfaction and expectations. The time to complete the questionnaires is <20 minutes.

Table 2 Participant Questionnaire Concepts

Concept	Time to complete	When to complete
1. Procedure objectives /goals	<5 minutes	Baseline, 3, 6, and 12 months
2. Recovery duration	1 minute	Every visit until return to pre-procedure activity is reported
3. Soreness/discomfort in recovery	1 minute	Daily for 7 days post-procedure; 30 day, 3 month, and thereafter will be administered by site if indicated*
4. VAS Numerical Pain Distress Scale	1 minute	During and after the procedure (before discharge) and daily for 7 days post-procedure; 30 day, 3 month, and thereafter will be administered by site if indicated*
5. Behavioral impact of cellulite	<5 minutes	3, 6 and 12 months
6. Outcome satisfaction and procedure experience	1 minute	3, 6, and 12 months
7. Participant symptom diary	3 minutes	Once a week for the first 4 weeks after index procedure.
*** Administered by study personnel, will not be in ePRO**		

4.1 MEDICAL PHOTOGRAPHY

Digital photography will be utilized in the assessment of the primary endpoint and other efficacy measurements at the intervals outlined in **Table 1**. The evaluations will occur in advance of each planned interim analysis as outlined in **Table 3**, and will follow the order outlined to ensure no pre-mature unblinding of the before/after that is required for the GAIS evaluation.

The medical photography which the independent evaluators will use, with a prescribed methodology, is distinguished here with name “Study Photography”, is described below.

Photographs captured outside of the study photography protocol, using methods normally used if not in a trial, will be included in the study dataset, but not utilized for endpoints, and will be referred to as "Standard photography".

4.1.1 Study Photography

The study endpoint relies on quality and consistent imaging. As such, it is imperative the images are taken under strict, standardized environments with only qualified photographers that are trained to the same methods. The Sponsor will ensure photographers are available for each site throughout the study and, if necessary, provide a contracted medical photographer. A chief photographer will be identified to develop and conduct training for all study site photographers. The training manual will outline the specific set-up including equipment, lighting, participant angles, and camera positioning.

Participants will be given reminders to wear loose fitting clothes without seams on the buttock or posterior thigh portions of the clothes before each required study photography visit and to prepare to stand until compression lines disappear, if present.

Prior to uploading images into the study database, the image metadata will be modified to include the participant ID and any date, location. PHI will be redacted.

For each photo session, the participant will stand and wear the provided standardized photographic garment as described in the CONFFIRM imaging protocol. The participant will be instructed to relax muscles and stand at ease.

All study photography from this study are the property of the Sponsor and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by the Sponsor.

4.2 INDEPENDENT IMAGE EVALUATION

4.2.1 Selection and Qualification of Evaluators

The primary endpoint and other effectiveness outcomes involving study photography will be independently evaluated by three (3) physicians with medical aesthetics specialty, cellulite or body contouring experience. The evaluators will not participate in the study, will not be on staff of any CONFFIRM study sites, and will have no financial interest in study sponsor. The panel of evaluators will be selected by a third party. In addition to meeting the qualifications criteria, each must have the ability to pass the initial Cellulite Severity Scoring (CSS) post-training test.

The following will not be disclosed to the evaluators:

1. Study device
2. Site names
3. Participant information

4.2.2 Frequency and Order of Evaluations

The evaluations will occur in advance of each planned interim analysis as outlined in **Table 3** and will follow the order outlined to ensure no pre-mature unblinding of the before/after that is required for the GAIS evaluation**.**

Table 3 Independent Image Evaluation Scope

Evaluation session number	Assessment type	Visit Time Points	Blinded
#1, at 3-month analysis	CSS ID of BL	Baseline and 30-day Baseline and 3-month	Yes, time point redacted
#1, at 3-month analysis*, after CSS*	GAIS	Baseline and 30-day Baseline and 3-month	No, improvement intentionally assessed
#2, at 6-month analysis	CSS ID of BL	Baseline and 6-month	Yes, time point redacted
#2, at 6-month analysis, *after CSS*	GAIS	Baseline and 6-month	No, improvement intentionally assessed
#3, at 12-month analysis	CSS ID of BL	Baseline and 12-month	Yes, time point redacted
#3, at 12-month analysis, *after CSS*	GAIS	Baseline and 12-month	No, improvement intentionally assessed

4.2.3 Study Image Evaluation

At study photography visits, each participant will be photographed per the study photography manual to generate a minimum of three (3) images from a minimum of three (3) different angles (Section 4.1). The images for each participant will be available for the evaluator to assess per visit. The CONFFIRM effectiveness outcomes are specific to the treated regions only, therefore, scoring will be considered on a participant level, but include scoring of the treated regions only. The treated regions will be disclosed to the evaluator by sextant (right buttock, right posterior thigh, right lateral thigh, left buttock, left posterior thigh, left lateral thigh) as well as a supplemental image set with an outline around the treated region per sextant. The training will also mimic this approach.

Evaluators will always be blinded to any participant ID, and for the CSS, the evaluator will not know which of the two (2) sets of images is before or after the index procedure. To further reduce bias, images will be scored under a different photo ID to ensure blinding is maintained. Evaluators will also be presented with two (2) sets of images where the set of three (3) angles of the same pre-treatment visit and three (3) angles of the post-treatment visit in a randomly assigned order (e.g., 3 pre-images on top of screen, 3 post images on bottom of screen or vice versa). Evaluators will be asked to identify which image is before and after the index procedure.

