Information Cover Page

Zeltiq Aesthetics Protocol ZA17-005

Fat Reduction in the Submental Area – A Sequential Treatment Approach with CoolMini and KYBELLA®

Clinicaltrials.gov Identifier: NCT03510598

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FAT REDUCTION IN THE SUBMENTAL AREA – A SEQUENTIAL TREATMENT APPROACH WITH COOLMINI AND KYBELLA®

Investigational Plan

Sponsor	ZELTIQ Aesthetics, Inc., An Allergan Affiliate 4410 Rosewood Dr. Pleasanton, CA 94588
Protocol Number:	ZA17-005
Protocol Version: Protocol Date:	1.0 February 27, 2018
Product (s)	ZELTIQ CoolSculpting® System KYBELLA®
Investigator / Co-Investigators:	H. Ray Jalian, MD Rebecca Fitzgerald, MD
Study Location:	321 N. Larchmont Blvd. Suite 906 Los Angeles, CA 90004

Sponsor Contact: Allergan Medical Monitor Contact: Safety Reporting:	[redacted] [redacted] KYBELLA® [redacted] KYBELLA GRID® [redacted] CoolSculpting CoolMini [redacted]

Summary of Changes to Protocol from Previous Version

ZELTIQ Part Number	Protocol Version	Date
CS-300548	1	
	N/A	
Affected Section (s)	Summary of Revisions Made	Rationale
	N/A	
	N/A	

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with this protocol, GCP, and all applicable laws and regulations.

- Maintain all information supplied by the Sponsor, ZELTIQ Aesthetics, an Allergan affiliate, in confidence and, when this information is submitted to an Ethics Committee (EC), or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

_____	_____	_____
Investigator printed name	Signature	Date
_____	_____	_____
Co- Investigator printed name	Signature	Date

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Protocol Summary

Title	Fat Reduction in the Submental Area – A Sequential Treatment Approach with CoolMini and KYBELLA®
Design	Prospective, controlled, open-label interventional study
Purpose	Evaluate the safety and efficacy of subcutaneous fat layer reduction in the submental area using multiple therapeutic tools
Enrollment	Up to twenty (20) subjects
Clinical Site	Up to three (3) investigational sites
Subject Population	Healthy adult men and women with clearly visible fat in the submental area, rated a 4 or extreme in the CR-SMFRS, that they wish to have reduced.
Treatment	[redacted]
Primary Endpoint	• Safety endpoint: incidence of device, drug or procedure-related adverse events. • Efficacy endpoint: 1. The reduction, from baseline to final follow-up, of submental fat (SMF) as assessed by the proportion of subjects who have at least a 1-grade improvement on the Clinician Reported-Submental Fat Rating Scale (CR-SMFRS), and 2. The reduction, from baseline to final follow-up, of SMF as assessed by the proportion of subjects who have at least a 2-grade improvement on the CR-SMFRS.
Secondary Endpoints	1. Reduction in fat layer thickness, as measured by ultrasound at week 12 post-final treatment. 2. Subject satisfaction as assessed by the Subject Self-Rating Scale score.
Sponsor	ZELTIQ Aesthetics, Inc., An Allergan Affiliate 4410 Rosewood Dr. Pleasanton, CA 94588

1. Introduction

1.1. Background

Fat reduction and body contouring procedures, which include invasive, minimally-invasive, and non-invasive procedures, have become increasingly popular aesthetic procedures. Patients who are obese and do not have specific fat bulges but require significant fat reduction to achieve aesthetic results are candidates for invasive and minimally-invasive procedures, such as liposuction and laser-assisted liposuction. Although effective at reducing fat, these invasive and minimally-invasive procedures involve significant patient pain, expense, downtime, and the risks typically associated with surgical procedures. As a result, patients who do not require significant fat reduction to achieve meaningful aesthetic results typically seek non-invasive fat reduction and body contouring procedures to avoid the pain, expense, downtime, and surgical risks associated with invasive and minimally-invasive procedures.

ZELTIQ Aesthetics has developed and commercialized a technology to non-invasively reduce subcutaneous fat. The technology utilizes the sensitivity of fat cells to cold injury in order to selectively eliminate subcutaneous fat tissue without affecting the skin or other surrounding tissues. Termed cryolipolysis, this technology enables a non-invasive alternative for subcutaneous fat reduction through cellular apoptosis. The CoolSculpting System, which is cleared for use in the United States for fat layer reduction through cold-assisted lipolysis, has been clinically proven to reduce fat bulges, allowing patients to achieve noticeable and measurable aesthetic results without the pain, expense, downtime, and risks associated with existing invasive and minimally-invasive procedures.

Allergan commercialized a first in class, injectable drug called KYBELLA® (deoxycholic acid), indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. Administrations are given at intervals of no less than 4 weeks until the desired result is achieved, up to a maximum of 6 treatment sessions. The total dose of KYBELLA® administered in each treatment session and the overall number of treatments are both tailored to the individual patient based on the amount and distribution of SMF as well as the patient's desired result. This minimally invasive procedure is another treatment option for patients looking to reduce the double-chin appearance.

Both CoolSculpting and KYBELLA® are important treatment options for aesthetically-minded patients who are interested in reducing submental fat using minimally invasive interventions.

The purpose of this study is to evaluate the safety and efficacy of subcutaneous fat

reduction in the submental area in subjects initially with extreme submental fullness (Grade 4) based on the Clinician Reported-Submental Fat Rating Scale (CR-SMFRS), using sequential treatments of CoolSculpting (with the CoolMini applicator) and KYBELLA®. [redacted]

In this study, subjects will receive two CoolSculpting treatments sessions each consisting of one cooling cycle with CoolMini, spaced 6 weeks apart, followed by at least one and up to two (2) KYBELLA® treatment sessions 6 weeks post the final CoolMini treatment, spaced 4-7 weeks apart.

After the completion of all treatment visits, subjects will be followed for 12 weeks post-final treatment. Safety information will be collected at study visits. Primary efficacy assessment will be evaluated at 12-weeks post-final treatment.

Results from this clinical trial will be used to provide feasibility data on the use of both CoolSculpting and KYBELLA® treatments sequentially to improve the treatment approach and availability for extreme submental fullness.

1.2. Device and Drug Description

1.2.1. The Device – CoolSculpting System

[redacted]

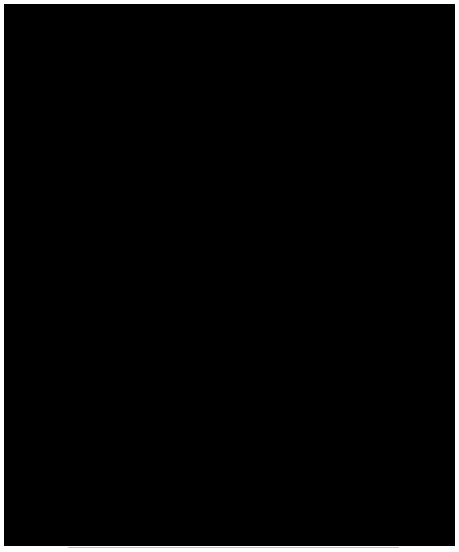

Figure 1. Representative CoolSculpting System control unit.

