NCT04142450

Study ID: MED-MA-PLS-0633

Title: CoolSculpting® the Upper Arms and Inner Thighs in Participants of Chinese Descent (XinCOOL)

Protocol Date: October 2, 2019

CLINICAL INVESTIGATION PLAN

CoolSculpting® the Upper Arms and Inner Thighs in Participants of Chinese Descent (XinCOOL)

Protocol Number:	MED-MA-PLS-0633
Investigational Product:	CoolSculpting®
Phase:	Post-marketing
Sponsor:	Allergan Sales, LLC 5 Giralda Farms Madison, NJ 07940 USA
Serious Adverse Event Reporting	Email: CoolSculptingProductSurveillance@allergan.com
Allergan Device Medical Safety Physician Contact Information	[redacted] Allergan plc 95 Corporate Drive Bridgewater, NJ 08807, USA [redacted]
Protocol Date:	02 October 2019
Protocol Version:	Version 1.0

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: CoolSculpting® the Upper Arms and Inner Thighs in Participants of Chinese Descent (XinCOOL)

Protocol Number: MED-MA-PLS-0633

This study will be conducted in compliance with the clinical study protocol (and amendments, if applicable), International Organization for Standardization (ISO) 14155(2011), guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatories

[redacted]

Signature

Date

[redacted]

Signature

Date

2 SYNOPSIS

Protocol Number: MED-MA-PLS-0633

Title:

CoolSculpting® the Upper Arms and Inner Thighs in Participants of Chinese Descent (XinCOOL)

Investigational Product:

CoolSculpting®

Study Sites:

Approximately 2 to 3 study sites

Phase:

Post-marketing

Objective:

The objective of this study is to evaluate the safety and effectiveness of the Allergan CoolSculpting® system using CoolAdvantage applicators for non-invasive subcutaneous fat reduction of the upper arms and inner thighs in participants of Chinese descent.

Study Design:

This is a multi-center, prospective, open-label, nonrandomized, interventional cohort, medical device post-marketing study.

Number of Participants:

Approximately 42 participants will be enrolled.

Treatment:

Participants will undergo CoolSculpting treatment(s) in an outpatient clinical setting using CoolAdvantage and/or CoolAdvantage Petite applicators. Each participant will undergo a single treatment session that comprises timed segments of cooling followed by 2 minutes of manual massage. Each treated arm will have up to two timed segments (or cycles) in the treatment session, each treated thigh will have one timed segment (or cycle) in the treatment session. Treatments will be administered according to the Canadian CoolSculpting System User Manual.

Study Duration:

Screening (8 days), enrollment, and follow-up is expected to take approximately 3 months in total for each participant.

Study Population:

To be eligible to participate, participants must meet all of the inclusion criteria and none of the exclusion criteria listed below.

Inclusion Criteria

1. Participant (healthy volunteers) has read and signed the study written informed consent form.

2. Male or female participant ≥ 18 years of 1st or 2nd generation, non-mixed race, Chinese descent.

3. Participant has clearly visible and palpable fat on the left and right lower aspects of the upper arms and/or left and right inner thighs, which in the investigator's opinion is appropriate and may benefit from the treatment.

4. Participant has not had weight change fluctuations exceeding 4.5 kg (or 5% of body weight) in the preceding month.

5. Participant has a body mass index (BMI) of ≥ 18.5 to ≤ 30. A BMI is defined as weight in kilograms divided by height in meters squared (kg/m^2).

6. Participant agrees to maintain weight (ie, within 5% of body weight) by not making any changes in diet or exercise routine during the course of the study.

7. Participant agrees to have photographs taken of the treatment area(s) during the scheduled time periods.

[redacted]

Exclusion Criteria

1. Participant has a history of an invasive fat reduction procedure (eg, liposuction, surgery, lipolytic agents, etc), or implants in or immediately adjacent to the area of intended treatment.
2. Participant has a history of prior surgery or scar tissue on the arms and/or inner thighs related to the area being considered for treatment.
3. Participant has a known history of cryoglobulinemia, cold urticaria, cold agglutinin disease, or paroxysmal cold hemoglobinuria.
4. Participant has a known sensitivity to cold or has any condition with a known response to cold exposure that limits blood flow to the skin, such as cold urticaria, Raynaud's disease, or Chilblains (pernio).