4.2.4 Blinding plan – unblinding plan

When assigning the CSS, the evaluators will be blind to the image time point and therefore, will not know whether the image is prior to or post-procedure. The evaluators will not know which image is baseline or follow-up and will be asked to identify the baseline.

Once the CSS and baseline image estimates are completed, the image pairs will then be presented with the baseline and follow-up known for the GAIS in the unblinded assessment.

4.2.5 Cellulite Severity Score (CSS)

Severity scoring by the independent, blinded assessors	
PART A- Number of evident depressions	
0	None
1	Mild (≤4 depressions)
2	Moderate (5 to 9 depressions)
3	Severe (≥ 10 depressions)
PART B – Average depth of depressions	
0	None
1	Mild (1-2 mm)
2	Moderate (3-4 mm)
3	Severe (≥5 mm)
TOTAL CSS SCORE	= (PART A + PART B) – 1
Note: If both CSS A and CSS B have classifications of 0, the CSS total score will be 0.	

4.2.6 Global Aesthetic Improvement Scale (GAIS) Evaluation

The evaluators will rate the overall improvement on the follow-up image according to the GAIS, per the scale outlined below.

Table 4 GAIS Categories

Rating	Assessment	Description
-3	Very much worse	The treated area appearance is obviously worse than before procedure
-2	Much Worse	The treated area appearance is markedly (or significantly) worse than before procedure
-1	Worsened	The treated area appearance is slightly worse than before procedure
0	Unaltered (no change)	The treated area appearance is essentially the same

Rating	Assessment	Description
+1	Improved	Noticeable improvement in appearance of the treated areas, but subtle in magnitude
+2	Much improved	Marked or significant improvement in appearance in the treated areas
+3	Very much improved	Optimal cosmetic result in the treated areas for this subject. No additional treatment is indicated.

5 CLINICAL EVENTS

At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this protocol, an adverse event is any undesirable medical occurrence in a device user or participant. This definition does not depend on a causal relationship with the device or the protocol requirements. Adverse events reporting will begin at the time the deployable hook procedure is initiated and through participant exit. An adverse event eCRF will be completed for each diagnosed adverse event and followed through resolution or study exit.

5.1 ADVERSE EVENT TYPES AND DEFINITIONS

5.1.1 Adverse Event

For the purpose of this protocol, to simplify across USA and Australia, an adverse event will be defined broadly as any undesirable medical occurrence in a device user or participant.

Only procedure-emergent adverse events will be captured. Therefore, all adverse events or pre-existing events that worsen in severity will only be captured after the index procedure.

5.1.2 Serious Adverse Events (SAEs)

An adverse event that led to any of the following:

a) Death
b) Serious deterioration in the health of the participant, users, or other persons as defined by one or more of the following:
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function including chronic diseases, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
c) Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

5.1.3 Anticipated Adverse Events

The anticipated risks associated with body contouring procedures in general are listed in **Table 5.** There are no additional unique risks associated with this procedure. The list covers the scope of risks anticipated for device use and procedure. Therefore, these could potentially be associated with anesthesia infiltration, subcutaneous tissue release, liposuction, cellulite reduction procedures and other methods of body contouring in general.

Table 5 Anticipated Adverse Effects

Anticipated Adverse Effects List	
Abscess	Inflammation / generalized redness
Anetoderma	Nausea/vomiting
Anxiety (nervousness, apprehension)	Numbness, tingling, or sensitivity change
Blanching (generalized whiteness)	Red Spots (from needle punctures related to anesthesia delivery)
Bleeding	Redness, erythema, or rash
Blurred or double vision	Scarring or keloid formation
Dizziness, drowsiness, confusion, fainting	Sensations of heat or cold
Ecchymosis/bruising	Seroma
Fluid extravasation (leakage of fluid)	Skin necrosis
Hematoma or hard bruise	Skin surface convexity, depression or other irregularity
Hemosiderosis	Soreness or discomfort (pain)
Hyperpigmentation	Swelling/edema
Hypopigmentation	Tinnitus
Induration, fibrosis	Toxic, allergic, or other reaction from the injected anesthetic
Infection	-----

5.1.4 Unanticipated Adverse Events

5.1.4.1 Unanticipated Adverse Device Effects (UADEs) For sites in the United States

Any serious adverse effect on health or safety, 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 application; or any other unanticipated serious

problem associated with a device that relates to the rights, safety, or welfare of participants per 21 CFR 812.3.

5.1.5 Adverse Device Effect (ADE)

This type of AE is specifically related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

It is important to point out the difference between a device related AE and an ADE. A device related AE could also qualify as an ADE, with ADE being a subset of device related AEs. For example, mild to moderate bruising is a device related AE, but is a part of a normal recovery course for a cellulite procedure.

5.2 NOT CONSIDERED ADVERSE EVENT

- Pre-existing Conditions: Any condition that is recorded in medical records and diagnosed prior to the deployable hook procedure, is considered a pre-existing condition. This condition is not considered an adverse event unless there is a clinically significant worsening of that condition in terms of nature, severity, or degree of incidence.
- Device Deficiencies or Malfunctions: An undesirable technical event during procedure is not an adverse event in itself. However, if a device deficiency or malfunction leads to a medically undesirable situation, then that event must be reported on an Adverse Event Form and is an Adverse Device Effect (ADE).
- Lack of improvement of cellulite is not considered an adverse event.
- Pre-planned hospitalization for any pre-existing condition.
- Any procedure the participant undergoes after the deployable hook is not considered an adverse event, however, the condition leading to the procedure is an adverse event.