Figure 2: CoolMini Applicator

1.2.2. The Drug – KYBELLA®

[redacted]

[redacted]

Figure 3: Molecular Structure of Synthetic Deoxycholic Acid

Figure 4: Representative packaging of KYBELLA® 2 mL vials

[redacted] Completion of this training is to be documented in the study file.

[redacted]

- At the discretion of the investigator, topical or local anesthesia (e.g., topical or injectable lidocaine preparations without epinephrine, ice) may be applied in the planned treatment area and any medications will be recorded on the appropriate case report form (CRF).

- [redacted] A grid, specifically developed to be applied to the treatment area to guide the placement of injections, will be used.

- For each KYBELLA® injection, the investigator will palpate the treatment area to determine the approximate thickness of the targeted SMF and inject KYBELLA® into fat tissue at a depth of approximately mid-way into the SMF.

- If at any time resistance is met as the needle is inserted, indicating the possibility of contact with fascial or nonfat tissue, the needle will be withdrawn to an appropriate depth before the injection is given.

- Upon needle withdrawal, pressure will be applied to each injection site as necessary to minimize bleeding; an adhesive dressing may be applied. Upon completion of the injections, the area may be gently massaged.

- At each treatment session, the investigator will determine the number and locations of injections. He or she will evaluate each planned injection location to avoid sites for which an injection may not be appropriate (e.g., nodule formation, significant residual inflammation, other adverse event that warrants a delay, or lack of SMF).

- [redacted]

Subjects may be discharged from the research facility approximately 30 minutes after KYBELLA® is administered, provided it is medically appropriate to do so.

At no time is the dilution of KYBELLA® permitted.

1.3. Regulatory Status

[redacted]

[redacted]

2. Study Protocol

2.1. Design

Prospective, controlled, open-label, interventional study.

2.2. Study Duration

Enrollment and follow-up is expected to take up to nine (9) months for each subject.

2.3. Physician Participants

Study investigators must be practicing medical physicians with experience in the use of both the CoolSculpting System and KYBELLA® injections. Given the importance of assuring consistent ratings, and in consideration of investigational site logistics, the same evaluating investigator will perform the CR-SMFRS scoring for the same patient through all study visits.

2.4. Site Requirements

Site investigators must have at least one study coordinator with experience in conducting aesthetic research and with sufficient time to conduct the study.

2.5. Subject Recruitment

Subjects who seek reduction of submental fat will be recruited from the general population.

2.6. Sample Size

A maximum of twenty (20) subjects will be treated at up to three (3) investigational sites.

2.7. Subject Eligibility

To be eligible to participate in the study, subjects must meet all of the inclusion criteria and none of the exclusion criteria listed in **Table 1**.

Table 1. Eligibility criteria.

Inclusion Criteria
a) Male or female subjects ≥ 22 years of age and ≤ 65 years of age.
b) Women of childbearing potential must have a negative urine pregnancy test result at screening and agree to practice adequate contraception.
c) CR-SMFRS grade of 4 (extreme) as determined by the evaluating investigator at screening.
d) Dissatisfaction with the submental area expressed by the subject as a rating of 0, 1 or 2 using the Subject Self Rating Scale (SSRS) as determined at Screening visit.
e) History of stable body weight confirmed by the subject, for at least 6 months prior to the first treatment session.
f) Subject agrees to maintain his/her weight (i.e., within 5%) by not making any major changes in their diet or exercise routine during the course of the study.
g) Subject agrees to forgo any treatment or behavior (e.g., unshaven facial hair) during the subject's participation in the study that may affect the assessments of the submental area.
h) Subject is medically able to undergo the administration of KYBELLA® determined after review of the subject's medical history for which the evaluating investigator identifies no clinically significant abnormality.
i) Subject has read and signed the study written informed consent form.

Exclusion Criteria

a) Body Mass Index ≥40 as determined at screening.
b) Subject has excessive skin laxity, as determined by the evaluating investigator, in the neck or chin area or other anatomical feature (e.g., predominant subplatysmal fat, loose skin in the neck or chin area, prominent platysmal bands) for which reduction in the submental fat may result in an aesthetically unacceptable outcome.
c) There is evidence of any cause of enlargement in the submental area (e.g., thyroid enlargement, cervical adenopathy) other than localized submental fat.
d) Subject has a history of trauma associated with the chin or neck areas, which in the judgement of the investigator may affect evaluation of safety or efficacy of treatment.
e) Subject has a history of treatment with CoolSculpting or KYBELLA® in the intended treatment area or has a history of any intervention to treat submental fat (e.g., liposuction, surgery, or lipolytic agents).
f) Subject has a history of treatment with radiofrequency, micro-focused ultrasound, laser procedures, chemical peels, or dermal fillers in the neck or chin area within 12 months before the first treatment session.
g) Subject has a history of treatment with botulinum toxin injections in the neck or chin area within 6 months before the first treatment session.
h) Subject has a known history of cryoglobulinemia, cold urticaria, paroxysmal cold hemoglobinuria or cold agglutinin disease.
i) Subject has a known history of Raynaud's disease, or any known condition with a response to cold exposure that limits blood flow to the skin.
j) Subject has a history of facial nerve paresis or paralysis (such as Bell's palsy)
k) Subject has a history or current symptoms of dysphagia.
l) Subject has a history of prior neck surgery, or prior surgery in the area of intended treatment, or implant in or adjacent to the area of intended treatment.
m) Subject has a history of sensitivity to any components of the KYBELLA® or to topical or local anesthetics (e.g., lidocaine, benzocaine, novocaine).
n) Subject has a history of bleeding disorder or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
o) Subject is currently taking or has taken diet pills or weight control supplements within the past month.
p) Subject has any dermatological conditions, such as scars in the location of the treatment area that may interfere with the treatment or evaluation.

q) Subject has an active implanted device such as a pacemaker, defibrillator, or drug delivery system.
r) Women of childbearing potential not using a reliable means of contraception.
s) Subject is unable or unwilling to comply with the study requirements.
t) Subject has received treatment with an investigational device or agent within 30 days before the subject's first treatment session.
u) Any other condition or laboratory value that would, in the professional opinion of the investigator, potentially affect the subject's response or the integrity of the data or would pose an unacceptable risk to the subject.

2.8. Informed Consent

Study candidates shall receive an explanation of the study objectives, possible risks and benefits of the study, and be given adequate time to read the information included in the informed consent document. Candidates will be given an opportunity to ask questions about any of the information contained in the informed consent. Candidates must verbally acknowledge understanding of the informed consent, and sign the consent form accordingly. This form must have prior approval of the Institutional Review Board.

2.9. Screening Procedures

2.9.1. Screening Visit; Required; Week -4 to Day 0

The subject shall be consented for study participation as described in Section 2.8. After the informed consent form is signed, subjects will be screened for eligibility. Each subject will be evaluated to determine that all eligibility criteria are met. The investigator or designee shall complete a brief medical history and examine the subject to confirm eligibility for the study.