5.3 ADVERSE EVENT ASSESSMENT

5.3.1 Adverse Event Evaluation and Categorization

All AEs will be assessed by the investigator(s). The study will use the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 for AE terminology and severity grading. In addition, the investigator will assess relatedness (device or procedure, none). Guidelines for Investigators follow.

Table 6 CTCAE Guidance and Database Access

Search database	https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx
Printable Quick Reference	https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ CTCAE_v5_Quick_Reference_8.5x11.pdf

Clean, Tracked and Mapping Document	Will be provided by Sponsor in study files

5.3.2 Severity (Grades)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Table 7 CTCAE Library Example

CTCAE TERM	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective invasive intervention indicated	-	-
Bruising	Localized or in a dependent area	Generalized	-	-	-
Pain of skin (***characterized by a sensation of marked discomfort in the skin***)	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-

5.3.3 Determination of the Relationship (Causality)

The Investigator, on the basis of his or her clinical judgment, should determine whether there is a reasonable possibility the study device or procedure caused or contributed to the event. Guidelines to assess AE/SAE/UADE are provided below:

> **Not related:** The adverse event is determined to be solely caused by the underlying disease, disorder or condition of the participant, or attributable solely to other extraneous causes (unrelated to the device, device malfunction, or the procedure).

Unlikely related: The adverse event has onset within a clinically relevant temporal relationship to exposure to the device or procedure and is plausibly at least partially caused by or aggravated by the use of the device, device malfunction, or the procedure. It must also meet one of the following criteria: (1) follows a known or easily foreseen pattern of response to device use or procedure and (2) is not fully attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes.

Possibly related: The adverse event has onset within a clinically relevant temporal relationship to exposure to the device or procedure and is more likely than not to be at least partially caused by or aggravated by the use of the device, device malfunction, or the procedure. It must also meet both of the following criteria: (1) follows a known or easily foreseen pattern of response to device use or procedure; and (2) is not fully attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.

Probably/highly probably related: The adverse event is clearly caused by the use of the device, device malfunction, or the procedure. It must meet all the following criteria: (1) has a clear temporal relationship between device exposure and onset of the event; (2) follows a known pattern of response to device use or procedure; and (3) is not reasonably attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.

5.4 REPORTING REQUIREMENTS FOR SAES OR UADES

It is the responsibility of the Principal Investigator to report SAEs or UADEs to the sponsor within 24 hours. Reporting of the event to applicable regulatory bodies should occur per the established reporting criteria. For UADE reports, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event (§ 812.150(a)(1)). Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

5.5 MEDICAL TREATMENT FOR AES, SAES AND UADES

Medical treatment for adverse events during and following the study procedure will be at the discretion of the Investigator.

5.6 MEDICAL MONITOR

The Medical Monitor (independent of the study sites or Sponsor) with dermatologic or plastic surgery expertise will oversee the safety aspects of this study. Review and MedDRA coding of all AEs and assessment or identification of UADEs will be performed throughout study.

6 STATISTICAL METHODS

6.1 STATISTICAL AND ANALYTICAL PLANS

6.1.1 Analysis Cohorts

- **Modified Intent-to-Treat (mITT) Cohort:**
  The modified intent-to-treat mITTdata set will include all enrolled participants that underwent the DH procedure but exclude any roll-in[18] participants. The mITT analysis cohort will be used for all described analyses.
- **Per Protocol (PP) Cohort:**

  The PP cohort will be used as a secondary support of the primary effectiveness m-ITT analysis and may be used in exploratory analysis.

The PP analysis set will exclude participants with the following significant protocol deviations:

1) Participants with significant violations of the inclusion and exclusion criteria, including:
   - Mild cellulite
   - Impactful co-morbidity outlined in eligibility criteria
   - BMI >30.1
   - Pregnancy or weight gain/loss >10% of baseline weight
2) Participants who do not have images for primary effectiveness endpoint (missed, COVID-19, etc.)

Overall, protocol deviations for active participants will be summarized by severity (major/minor), type by visit, and by site. Any deviations or issues reported to IRB/HREC and will be described.

Roll-In and Intent-To-Treat Cohorts:

All roll-in cohort data will be summarized separately using descriptive statistics. In addition, an intent-to-treat (ITT) data set of all enrolled participants including any roll-in[19] participants that underwent the DH procedure will be analyzed to see whether there is a learning curve that effects the data.

[18] The Investigators without prior Deployable Hook experience will perform up to two (2) roll-in, or "training" procedures.

[19] The Investigators without prior Deployable Hook experience will perform up to two (2) roll-in, or "training" procedures.

6.2 SAFETY ANALYSIS

6.2.1 Primary Safety Endpoint

Safety will be demonstrated by the absence of device related Serious Adverse Events (SAEs) directly attributable to the device through 30 days post-procedure. All participants that underwent the index procedure will be included in this analysis.

6.2.2 Adverse Events

Procedure-emergent adverse events will be analyzed. All adverse events, new or worsening of pre-existing conditions, starting at the initiation of, or after, the deployable hook procedure, will be summarized. Adverse events will be coded using MedDRA and CTCAE severity grades.

Unless otherwise specified, at each level of participant summarization, a participant is counted once if she reported one or more events. Percentages will be calculated based on the number of participants.

The following specific AE summaries will be generated:

- Overall AEs by study visits, event type, relatedness, ADEs, SAEs, by CTCAE grades
- Grade 3 and higher AEs and related Grade 3 and higher AEs
- SAEs by relatedness (narratives will be provided)
- Unanticipated AEs and UADEs

6.3 PRIMARY EFFECTIVENESS ENDPOINT

6.3.1 Endpoint Definition

The primary effectiveness endpoint is the change in CSS score at 3 months from baseline. The CSS includes a 6-point (range of 0–5) **(**
Table 8) and will be determined by three (3) independent, blinded physician assessors of participant images obtained before and 3-months after treatment. For clarity, the endpoint will test the mean of the changes for each treated participant, not a 1 point change between mean score of the group at baseline versus 3 months. Success is achieved when the mean change across all treated participants is at least one point.

Long term success: The change in CSS and proportion of responders will be summarized at the 12 month visit. The 95% confidence intervals are intended to support long-term performance claims.

Table 8 Cellulite Severity Score

Severity scoring by the independent, blinded assessors	
PART A- Number of evident depressions	
0	None
1	Mild (≤4 depressions)
2	Moderate (5 to 9 depressions)
3	Severe (≥ 10 depressions)
PART B – Average depth of depressions	
0	None
1	Mild (1-2 mm)
2	Moderate (3-4 mm)
3	Severe (≥5 mm)
TOTAL CSS SCORE	=(PART A + PART B) – 1
One CSS is rendered per participant. Part A is the number of depressions across all treated regions, and Part B the average across all treated regions. This study does not prescribe if participant treated unilaterally or bilaterally.	

6.3.2 Hypothesis

Ho: $D < 1$

Ha: $D \geq 1$,

where D = reduction in the CSS score from baseline to 3 months, and 1 is the performance goal.

6.3.3 Analysis cohort

The mITT cohort will be the primary analysis, but supplemental analysis will also be performed using the PP cohort.

6.3.4 Statistical Analyses

The reduction in CSS will be calculated and descriptive statistics including mean, standard deviation, median and range will be summarized. The 2-sided 95% confidence interval for the mean reduction in CSS[20] will be calculated along with the corresponding p-value (Student's t-test).

[20] CSS = CSS-A (Number of Evident Depressions) + CSS-B (Average Depth of Depressions) – 1

6.3.5 Definition of Success

If the lower bound of the two-sided 95% confidence interval is greater than or equal to 1 then we will reject the null hypothesis and conclude the device performs effectively.

6.3.6 COVID-19 Contingency

As outlined in section Error! Reference source not found., before blinded photometric evaluation of CSS, the number of participants with images available for the 3-month endpoint will be confirmed. If the number of participants with images cannot adequately power the endpoint (N=54) due to excessive 3-month COVID 19 related missed visits, the primary endpoint time point will be changed to 6-month. Of note, the inferential secondary endpoints will similarly change to 6-month (section 6.5).

6.3.7 Determination of Sample Size

Sample size calculations were estimated using PASS 14 (Kaysville, Utah, USA), using Wilcoxon Signed Rank test for superiority by a margin (the more conservative approach compared to t-test)

Hypothesis:

- Ho: $D < 1$
- Ha: $D \geq 1$,

where D = improvement in the CSS score from baseline to 3 months, and 1 is the performance goal.

The endpoint with a sample size of 54 participants will be adequately powered with at least 90% power to test the hypothesis that the mean reduction at 3-months is equal to or greater than 1. This study's sample size will be increased by 25% for a total N of 68 to account for the potential of missed visits amid the pandemic.

6.3.8 Poolability Analysis

Analyses of the primary effectiveness endpoint will be performed to assess the comparability of study sites. Sites with fewer than 5 participants each will be pooled into a composite site.

Change in CSS will be analyzed by ANOVA to assess if the improvement in CSS differs among study sites. If the study sites have a difference ($p<0.15$), then additional analyses will be performed to explore the cause of the difference, in particular, if the differences are caused by differences in some baseline factor.

6.3.9 Covariate Adjustment and Exploration

An ANCOVA model, which allows adjusting for covariates, will be used on the 3-month endpoint to uncover important prognostic factors. If any of the following factors: age, race, baseline BMI, indicator variable of change in body weight of ±10% (compared to baseline), or, number of regions treated are not significant (p-value ≥0.10), they will be dropped from the

model. This is not intended to be the primary analysis of the 3-month endpoint, it is only an exploratory analysis that will be used to look for possible important prognostic factors. This analysis may be repeated on the change in CSS data at 6 and 12-month visits once data are complete.

6.4 HANDLING MISSING DATA

Every effort will be made to collect all data points in the study. The sponsor plans to minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of study participants, and training of participating investigators, monitors and study coordinators.

A sensitivity analysis will be performed for the primary effectiveness endpoint where a missing 3-month assessment of CSS will be replaced using the following imputations for calculating the improvement in CSS:

- Worst case (highest CSS score observed for all follow-ups available)
- Last observation carried forward (30 day or baseline assessment).
- Best case (lowest CSS score observed for all follow-ups available for a subject)

Imputations will not be made on secondary endpoint data, but all data available will be summarized.