1. Obtain Subject Self-Rating Scale score.
2. Obtain height and weight.
3. Evaluating investigator to assess intended treatment area and determine severity of submental fullness based on Clinician Reported-Submental Fat Rating Scale (CR-SMFRS).
    a. Subjects must score a 4 (extreme) in order to be enrolled.
4. Assess oral cavity for current dental infection or evidence of dry mouth.
5. Assess function of the marginal mandibular nerve (grimace with ability to show lower teeth) and hypoglossal nerve (tongue does not deviate upon protrusion).

6. Assess upper neck to rule out enlarged lymph nodes or glands.
7. Assess for dermatological conditions that may lead to exclusion of the subject from the study.
8. Document subject's medication use (including over-the-counter medications, vitamins and herbs), Fitzpatrick Skin Type, and ethnicity, as well as any skin irregularities (e.g. moles, birth marks, scars, discoloration).
9. All female subjects of childbearing potential will be asked to take a pregnancy test (urine) prior to being treated. If the subject is pregnant, she will be excluded from participation.

Female subjects of childbearing potential will be advised to avoid becoming pregnant during the course of the study by agreeing to practice adequate contraception, in the judgement of the investigator, during the course of the study. If the subject becomes pregnant during the course of the study, she will not be treated subsequently with the study device or drug and she will be required to have follow-up photographs and ultrasounds. She will also be asked for information about the pregnancy and the birth of the child.

All subjects will be asked to maintain their weight by not making any major changes to their diet or exercise regimen during the course of the study. If the weight change is more than 5% at the final visit, the subjects' data will be excluded from the primary Efficacy analyses. Subjects who do not maintain their weight within 5% will continue in the study, however their data will be excluded from Efficacy analyses.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria shall be eligible to participate in the study and the first treatment will be scheduled.

2.10. Study Enrollment

Study Candidates who sign the informed consent form, meet eligibility criteria and undergo initiation of study treatment are considered enrolled. Study treatment initiation is defined as the initiation of cold therapy after the placement of the applicator on the intended treatment area on the scheduled treatment day.

2.11. Study Treatment

2.11.1. Treatment Visit 1; Required; Day 0

1. Review inclusion and exclusion criteria.

2. Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
3. If the subjects meet all of the inclusion criteria and none of the exclusion criteria, then proceed with the study treatment.
4. Obtain weight
5. Obtain baseline photographs using custom standardized setup and settings.
6. Cleanse the treatment area with isopropyl alcohol.
7. Mark or outline the intended treatment area.
8. Measure the fat layer thickness of the intended treatment area with a commercially-available ultrasound device using a standardized protocol.

[redacted]

The investigator or staff will be present during the treatment to monitor the progress. Treatment may be discontinued due to subject discomfort or device malfunction. The need for post-treatment care is not expected for this study. Subjects will be encouraged to call the study site if they experience any unusual effects (e.g., severe discomfort or pain, severe and/or prolonged erythema, bruising, swelling, blistering, etc.). Refer to Section 6.2 for a listing of the expected side effects of the procedure.

2.11.2. Treatment Visit 2; Required; 6 Weeks +/- 7 days post Treatment 1

Six-weeks after CoolSculpting Treatment #1, the same evaluating investigator from Screening will evaluate the aesthetic result of Treatment #1. A second CoolSculpting treatment will be performed in the submental region to achieve the desired aesthetic effect. The second treatment will be performed following the steps outlined in Section 2.11.1.

The following evaluations will be performed at the 2nd Treatment Visit prior to CoolSculpting treatment #2:

1. Obtain weight.
2. Clinical assessment of the treatment area for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling).
3. Examine the oral cavity for evidence of dry mouth.
4. Assess lower face motor nerve function.
5. Obtain adverse event information.
6. Photography using the same custom standardized setup and settings as the pre-treatment photographs (optional) prior to CoolSculpting treatment #2.
7. Perform CoolSculpting treatment #2 as described in Section 2.11.1

2.11.3. Treatment Visit 3; Required; 6 Weeks +/- 7 days post Treatment 2

Six-weeks after CoolSculpting Treatment 2, the same evaluating investigator will evaluate the aesthetic result of Treatment #2, A KYBELLA® treatment will be performed in the associated submental region in patients assigned a CR-SMFRS of 3 or 2 to further reduce the fat and enhance the aesthetic appearance in the submental region.

The following evaluations will be performed at the 3rd Treatment Visit:

1. Obtain Subject Self-Rating Scale score.
2. Obtain weight.
3. Clinical assessment of the treatment area for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling).
4. Examine the oral cavity for evidence of dry mouth.
5. Assess lower face motor nerve function.
6. Obtain adverse event information.
7. Photography using the same custom standardized setup and settings as the pre-treatment photographs.
8. Measure the fat layer thickness of the intended treatment area with a commercially-available ultrasound device using a standardized protocol.
9. Assess intended treatment area and determine severity of submental fullness based on CR-SMFRS score at this visit. Patients who are assigned a score of 3 (CR-SMFRS=severe) or 2 (CR- SMFRS=moderate) by the evaluating investigator will move on to the KYBELLA® treatment phase.
10. To perform a KYBELLA® treatment:

[redacted]

a. [redacted]

f. [redacted]

i. Immediately post treatment, the treatment site will be examined for any epidermal, dermal or subcutaneous findings (e.g., blanching, erythema, bruising, swelling); alterations in sensation (e.g., numbness, tingling) [redacted]
j. Obtain adverse event information.

Treatment may be discontinued due to subject discomfort. The need for post-treatment care may include, the optional use of compression dressing, icing for pain and local discomfort and hot packs for indurations. Subjects may be discharged from the research facility approximately 30 minutes after KYBELLA® is administered, provided it is medically appropriate to do so.
Subjects will be encouraged to call the study site if they experience any unusual effects and/or adverse events (e.g., severe discomfort or pain, severe and/or prolonged erythema, bruising, swelling, blistering, etc.). Refer to Section 6.2 for a listing of the expected side effects of the procedure.

2.11.4. Treatment Visit 4; Optional; 4 to 7 Weeks post Treatment 3

Four to seven weeks after Treatment 3 (first treatment with KYBELLA®), the same evaluating investigator will evaluate the aesthetic result of Treatment #3 (KYBELLA®) and assign a CR-SMFRS score. Per the investigator's discretion and with the subject's concurrence, another KYBELLA® treatment will be performed in the submental region in patients assigned a CR-SMFRS <Grade 4 (extreme) to further enhance the aesthetic effect. The KYBELLA® treatment will be performed following the steps outlined in Section 2.11.3.

The following evaluations will be performed at the 4th Treatment Visit:

1. Obtain weight.
2. Clinical assessment of the treatment area for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling).
3. Examine the oral cavity for evidence of dry mouth.
4. Assess lower face motor nerve function.
5. Obtain adverse event information.
6. Assess intended treatment area and determine severity of submental fullness based on CR-SMFRS score at this visit. Patients who are assigned a score of <4 (extreme) by the evaluating investigator may proceed with another KYBELLA® treatment session at this visit.
7. Photography using the same custom standardized setup and settings as the pre-treatment photographs (optional). Perform treatment as described in Section 2.11.3 with investigator's discretion.