6.5 SECONDARY EFFECTIVENESS ENDPOINTS

Descriptive statistics will be used to summarize the secondary endpoints including mean, standard deviation, median, range for continuous data and frequency and percentage for categories values.

The secondary endpoints will be split into two categories, either Inferential or simply Descriptive. The inferential secondary endpoints will be tested using the hierarchical approach of gatekeeping to ensure the overall alpha for the trial is maintained. Descriptive secondary endpoints will not have any hypothesis testing performed.

In additional to regular annual reports, there are expected to be 3 reports prepared (3-month, 6 month, final – see **Section** Error! Reference source not found.), and the first report will have the 3 month results including the primary endpoint and all inferential secondary endpoints tested. The 6 month and final reports will include 95% confidence intervals for the endpoints that were used in the primary and inferential secondary endpoints for the longer-term visits to provide support for longer-term performance of these same endpoints.

6.5.1 Hierarchical testing

If the primary endpoint passes, a subset of the secondary endpoints (inferential) will have hypothesis tests performed for potential labeling claims. These endpoints will be tested the specific order presented below. If the first secondary endpoints passes the hypothesis test (rejects the null hypothesis), then the next secondary endpoint will be tested. Testing will continue up to the point that a hypothesis test fails. Endpoints that follow will then simply use descriptive statistics and no p-values will be presented. Since this testing relies first on the primary endpoint

passing, the 6-month data will be used instead should 3-month COVID 19 related missed visits reduce the evaluable data to <54.

6.5.2 Secondary Endpoint 1 (Inferential) – CSS Responders at 3 months

Endpoint Definition: The CSS score at 3 months. A participant is considered a responder if the 3-month CSS score has improved by at least 1 point from the baseline CSS score.

Hypothesis:

Ho: p <= 60%

Ha: p > 60%,

where p=proportion of responders and 60% is the same performance goal that Cellfina used to achieve approval.

Analysis cohort: The mITT cohort.

Statistical Analyses: The count and proportion of responders will be summarized along with a exact binomial 2-sided 95% confidence interval for the proportion of responders along with a p-value.

Definition of Success: If the lower bound of the 2-sided 95% confidence interval is greater than or equal to 0.6 then we will reject the null hypothesis and declare proportion of responders are greater than 60%.

6.5.3 Power calculation: The sample size for this trial is based upon the primary endpoint. With an observed performance of 81% responder in initial pilot data and expected sample size of 54, a one-sided alpha of 0.025 and performance goal of 60%, there will be > 90% power to test this hypothesis.Secondary Endpoint 2 (Inferential) – Improvement in GAIS at 3 months

Endpoint Definition: The GAIS score at 3 months as determined by a blinded and independent evaluator. A participant is considered improved if the GAIS assessment is improved (1), much improved (2) or very much improved (3).

Hypothesis:

Ho: p <= 60%

Ha: p > 60%,

where p=proportion of Improved and 60% is an assumed acceptable performance goal for this endpoint and trial size.

Analysis cohort: The mITT cohort.

Statistical Analyses: The count and proportion of participants with GAIS evaluations of improved will be summarized along with an exact binomial 2-sided 95% confidence interval for the proportion of responders along with a p-value. Additionally, count and proportions will be summarized for each of the 7 categories of GAIS.

Definition of Success: If the lower bound of the 2-sided 95% confidence interval is greater than or equal to 0.6 then we will reject the null hypothesis and declare proportion of responders are greater than 60%.

Power calculation: The sample size for this trial is based upon the primary endpoint. With an observed performance of >95% improved in initial pilot data and expected sample size of 54, a one-sided alpha of 0.025 and performance goal of 60%, there will be > 90% power to test this hypothesis.

Long term success: The change in GAIS and proportion of responders will be summarized at the 12 month visit. The 95% confidence intervals are intended to support long-term performance claims.

6.5.4 Secondary Endpoint 3 (Inferential) – Patient Satisfaction at 3 months

Endpoint Definition: The patient satisfaction assessment measured at 3 months. Patient satisfaction is collected using an evenly balance scale with 5 categories: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied. The general "Satisfied" category is defined as those that indicated they were satisfied or very satisfied with their outcome.

Hypothesis:

Ho: $p <= 60\%$

Ha: $p > 60\%$,

where p=proportion satisfied and 60% is an assumed acceptable performance goal for this endpoint and trial size.

Analysis cohort: The mITT cohort.

Statistical Analyses: The count and proportion of participants satisfied with their outcome will be summarized along with an exact binomial 2-sided 95% confidence interval for the proportion of responders along with a p-value. Additionally, count and proportions will be summarized for each of the 5 levels of patient satisfaction.

Definition of Success: If the lower bound of the 2-sided 95% confidence interval is greater than or equal to 0.6 then we will reject the null hypothesis and declare proportion of responders are greater than 60%.

Power calculation: The sample size for this trial is based upon the primary endpoint. With an observed performance of 67% satisfied in initial pilot data and expected sample size of 54, a one-sided alpha of 0.025 and performance goal of 60%, there will be ~17% power to test this hypothesis, however it is believed performance will be better in this trial.

6.5.5 Secondary Endpoints (Descriptive)

Descriptive statistics were used to summarize other secondary endpoints including mean, standard deviation, median, range for continuous data and frequency and percentage for categories values.

6.6 ADDITIONAL OUTCOME MEASURES

6.6.1 Learning Curve Analysis

To explore the potential for possible learning curves, descriptive analyses will be made using sites with at least 5 participants enrolled (including roll-in participants). Note that if more than one investigator should be active at a site, for this analysis each investigator will be treated as a site, but it is not expected.

The following summaries will be prepared in sequentially treated participants across these sites for 1st participant, 2nd participant, 3rd participant, etc.:

- Mean Baseline CSS
- Mean Change in CSS at 3 months
- Proportion of participants with device related AE
- Proportion of participants with serious device related AE

Because multiple procedures may occur on the same day, additional descriptive analyses will summarize these same values for sequentially treated participants across these same sites for 1st procedure date, 2nd procedure date, 3rd procedure date, etc.

6.7 EXPLORATORY ANALYSIS

Additional exploratory statistical analysis may be performed including subgroup analyses and participant reported outcomes.

6.8 PARTICIPANT ACCOUNTABILITY

The disposition of participants will include the number and percentages of participants for the following categories:

- Participants who enrolled
- Participants who screen failed
- Participants who underwent the deployable hook procedure in the ITT
- Participants who are in the mITT
- Participants who are in the PP

All percentages will be based on the number of subjects who underwent the deployable hook procedure. The primary reason for screen failure and early termination will also be summarized.

The participant accountability for each study follow-up will be presented. The following categories will be included:

- Theoretical number of participants
- Active (not terminated) participants or expected
- Number of participants who completed (at least partially) the visit
- Participants included in effectiveness data
- Participants included in safety data
- Participants who missed a visit
- Participants who terminated prior to the 12-month visit

The reasons for terminating early will be listed, as will the participants and visits that were affected by COVID-19.

6.9 OTHER STUDY SUMMARIES

- Protocol Deviations
    - Minor and major deviations will be summarized together and separately
- The following will be tabulated with appropriate summary statistics:
    - Demographics/Ethnicity
    - Medical History
    - Procedural Data

6.10 DATA COLLECTION AND ELECTRONIC CASE REPORT FORM (eCRF) COMPLETION

The Investigator, or designee, will enter data from the clinic's medical records and study source worksheets into an online electronic data capture (EDC) system. The data will remain secure as study personnel will be trained to use a password protected login. Sponsor designated monitors will perform clinical monitoring, including verification of eCRFs and the source documentation.

Data entry should occur in a timely manner for accuracy, but, especially for complying with regulations if unanticipated or serious adverse event occurs (within 24 hours). If significant delays in entry occur frequently, formal corrective plan will be established.

7 INVESTIGATOR RESPONSIBILITIES

7.1 INVESTIGATOR FILES

For the study duration the Investigator will:

- maintain complete and accurate documentation, including but not limited to, medical records, study progress records, laboratory reports, CRFs,
- signed and dated informed consent forms,
- all correspondence with the IRB/HREC,
- Sponsor personnel/representatives, and other regulatory agencies,
- the protocol, and
- documentation for each deviation from the protocol,
- records of receipt, use, or disposition of each device,
- record of the exposure to the study device,
- adverse event records,
- information regarding participant discontinuation or completion of the study,
- any other supporting data, and
- any other records that FDA or local regulation requires to be maintained

7.2 INSTITUTIONAL REVIEW BOARD PROTOCOL/ HUMAN RESEARCH ETHICS COMMITTEE AND INFORMED CONSENT APPROVALS

The ICFs that are used should be in accordance with the current guidelines as outlined by local regulations (i.e.21CFR Part 50, Good Clinical Practices (GCP) guidelines and ISO 14155).

The Investigator must have a written approval from the IRB/HREC prior to recruiting participants in the study. Any materials used for recruitment, as well as any other participant facing materials such as questionnaires, must also be approved by IRB/HREC. A copy of the written approval must be provided to the study sponsor and should include the following.

- A statement of IRB/HREC approval for the proposed study at the institution
- The date the study was approved
- A statement that the informed consent document (version date referenced) has been approved (may be a separate documented letter)
- A listing of any conditions or requirements attached to the approval imposed by the IRB/HREC
- Identification of the approved Principal Investigator
- The signature of the IRB/HREC chairperson

If the Investigator or Sub-Investigator is a member of the IRB/HREC, the letter should state that he/she did not participate in the review or approval of the protocol or informed consent (may be provided under a separate letter).

Until the study is completed, the Investigator will advise their IRB/HREC of the study progress, minimally, on an annual basis. Written approval must be obtained yearly to continue the study. Any amendments to the protocol, as well as associated consent form changes and participant facing materials, will be submitted to the IRB/HREC and written approval obtained prior to implementation. Serious adverse event reports will be submitted as requested by the Sponsor and per IRB/HREC policies and regulations.

The potential participant must sign the consent form that is currently approved by the study site's IRB/HREC. Failure to provide informed consent renders the participant ineligible for the study.

7.3 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol or a failure to adhere to the IRB/HREC reporting procedures and policies.

The study sponsor reserves the right to terminate an investigator/investigational site for any of the following reasons:

- Failure to secure participant informed consent including protection of personal data prior to enrollment.
- Failure to report serious adverse device effects within 24 hours of discovery.
- Repeated investigational plan deviations.
- Repeated failure to appropriately complete case report forms.

- Failure to enroll participants within the planned enrollment period.
- Loss of or unaccounted for investigational product inventory.