2.12. Follow-up Procedures

2.12.1. Two-Week Follow-Up (after each treatment of either CoolSculpting or KYBELLA®); Required: 2 Weeks (± 3 days) after each treatment visit

The following evaluations will be performed at the 2-week post-treatment follow-up visit:

1. Obtain weight.
2. Clinical assessment of the treatment area for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling).
[redacted]
3. Examine the oral cavity for evidence of dry mouth.
4. Assess lower face motor nerve function.
5. Obtain adverse event information.

2.12.2. Final Follow-Up Evaluation; Required: 12 Weeks (± 3 weeks) after final treatment visit

The following evaluations will be performed at the final post-treatment follow-up visit:

1. Obtain Subject Self-Rating Scale score.
2. Obtain weight.
3. The same evaluating investigator from prior visits will assess treatment area and determine severity of submental fullness based on CR-SMFRS score at this visit.
4. Photograph the treatment area using the same custom standardized setup and settings as the pre-treatment photographs.
5. Measure the fat layer thickness of the treatment site with a commercially available ultrasound device.
6. Clinical assessment of the treatment area for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling). [redacted]
7. Examine the oral cavity for evidence of dry mouth.
8. Assess lower face motor nerve function.
9. Obtain adverse event information.

Figure 5 illustrates subject enrollment and study flow. Table 2 summarizes the study schedule and events at each visit.

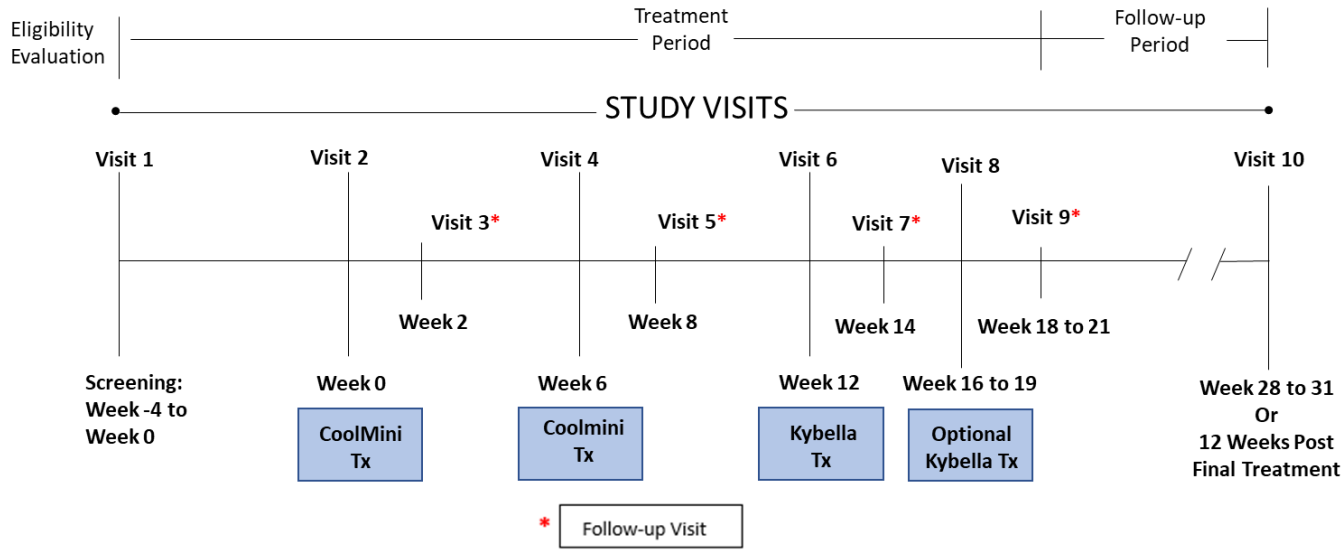

Figure 5. Subject enrollment and study flow.

Table 2. Schedule of assessments.

	Screening (< 1 hr)	Treatment Visit 1 (< 3 hrs)	Treatment Visit 2 (< 3 hrs)	Treatment Visit 3 (< 3 hrs)	Treatment Visit 4 (Optional) (< 3 hrs)	2 Week Follow-Up (< 1 hr) †	Final Follow-Up (< 1 hr)
Time Frame	Day - 30 to 0	Day 0	6 ± 1 weeks post last tx	6 ± 1 weeks post last tx	4-7 weeks post last tx	2 weeks ± 3 days post each tx	12 ± 3 weeks post final tx
Informed Consent*	X						
Inclusion/Exclusion Criteria	X	X	X	X	X		
Pregnancy Test	X	X	X	X	X		
Medical History	X						
Tx Site Assessment	X	X	X	X	X	X	X
Oral Cavity Assessment	X		X	X	X	X	X
Nerve Function Assessment	X		X	X	X	X	X
Height	X						
Weight	X	X	X	X	X	X	X
CR-SMFRS Assessment	X			X	X		X
Photography	**X	X	**X	X	**X	**X	X
Ultrasound		X		X			X
CoolMini Treatment		X	X				
KYBELLA® Treatment				X	**X		
[redacted]		X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X
Subject Self Rated Scale	X			X			X

* Informed consent to be signed by subject prior to the collection of any data or completion of any study procedures.
** Optional
† Follow-up after each treatment

2.13. Assessments

Study-related assessments are described below.

2.13.1. Safety Assessments

The primary safety endpoint is the incidence, seriousness, severity and duration of device, drug and/or procedure-related adverse events at the final follow-up visit. Safety will be monitored by documentation of adverse events and clinical assessment of the treatment site.

2.13.2. Clinician Evaluation using CR-SMFRS

The primary measure will be clinician live assessment of the patient's severity of submental fat as determined by the CR-SMFRS (Table 3). The CR-SMFRS score will be based on the investigator's clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; and observation of pronation, supination, and lateral movement of the head. The score will be determined using the rating scale definitions and the representative photographs associated with each score. The final score will be determined while the subject's head is in the Frankfort plane posture as described in the CR-SMFRS. The score will be recorded as a whole number.

Table 3. Clinician Reported-Submental Fat Rating Scale (CR-SMFRS)

Score	SMF Description
0	Absent Submental Convexity: No localized submental fat evident.
1	Mild Submental Convexity: Minimal, localized submental fat.
2	Moderate Submental Convexity: Prominent, localized submental fat.
3	Severe Submental Convexity: Marked, localized submental fat.
4	Extreme Submental Convexity.

2.13.3. Photography

Photography will be performed by a qualified representative of the sponsor.

A series of photos of the treatment areas will be obtained at the pre-treatment, prior to first KYBELLA® injection (Treatment visit 3) and final follow-up visits, using custom standardized setup, lighting, and camera settings to ensure consistency. All photographs will be captured at fixed angles and posture (Frankfort plane). Using a series of pre-determined markings on the floor, the photographer will position the camera at the pre-determined reference points to ensure that the reproduction ratio and focal

distance are maintained throughout the image series during the study. During follow-up visits, the photographer will re-align subjects by referencing baseline images.