7.3.1 Investigator Reporting

Deviations must be reported regardless of whether medically justifiable or taken to protect the subject in an emergency. Participant specific deviations will be reported on the Protocol Deviation eCRF. Non-subject specific deviations, (e.g. unauthorized use of a study device outside the study, unauthorized use of a study device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to directly to the study sponsor. Any serious breaches of the protocol or the conditions and principles of GCP in connection to this trial will be reported to the IRB/HREC in accordance with their reporting policies and procedures. A serious breach is likely to impact to a significant degree: (a) the safety or physical well-being of the participants of the trial; or (b) the scientific value of the trial.

All major deviations will be reported to the Sponsor within 24 hours of the Investigator becoming aware.

Protocol deviations to the inclusion/exclusion criteria and deviations that affect the primary endpoints are considered major protocol deviations. Protocol deviations that may affect the secondary endpoints are considered minor protocol deviations.

7.4 STUDY DEVICES

7.4.1 Labeling

The study sponsor will label all study devices in accordance with FDA regulations per 21CFR 812.5 and other local regulatory requirements where the study is being conducted.

7.4.2 Ordering and Storing Study Device

Study devices will be stored in a secure area, where only study personnel can access. The PI or designee will be responsible for maintaining control of and verifying each device's disposition.

7.4.3 Study Device Accountability

The Investigator shall maintain adequate records of the receipt, use, and disposition of the study device.

Study devices will only be used with this clinical investigation. The PI or an authorized designee shall keep device accountability log tracking documenting the receipt, use, return and disposal of the study devices, which shall include:

a) the date of receipt and the signature of the individual who received the product(s),

b) identification of each study device (batch number/serial number or unique code),

c) the expiry date, if applicable,

d) the date or dates of use,

e) unique participant identification number,

f) date when the study device was returned (for any reason), and

g) the date of return of unused, expired or malfunctioning study devices, if applicable.

This log must be maintained at each investigational site and must be filed in the regulatory binder. At the end of enrollment, the study sponsor or designee shall ensure that documentation of the final reconciliation of all devices is signed or initialed by the PI or authorized designee.

7.4.4 Device Disposal or Return

Devices are to be disposed of utilizing clinic specific biohazard procedures unless return is required or requested by the sponsor. Details outlining study sponsor returned goods policy will be provided in the training materials. The site will return all unused devices remaining at the end of the enrollment period.

7.5 FINANCIAL DISCLOSURE

All Investigators must provide the sponsor with documentation of financial interest related to the study sponsor. Investigators must complete and provide Financial Disclosure in compliance with 21CFR 812.43 (c) (5) to the sponsor during the approval process of the site and maintain this documentation throughout the study and for 1 year following completion of the study.

7.6 PARTICIPANT PRIVACY

The Investigator agrees to comply with all applicable local regulations relating to the privacy of participants' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 and in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which states all participants should be informed of potential uses and disclosures of their medical information for research purposes, and their rights to access information about them by covered entities. Each Investigator will follow the procedures for securing HIPAA compliance as directed by their respective IRB/HREC or Privacy Board, and to obtain written authorization to use and disclose participant information for all clinical research and research involving questioning of the participant's or participants' physician(s). Per individual site procedures, this authorization may be included as part of the participant informed consent form.

The Investigator agrees to maintain all essential study documents and source documentation, in original format, that support the data collected on the study participants in compliance with the ICH/GCP guidelines (the Investigator's File, including signed Informed Consent forms and participant-related materials) in a location that is secure and to which access can be gained if required.

Participant confidentiality will be maintained throughout the clinical investigation in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique participant identification code will be used that allows identification of all data reported for each participant. Data relating to the clinical investigation might be made available to third parties (for

example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the participant's privacy is guaranteed

8 SPONSOR RESPONSIBILITIES

8.1 GENERAL DUTIES

Prior to shipping devices, the study sponsor is responsible for selecting Investigators, obtaining and reviewing copies of IRB/HREC approvals. It is the study sponsor's responsibility to ensure that the study is conducted according to Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements, the Study Protocol, or any conditions of approval imposed by the IRB/HREC or local regulatory authorities. Additionally, the study sponsor will ensure proper clinical site monitoring, and ensure study subject informed consent is obtained.

8.2 SELECTION OF SITES AND INVESTIGATORS

The investigators have been selected because of their medical qualifications, education and training, interest in participation, ability to conduct and document the results of the study, ability to accrue participants, and expertise in the therapeutic area.

The sponsor will ascertain the suitability of the Investigator to conduct the study according to applicable guidelines and local regulations.

8.3 SITE TRAINING

The initial training of appropriate clinical site personnel to the study will be the responsibility of the study sponsor or their designee.

8.4 DEVICE TRAINING

Investigators responsible for treating participants with the deployable hook device will receive sufficient training to ensure competence in the execution of all aspects of the procedure. Training will include demonstration videos, didactic presentation, and as may include hands-on experience. Training will also include all of the elements in the Instructions for Use (IFU). Training for first use will be conducted before the first cases, and subsequent cases preceded by refresher training as necessary.

Investigators without prior deployable hook experience will perform up to two (2) training cases, depending on the Investigator comfort level. As well, these Investigators should plan at least 2 stacked cases in one day for good technique adoption.