2.13.4. Ultrasound Measurements

Ultrasounds will be performed by a qualified representative of the sponsor.

After treatment sites have been identified, the ultrasound measurement locations will be marked. Up to 3 measurement locations will be marked on the intended treatment area. A template may be created prior to treatment to mark the locations for ultrasound measurements. This template (transparency) will be created using external landmarks (e.g., skin imperfections) as reference points, identifying the peak of the bulge and the locations for ultrasound measurements. At follow-up visits, the template will be used to mark the locations for ultrasound measurements. A SonoSite TITAN® ultrasound system (or equivalent approved by Sponsor) will be used in this study. A high frequency linear transducer array (L38/10-5: 38-mm broadband, 10-5 MHz, optimized for breast, small parts, interventional, musculoskeletal and vascular imaging) provides sufficient spatial resolution to visualize anatomical features for image plane alignment for fat layer measurement. Stored images will be transferred to an off-line PC based image analysis tool for fat layer measurements. These files will be stored by the Sponsor and indexed by subject identifier. Standardized techniques for obtaining images will be used to ensure consistency throughout the study.

The individual(s) analyzing the images will be presented with two series of images for each measurement site, the pre-treatment and the final post-treatment series, and asked to measure the depth of fat layer in each image. The order in which the images are presented will be randomized by subject.

2.13.5. Subject Self-Rating Scale (SSRS)

Subject's assessment of overall satisfaction with their face and chin using the SSRS will be obtained at Screening (baseline score), at Treatment Visit 3 (prior to first KYBELLA® treatment) and at the final 12-week follow-up visit.

SSRS is a subject self-rating scale, scored on a 7-point scale with 0=extremely dissatisfied, 1=dissatisfied, 2=slightly dissatisfied, 3=neither satisfied not dissatisfied, 4=slightly satisfied, 5=satisfied, and 6=extremely satisfied.

2.14. Endpoints

The objective of this study is to evaluate the safety and efficacy of subcutaneous fat layer reduction in the submental area on subjects with extreme submental fullness defined by the CR-SMFRS as Grade 4 using CoolSculpting and KYBELLA® in sequence.

2.14.1. Primary Endpoints

The primary endpoints of the study will be defined as follows:

- Safety endpoint: incidence of device, drug or procedure-related adverse events.

- Efficacy endpoint:
  1. The reduction, from baseline (CR-SMFRS =4) to final follow-up, of submental fat (SMF) as assessed by the proportion of subjects who have at least a 1-grade improvement on the Clinician Reported Submental Fat Rating Scale (CR-SMFRS), and

  2. The reduction, from baseline (CR-SMFRS=4) to final follow-up, of SMF as assessed by the proportion of subjects who have at least a 2-grade improvement on the CR-SMFRS.

2.14.2. Secondary Endpoints

Secondary endpoints in the study are as follows:

1. Reduction in fat layer thickness, as measured by ultrasound at Week 12 post-final treatment.
2. Subject satisfaction as assessed by Subject Self-Rating Scale scores.

2.15. Statistical Analysis Plan

2.15.1. Statistical Methods: Overall Plan

Data will be summarized based on the nature of the data. Dichotomous (e.g., gender, independent photographic review) and ordinal (e.g., Fitzpatrick Skin type) data will be tabulated by category. The mean, standard deviation, maximum, and minimum will be tabulated for continuous data (e.g., age, fat thickness). The significance level will be two-sided 0.05 for all statistical tests.

2.15.2. Analysis Population

Analysis Populations are defined as following:

Per-protocol Population (PP):

The Per-protocol Population will consist of all the treated subjects followed through to the final post-treatment visit and with weight change of no more than five percent at the time the final post-treatment visit images are taken. Since a weight change of more than 5 percent will affect the images, the primary Efficacy analysis will be performed based on this study population. Subjects who do not complete the treatment or had an interruption in the treatment will not be included in the primary and secondary Efficacy analyses.

As-Treated Population (AT):

This population consists of all treated subjects regardless of whether they become pregnant, undergo weight change during the study, or had interrupted treatment.

Safety Population (SA):

This population will consist of all the treated subjects with safety evaluation after the treatment. This population should be identical to the AT population. The safety data analyses will be performed based on the Safety Population.

2.15.3. Endpoint Analysis

2.15.3.1. Primary Safety Endpoint:

The primary safety endpoint is incidence of all device, drug – and/or procedure-related adverse events. All adverse events reported during and following the treatment will be included in the safety analysis. The frequency and proportion of subjects reporting each type of adverse event will be tabulated by relationship with the treatment and seriousness as well as severity of the event.

2.15.3.2. Primary Efficacy Endpoint: Reduction in CR-Submental Fat Rating Scale

The primary efficacy endpoint is the change in subcutaneous fat layer in the submental area as measured between the baseline and final post-treatment visit CR-Submental Fat Rating Scale scores. Since weight change may affect the fat layer thickness, the analysis will be based on the evaluation of the PP population, i.e. treated subjects followed through to the final post-treatment visit who did not become pregnant, and with weight change of no more than 5 percent at the final post-treatment visit.

2.15.3.3. Secondary Endpoint: Ultrasound

A secondary efficacy endpoint is the change in subcutaneous fat layer as measured between the pre- and final post-treatment visit images. Since weight change may affect the fat layer thickness, the analysis will be based on the evaluation of the PP population, i.e. treated subjects followed through to the final post-treatment visit who did not become pregnant, and with weight change of no more than 5 percent at the final post-treatment visit.

2.15.3.4. Secondary Endpoint: Subject Self-Rating Scale

[redacted]

2.15.3.5. Sample Size Requirement

Up to twenty (20) subjects is thought to be appropriate to provide feasibility information regarding safety and efficacy of submental treatment using CoolMini vacuum applicator and KYBELLA® sequentially.

2.16. Missing Data Handling

In general, no imputation for missing data will be made. Data will be analyzed "as-is" where subjects with missing data not being included in the analysis.

2.17. Protocol Adherence

The study investigators are responsible for performing the study in compliance with the protocol. Non-adherence to the protocol is to be classified as a protocol violation or protocol deviation, as defined below.

Protocol Violation

Non-adherence to the protocol that may result in significant additional risk to the subject (e.g., enrollment of a subject who does not meet the study criteria). Or, non-adherence to Good Clinical Practices (GCP) that may impact patient safety (e.g., failure to obtain proper consent prior to performing study procedures). Violations should be reported to the study Sponsor within 5 working days and reported to the IRB per IRB guidelines.

Protocol Deviation

Non-adherence to study procedures which does not result in additional risk to the subject (e.g., subject missed visit). Protocol deviations are not required to be reported to the IRB; however, they must be recorded on the study case report forms and may be reported and reviewed in conjunction with the progress report as part of the annual review process.