8.5 MONITORING

8.5.1 Site Monitoring Procedures

All study monitoring activities will be managed and performed by the Sponsor or designee monitors. eCRFs will be source-document verified according to the monitoring plan. The extent, nature, and frequency of on-site visits will be based on considerations such as study objectives

and/or endpoints, study design and complexity, and enrollment rate. These tasks will be performed according to relevant SOPs and the detailed study monitoring plan. The detailed monitoring plan will describe who will conduct the monitoring and at what frequency, and distribution of monitoring reports. It will focus on preventing or mitigating non-compliance and identify risks to critical data and processes.

At regular intervals during the study, the study monitors will contact the study sites via on-site visits, video/audio calls, emails and/or letters in order to review the study progress, CRF completion and to address any concerns or questions regarding study conduct. By verifying compliance, these activities will ensure:

- The study is conducted in accordance with the study protocol, relevant Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, as well as in conjunction with 21 CFR Part 812, 50, 54, 56 and ISO 14155; Protection of Human Patients (Informed Consent) (21 CFR Part 50), Financial Disclosure by Clinical Investigators (21 CFR Part 54), Institutional Review Boards (21 CFR Part 56), Investigational Device Exemptions (21 CFR Part 812), the Declaration of Helsinki, the privacy requirements of the Health Information Portability and Accountability Act (HIPAA);
    - Adequate protection of the rights and safety of the informed patients involved in the study by thoroughly providing accurate and complete data; and
    - Quality and integrity of the data.

The frequency and scope of periodic site visits will be determined according to the site performance, enrollment, and public health emergency status. There will be remote or on-site monitoring in advance of data locks in preparation of clinical study reports.

Monitoring activities will include: review of the informed consent process and research authorization confirmation, regulatory document review, overall investigational plan adherence, GCP/ICH compliance, facility assessment, study staff assessment and additional study related functions that contribute to the safety of study Patients and the integrity of study data.

Investigators must provide adequate time and resources to comply with the study protocol and will be available to the study monitor and/or designee via telephone, and in person during site visits. The Investigator will also provide the study monitor with a suitable working environment for review of study-related documents.

8.6 ON-SITE AUDITS AND INSPECTIONS

The study sponsor, or designee, a regulatory authority, or an IRB/HREC representative may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of these audits or inspections is to examine systematically and independently all study-related activities and documents to determine whether they were conducted in accordance to the protocol, GCP, and any other applicable regulatory requirements.

In the event that an Investigator is contacted by a Regulatory Agency in relation to this study, the Investigator shall notify the study sponsor immediately.

The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by authorized regulatory representatives during the audit process. The Investigator must provide the study sponsor with copies of all correspondence that may affect the review of the current study (e.g., inspection observations) or their qualification as an Investigator in studies conducted by the study sponsor. The study sponsor will provide any needed assistance to regulatory inspections or correspondence.

8.7 PROTOCOL AMENDMENTS

Any amendments to the study protocol will be written by sponsor. Amendments cannot be implemented without prior written IRB/HREC approval and FDA approval (if required).

8.8 SUBMITTING REPORTS

The study sponsor will submit the appropriate reports identified by local regulations. This includes unanticipated adverse device effects, withdrawal of IRB approval or FDA approval, 6-month update, annual progress reports, recall information, final reports and device use without informed consent.

8.9 MAINTAINING RECORDS

The study sponsor will maintain copies of correspondence, data, shipment of devices, unanticipated adverse device effects and other records related to the clinical study. In addition, the study sponsor will maintain records related to the signed Investigator agreements according to requirements set forth by GCP.

All clinical sites in the United States will be instructed to maintain study records for at least 2 years after the study is terminated or per the requirements of the clinical investigation research agreement (as dictated by local regulations).

Study records are to be discarded only upon notification by the study sponsor unless the 15-year period has not been reached. The Investigator must contact the study sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the sponsor should be contacted if the Investigator plans to leave the investigational site.

8.10 CONFIDENTIALITY

All data and information collected during this study will be considered confidential by the study sponsor. All data used in the analysis and summary of this study will be anonymized, and without reference to specific study subject names. Access to study subject files will be limited to authorized personnel of the study sponsor, the Investigator, and research staff. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study.

9 TRIAL TERMINATION

If Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate the study should be halted or that the study site should be closed, this action

may be taken after appropriate consultation between Sponsor and Investigator. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform the IRB/HREC and provide reason(s) for the termination or suspension and the plan for continued follow-up of participants. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to potential participants or to the participants already enrolled in the study
- Submission of knowingly false information from the research facility to sponsor, study monitor, or regulatory agencies.
- Deliberate or repeated failure of the Investigator to comply with GCP (e.g., ICH guidelines, regulatory agency guidelines).
- Insufficient adherence to protocol requirements or unacceptable high rate of missing, erroneous, or improperly collected data.
- A decision from sponsor to suspend or discontinue testing evaluation or development of the product.
- Failure of the Investigator to enroll participants into the study at an acceptable rate.

10 PUBLICATION POLICY

All information and data generated in association with this study will be held in strict confidence and remains the sole property of the study sponsor. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the study sponsor.

At the conclusion of this study, a multi-center abstract reporting the primary results may be prepared by the Lead Principal Investigator and the study sponsor and/or presented in an appropriate international forum. A multi-center peer-reviewed manuscript may also be prepared for publication in a scientific journal. The publication of the principal results from any single center experience within the study will be coordinated with the study sponsor.