2.18. Adverse Events

Adverse events (AE) will be assessed continuously throughout the study. An AE is defined in accordance with ISO 14155 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in study participants, users, or other persons temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Disease signs and symptoms that existed prior to the study treatment are not considered AEs unless the condition recurs after the patient has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

AEs will be monitored throughout the study beginning with signing of informed consent. At each post-baseline visit, the investigator will begin querying for AEs by asking each patient a general, non-directed question such as “Have you had any changes to your condition since your last visit?” Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate CRF.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study

Adverse Device Effect (ADE)

Any sign, symptom, or disease in a study subject that occurs during the course of a clinical trial that is determined by the Investigator to have a causal relationship or possible causal relationship with the device under investigation. This definition includes any AE s resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is defined in accordance with ISO 14155 as "an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event."

Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated serious adverse device effect (USADE) is defined in accordance with ISO 14155 as "any serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report." The investigator is to consult the IDFU for anticipated risks or anticipated AEs.

Device Deficiency

A device deficiency is defined in accordance with ISO 14155 as "inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance." Device deficiencies include malfunctions, use errors, and inadequate labeling.

If a device deficiency occurs, the investigator will notify the Sponsor using the fax number or email on the front page of the protocol. Device deficiencies shall be documented throughout the study and appropriately managed by the Sponsor. The Sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SADE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

Serious Adverse Event (SAE)

An SAE is defined in accordance with ISO 14155 as an AE that:

1. Led to death

2. Led to serious deterioration in the health of the patient, that either resulted in:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function, or
    c. inpatient or prolonged hospitalization, or
    d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or
    e. led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs from the signing of the ICF until the last follow-up visit will be collected at the timepoints specified in the schedule of activities, and as observed or reported spontaneously by study participants.

Medical occurrences that begin after signing of informed consent and before administration of study treatment will be recorded as an AE on the appropriate CRF.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours of learning about the report. All non-serious AEs related to the devices used in the study, as well as Device Complaints, will be reported to the sponsor within 7 working days. The investigator will submit any updates on these events to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the final visit of the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly report the event to the sponsor.

Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about possible AEs.

Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Reportable Incidents

Serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) must be reported within 24 hours of knowledge of the event to the Sponsor.

All adverse events observed by the investigator or reported by the subject will be recorded on the appropriate CRF, irrespective of relationship to CoolSculpting and KYBELLA®, as well as the KYBELLA® skin grid. Medically significant adverse events will be followed until resolved or considered stable. For each event, the investigator will record a description, dates of onset and resolution, severity, and relationship to CoolSculpting, KYBELLA® and KYBELLA® skin grid. The investigator may be required to provide follow-up information.

Any adverse event that results in withdrawal from the study must be reported to the Sponsor after the decision to withdraw the subject is made.

Any death occurring during the study must be reported to the Sponsor within 24 hours of the discovery of the event. This includes any death that occurs within 30 days after the subject's final visit, irrespective of when the final visit occurs.

Assessment of Severity

Severity of adverse events will be determined using the following scale:

- Mild: Event that is easily tolerated and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate: Events that interfere with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. It is usually alleviated with additional specific therapeutic intervention.
- Severe: Event that is incapacitating, with inability to work and do the usual activities of daily living, or significantly affects clinical status. This may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- For each AE/SAE, there are 5 levels of causality, as follows:
    - Not related
    - Unlikely
    - Possible
    - Probable
    - Causal relationship

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will determine the relationship of each adverse event to CoolSculpting and/or KYBELLA® using the question: "Is there a reasonable possibility that the event may have been caused by treatment with CoolSculpting and/or KYBELLA®? Answer 'yes' or 'no' for each adverse event."

The guideline below should be used to consider relatedness:

For a “no causal relationship” assessment, the adverse event:

- May be judged to be due to extraneous causes such as disease or environment or toxic factors
- May be judged to be due to the subject's clinical state or other therapy being administered
- Is not biologically plausible
- Does not reappear or worsen when CoolSculpting and/or KYBELLA® is re-administered
- Does not follow a temporal sequence from treatment with CoolSculpting or administration of KYBELLA®

For a causal relationship (including unlikely, probable and possible assessments) there is a reasonable possibility that the event may have been caused by CoolSculpting, KYBELLA® and/or the KYBELLA® Grid. The adverse event:

- Follows a temporal sequence from treatment with CoolSculpting and/or administration of KYBELLA®
- Is a known response to CoolSculpting and/or KYBELLA® based on clinical or nonclinical data

- Could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered
- Disappears or decreases upon cessation of CoolSculpting and/or KYBELLA® tx or reduction in total dose of KYBELLA®
- Reappears or worsens when CoolSculpting and/or KYBELLA® is re-administered

Serious Adverse Event Reporting Procedures

All serious adverse events must be reported to the Sponsor within 1 working day of discovery or notification of the event and according to IEC/IRB requirements and the institution at which the study is conducted, if applicable. Serious adverse event information and any follow-up information will be recorded on a Serious Adverse Event Form and transmitted to the Sponsor using the contact information provided by the Sponsor. Note that for each drug/device used in this study, a separate SAE form and contact information will be used. The Sponsor will be responsible for evaluating and reporting any serious adverse events and suspected unexpected serious adverse reactions in accordance with all applicable laws and regulations.

Safety Monitoring Considerations

If an adverse event occurs that in the judgment of the investigator represents a potential risk for new subjects, the investigator will contact the Sponsor within 1 working day after becoming aware of the event.

A full reporting of the event shall be provided within 10 working days of the event. The Sponsor is then responsible for notifying the IRB, as required.

Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment through the duration of the pregnancy.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.
- If a female of childbearing potential becomes pregnant during the study, the investigator should notify the participant's physician that the participant may have been treated with KYBELLA® and/or CoolSculpting and exit the participant from the study.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

- A pregnancy form will need to be filled out by the site and submitted to the sponsor.

3. Study Management and Quality Control

3.1. Study Data Collection

Standardized Case Report Forms (CRFs) will be provided to all participating sites. Data will be reviewed by the study monitor and Sponsor data management personnel to identify inconsistent or missing data and to ensure compliance with the study protocol.

3.2. Confidentiality

All information and data concerning study subjects will be considered confidential, and handled in compliance with all applicable regulations including the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Only authorized site staff, the study Sponsor or the Sponsor's designee, IRB and relevant Regulatory authorities will have access to these confidential files. A unique identification code will be assigned to each subject participating in this trial. All data used in the analysis, reporting and publication of this clinical trial will be maintained without identifiable reference to the subject. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity.

3.3. Investigator Responsibilities

3.3.1. General Responsibilities

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the Investigational Plan, and applicable FDA regulations. The investigator must protect the rights, safety, privacy and welfare of the subjects under the Investigator's care. Investigators will assume overall responsibility and accountability for study site staff and for the clinical data obtained during the study. The investigator assumes all responsibilities per 21 CFR 812, 21 CFR 312, and other applicable regulations, including but not limited to:

IRB Approval

The investigator may not begin the study until the governing institutional review board (IRB) provides written approval of the study protocol and consent form. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB.

Informed Consent

The investigator must ensure that informed consent is obtained from each prospective study subject in accordance with 21 CFR Part 50 and that the study is not commenced until IRB approval has been obtained.

Device and Drug Accountability

Device and drug accountability is not applicable for this non-significant risk study.

KYBELLA® is to be stored at room temperature in a locked storage area and, not to be exposed to extreme temperature (greater than 30°C or less than 15°C).

Financial Disclosure

Investigators shall provide financial disclosure according to federal regulations (21 CFR 54).

Study Coordinator

To assure proper execution of the study protocol, each investigator must identify a study coordinator for the site who will work with and under the authority of the investigator to assure that study requirements are fulfilled as appropriate.

3.3.2. Investigator Records

The investigator and study staff must maintain accurate, complete, and current records relating to the conduct of the investigation. Records must be retained for a period of two years following (1) the date the investigation was completed or terminated, or (2) the records are no longer required to support a regulatory submission or completion of a product development protocol, whichever is longer. Participating investigators shall maintain the following:

- All correspondence with the Sponsor, another investigator, the IRB, and a monitor
- Records of all persons authorized to conduct the study (e.g. Delegation of Duties/Signature Authorization, CV)
- Informed Consent documentation for all enrolled subjects
- Records of each subject's case history, including study-required Case Report Forms and source documentation (e.g. physician notes, lab reports, study worksheets, clinic charts)
- All relevant observations of adverse device effects
- Records of any protocol deviations

- The condition of each subject upon entering and during the course of the investigation and any relevant medical history and results of any diagnostic tests
- Investigational plan with all amendments
- Current IRB approved informed consent and all previously approved versions
- Signed Investigator agreement
- Investigators will be responsible for the accurate and timely completion of CRFs during the trial.

These records must be available and suitable for inspection at any time by Sponsor representatives (monitor), or the reviewing IRB. The Investigator will supply access to study-related medical records, original laboratory data, and other records and data as they relate to the trial. The investigator will ensure that both he/she and his/her study staff have adequate time and resources to devote to the study, including study enrollment, subject evaluations, study documentation and site monitoring.

3.3.3. Investigator Reports

The investigator is responsible for preparation and submission of the following reports:

- Report of any unanticipated adverse device effects or life-threatening suspected adverse reactions shall be submitted to the Sponsor within 1 working day after the Investigator first learns of the effect.
- Withdrawal of IRB approval of the investigator's part in the investigation shall be reported to the Sponsor within 5 working days.
- Progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB annually. Alternatively, the Sponsor may prepare the report.
- Deviations from the investigational plan shall be reported to the Sponsor and the IRB.
- Failure to obtain informed consent prior to use of a device in a subject shall be reported to the Sponsor and IRB within 5 working days after the use occurs.

A final report shall be submitted to the Sponsor and IRB within 3 months after termination or completion of the investigation, or the investigator's part of the investigation.

3.4. Sponsor Responsibilities

3.4.1. General Responsibilities:

As the Sponsor, ZELTIQ Aesthetics an Allergan affiliate assumes overall responsibility for the conduct of the study. ZELTIQ Aesthetics assumes all responsibilities per 21 CFR 812 and other applicable regulations, and shall:

IRB approval: Ensure IRB approval for the investigation before shipping the device to any Investigator.

Investigators: Select Investigators qualified by training and experience, and providing them with the information they need to conduct the investigation properly. Obtain a signed Investigator Agreement and Form FDA-1572 from each participating Investigator. Study sites will be evaluated to ensure that they have an adequate patient base and can provide sufficient staff and documentation support to conduct the study properly.

Monitoring: Select monitors qualified by training and experience to monitoring the study and ensure proper monitoring of the investigation.

Data Management and analysis: Ensure data collection, verification, analysis, records storage, etc. Sponsor will assist with presentation(s) and/or publication(s).

3.4.2. Training

Study Training: To ensure uniform data collection and protocol compliance, Sponsor personnel will provide an educational session to study site personnel as needed, which will cover the Investigational Plan, techniques for the identification of eligible subjects, study assessments, data collection and form completion, and the device directions for use as well as the drug labeling (including full prescribing information). The Investigator and study staff will be trained on the study device, drug and protocol, applicable regulations and requirements, and expectations of the study, enrollment expectations, subject selection, informed consent, required clinical data and record keeping, etc.

Study Material Use: Representatives of the Sponsor will train site staff in use of the study device and drug prior to study initiation. Sponsor representatives may be present at study procedures.

3.4.3. Site Monitoring

The Sponsor will ensure that qualified clinical monitors are available to monitor and oversee the conduct of the trial and that monitoring is performed in accordance with the Sponsor's approved procedures or third-party procedures approved by the Sponsor.

The clinical monitors will evaluate compliance with the investigational plan, FDA regulations, any specific recommendations made by the site's IRB and the signed Investigator Agreement.

Monitoring Visits

On-site monitoring visits will assess the progress of the clinical study and identify any concerns that result from the study drug or device performance or review of the Investigator's study records, study management documents, and informed consent documents.

Monitoring will ensure continued protocol compliance and accurate data reporting. Monitoring visits will occur at minimum once before study close-out.

During monitoring visits, the monitor will compare subject records and other supporting documents with reports at the site to determine that;

- The facilities used by the investigation continue to be acceptable for the purposes of the clinical study
- Informed consent was properly obtained and documented for all enrolled study participants
- The Investigational Plan is being followed, and only eligible subjects are being enrolled into the study
- Deviations to the Investigational Plan have been reported to ZELTIQ and the IRB, as appropriate
- Adverse events are promptly being reported
- Information recorded in the case report forms and study reports are accurate, complete, legible and consistent with source documentation.
- Subjects failing to complete the clinical study and the reason for failure are recorded.
- Missed follow-up visits are noted in the study documentation

Clinical monitors will provide feedback to the site regarding protocol or study compliance.

Study Site Closeout

At the close of the study at an investigational site, the monitor will ensure that all case report forms have been monitored and retrieved and that the Investigator's files are accurate and complete. The monitor will ensure that all investigational devices, drugs and study supplies are accounted for, and provide for appropriate disposition of any remaining supplies. The monitor will review record retention requirements with the Investigator and any remaining Investigator obligations are reviewed and ensure that all applicable requirements are met for the study. The monitor will prepare a report of the site closeout visit.

3.4.4. Final Report

A final report will be prepared at the conclusion of the trial. Copies of the final report will be provided to each Investigator and to the respective IRB.

3.4.5. Trial Registration

Prior to study initiation, the trial will be registered, if applicable, on a publicly accessible study database such as clinicaltrials.gov.

4. Data Ownership

ZELTIQ Aesthetics an Allergan affiliate, the study Sponsor, retains ownership of all data generated in this study, and controls the use of the data for purposes of regulatory submissions to the US and/or other governments. Investigator(s) and institution(s) (which shall include their employees, agents, and representatives) may not issue or disseminate any press release or statement, nor initiate any communication of information regarding this study (written or oral) to the communications media or third parties without the prior written consent of the Sponsor.

5. Publication Policy

Participating Investigators and/or Institutions may publish information or data collected or produced as a result of participation in appropriate scientific conference or journals or other professional publications subject to written permission from the Sponsor, provided that drafts of the material are provided to the Sponsor for purposes of review and comment at least sixty (60) days prior to the first submission for publication or public release. Investigators may not publish information regarding site-specific data until a multicenter study report has been published.

6. Risk/Benefit Analysis

The Sponsor has undertaken a comprehensive risk-benefit analysis.

6.1. Benefits

Fat reduction in the treatment area is anticipated to provide an aesthetic benefit and the use of this minimally-invasive drug and non-invasive device will eliminate the need for an invasive procedure that requires anesthesia or recovery time. Furthermore, the results of this study will help in the development of optimal treatment regimens for specific submental fullness severities. Considering the number of surgical procedures performed for the removal of fat each year (over 1.8 million procedures worldwide, according to the 2016 International Society of Aesthetic Plastic Surgeons Biennial Global Survey), the use of such a minimally-invasive and non-invasive procedure has the potential to significantly reduce the incidence of complications and post-surgical limitations associated with those procedures.

6.2. Risks

Although this study presents minimal risks to the subject, there is the potential for some risk when any medical procedure is performed.

Anticipated Device Effects

These are known effects of the CoolSculpting Procedure, previously recorded in prior studies as transient and/or temporary effects related to the cold application and/or vacuum pressure inherent in the treatment. Anticipated effects of the device which will not be considered adverse events include:

- inflammation of the subcutaneous fat layer, which is a desired effect of the procedure;
- sensations of coldness, stinging, burning, pinching, or pressure associated with placement of the applicator and the initiation of the cold treatment;
- known skin effects (e.g., blanching; erythema, bruising, purpura, petechiae, swelling, discomfort, tenderness, or soreness at the treatment site, all mild to moderate in nature) which are temporary effects that resolve spontaneously shortly after the procedure;
- localized sensory changes (e.g., numbness, tingling) at the treatment area resolving within 12 weeks of the procedure.

Adverse Effects for CoolSculpting

The following summarizes the potential adverse effects from CoolSculpting in this study:

Potential Adverse Effect	Description
Severe Bruising	The appearance of bruising (purple discoloration); purpura (purple colored spots or patches); or petechiae (pin point red dots) that is rated as severe by the investigator;
Prolonged Bruising	Bruising lasting longer than 1 month
Severe Erythema	The appearance of erythema (redness) that is rated as severe by the investigator
Prolonged erythema	Erythema lasting longer than 2 weeks.
Severe Swelling	The appearance of swelling (edema) that is rated as severe by the investigator
Prolonged swelling	Swelling lasting longer than 1 month.
First Degree Burn	A first-degree burn is superficial and causes local inflammation of the skin. The inflammation is characterized by pain, redness, and mild swelling. The skin may be very tender to touch.
Second Degree Burn	Second degree burns are deeper and in addition to the pain, redness and inflammation, there is also blistering of the skin.
Third Degree Burn	Third degree burns are deeper still, involving all layers of the skin. Because the nerves and blood vessels are damaged, third degree burns appear white, leathery and tend to be relatively painless.
Cold-induced Panniculitis	Severe inflammation which requires medical or surgical intervention.
Skin Pigment Changes	The appearance of hyperpigmentation or hypopigmentation in the treatment area.
Infection	Infection at the treatment site, diagnosed by a Physician and requiring medical intervention.
Discomfort During Procedure	Discomfort reported during the procedure that is intolerable to the subject and results in an interruption or discontinuation of the procedure
Discomfort Post Procedure	Significant discomfort, pain, cramping, tenderness, soreness, muscle spasm following the procedure which results in medical intervention (physician visit and/or prescription pain reliever)
Prolonged Sensory Alteration Post Procedure	Sensory changes (numbness, tingling, burning sensation) that are prolonged (i.e., lasting longer than 12 weeks).
Sensory Alteration Requiring Medical Intervention	Sensory changes (pain, burning, stinging, hypersensitivity) with a severity warranting medical intervention.

Potential Adverse Effect	Description
Vasovagal Symptoms	The occurrence of symptoms of anxiety, lightheadedness, dizziness, nausea, sweating, near syncope, or syncope (fainting).
Motor Nerve Injury	Injury to the lower face motor nerves such as marginal mandibular nerve (lower lip weakness) or hypoglossal nerve (tongue deviation).
Xerostomia	Injury to the submandibular gland as evidenced by the subjective decrease in saliva production.
Contour Irregularity	Significant indentation or contour irregularity in the treatment area that would require surgical intervention.
Allergic/Irritant Contact Dermatitis	Itchy rashes and skin peeling that may result from prolonged exposure to gel or applicator pressure
Subcutaneous Induration	Hardness within the treatment area, either as general firmness or discrete nodules. May present with pain and/or discomfort.
Paradoxical Hyperplasia	Visibly enlarged tissue volume within the treatment area which may develop 2-5 months after treatment. Surgical intervention may be required.
Other	Any other untoward medical event determined by the investigator to be an adverse event, regardless of the relationship to the device or treatment.

KYBELLA®

- KYBELLA® is contraindicated in the presence of infection at the injection sites.

- Marginal mandibular nerve injury
  Cases of marginal mandibular nerve injury, manifested as an asymmetric smile or facial muscle weakness (paresis), were reported during clinical trials. To avoid the potential for nerve injury, KYBELLA® should not be injected into or in close proximity to the marginal

mandibular branch of the facial nerve. All marginal mandibular nerve injuries reported from the trials resolved spontaneously (range 1-298 days, median 44 days).

- Dysphagia
  Difficulty swallowing (dysphagia) occurred in clinical trials in the setting of administration site reactions, e.g., pain, swelling, and induration of the submental area. Cases of dysphagia spontaneously resolved (range 1-81 days, median 3 days). Subjects with current or prior history of dysphagia were excluded from clinical trials. Avoid use of KYBELLA® in these patients as current or prior history of dysphagia may exacerbate the condition.

- Injection site hematoma/bruising
  In clinical trials, 72% of subjects treated with KYBELLA® experienced injection site hematoma/bruising.

  KYBELLA® should be used with caution in patients with bleeding abnormalities or who are currently being treated with antiplatelet or anticoagulant therapy as excessive bleeding or bruising in the treatment area may occur.

- Risk of injecting in proximity to vulnerable anatomic structures. To avoid potential tissue damage, KYBELLA® should not be injected into or in close proximity (1-1.5 cm) to salivary glands, lymph nodes and muscles.

- Injection site alopecia: withhold subsequent treatments until resolution.

- Injection site ulceration and necrosis: do not administer to the affected area until complete resolution.

Adverse Reactions

In clinical trials, the most commonly reported adverse reactions (≥ 2%) in KYBELLA®-treated subjects were:

- Injection site reactions including edema/swelling, hematoma/bruising, pain, numbness, erythema, induration, paresthesia, nodule, pruritus, skin tightness, site warmth and nerve injury; headache, oropharyngeal pain, hypertension, nausea and dysphagia.

- Other adverse reactions associated with the use of KYBELLA® include: injection site hemorrhage, injection site discoloration, pre-syncope/syncope, lymphadenopathy, injection site urticaria and neck pain.

- Adverse reactions that lasted more than 30 days and occurred in more than 10% of subjects were injection site numbness (42%), injection site edema/swelling (20%), injection site pain (16%), and injection site induration (13%).