5. Participant with a clinically significant bleeding disorder, or concomitant use of oral or subcutaneous anticoagulants, or is taking any medication that in the investigator's opinion may significantly increase the participant's risk of bruising.
6. Participant with a history of carpal tunnel syndrome, compartment syndrome, or deep vein thrombosis in the upper or lower extremities.
7. Participant is currently taking or has taken diet pills or weight control supplements within the past 6 months.
8. Participant has any dermatological conditions, such as moderate to excessive skin laxity, infection, open wound, or scars in the location of the treatment sites that may interfere with the treatment or evaluation (stretch marks are not an exclusion).
9. Participant has an active implanted device such as a pacemaker, defibrillator, drug delivery system, or any other metal-containing implant within or adjacent to the area being considered for treatment.
10. Participant is pregnant or intending to become pregnant in the next 3 months.
11. Participant is lactating or has been lactating in the past 6 months.
12. Participant is unable or unwilling to comply with the study requirements.
13. Participant is currently enrolled in a clinical study of any unapproved investigational device, investigational product, or any other type of medical research judged not to be scientifically or medically compatible with this study.
14. Participant has any other condition or laboratory value that would, in the professional opinion of the investigator, potentially affect the participant's response or the integrity of the data or would pose an unacceptable risk to the participant.
15. Participant has had a non-invasive fat reduction and/or body contouring procedure in the area(s) of intended treatment within the past 12 months.
16. Participant needs to administer, or has a known history of subcutaneous injections, into the area(s) of intended treatment (eg, cortisone, heparin, insulin) within the past 6 months.
17. Participant with known sensitivity or allergy to fructose, glycerin, isopropyl alcohol, or propylene glycol.
18. Participant with impaired peripheral circulation in the area to be treated.
19. Participant with neuropathic disorders such as post-herpetic neuralgia or diabetic neuropathy.
20. Participant with impaired skin sensation.
21. Participant with a history of hernia in or adjacent to the treatment area(s) site.
22. Participant with a skin condition such as eczema, dermatitis, or rashes in the area to be treated.
23. Participant diagnosed with a systemic fibrosing disease or fibrosis in the area intended or adjacent to the area to be treated.

Primary Endpoint:

- Correct identification of baseline versus 12-week treatment images of the upper arms by at least two out of three blinded, independent reviewers. Success will be defined as at least 75% correct identification of the pre-treatment images.

Secondary Endpoints:

1. Correct identification of baseline versus 12-week treatment images of the inner thighs by at least two out of three blinded, independent reviewers.
2. Participant response of 'satisfied' or 'very satisfied' for question 1 (overall satisfaction) on the following CoolSculpting participant questionnaires at the 12-week visit:
    a. Upper arms
    b. Inner thighs
3. Fat reduction using caliper measurements at 12-weeks compared to baseline for the following areas:
    a. Upper arms
    b. Inner thighs

Safety Endpoints:

- Adverse events (AEs), including serious AEs (SAEs); and adverse device events (ADEs), including serious ADEs (SADEs).

[redacted].

Statistical Methods

Analysis Populations

1. Per-protocol (PP) population: The PP population will consist of all treated participants followed for 12 weeks and with weight change of no more than 5% of total body weight at the time the 12-week images are taken. Because a weight change of more than 5% will affect the images, the primary effectiveness analysis will be performed based on this study population. Participants who do not complete treatment on the upper arms and/or inner thighs will not be included in the effectiveness analyses.
2. As-treated (AT) population: The AT population will consist of all treated participants regardless of weight change, etc.

3. Safety population: The safety population will consist of all the treated participants with at least one safety evaluation after the treatment. This population should be identical to the AT population. All safety data analyses will be performed based on the safety population.

Sample Size Determination

In this study, both arms and thighs will be evaluated by independent raters. The independent raters' evaluations will be combined into one clinical judgement on each arm and thigh. The evaluations on arms and thighs will be considered as independent.

A previous study described that the rate of correct identification was 83%. Using 75% as the lower bound of the 95% confidence interval (CI), the ½-width of the 95% CI will be 8%.

Based on these assumptions, we will need 60 evaluable arms or 32 evaluable participants for the arm evaluations with the assumption that less than 10% of participants have only one arm evaluation available. The same number of participants for thigh evaluations will be needed.

With an assumption that only 80% of all subjects will have both arms and thighs treated, we will need 38 evaluable participants in total for the study. Adding a 10% attrition rate, we will need to enroll 42 participants in the study.

Statistical Analyses

In general, disposition data, participant baseline and characteristics data, and concomitant therapy data will be summarized descriptively. The categorical variables will be presented with number and proportion while the continuous variables will be presented with mean, standard deviation, median, minimum, and maximum.

The primary effectiveness analysis will be based on the PP population. The number and proportion of participants with correct identification of baseline vs 12-week images of the upper arms by at least two out of three blinded, independent reviewers and the corresponding 95% CI of the proportion of participants with correct identification will be summarized.

The number and proportion of participants with correct identification of baseline vs 12-week images of the inner thighs by at least two out of three blinded, independent reviewers and the corresponding 95% CI of the proportion of participants with correct identification will be summarized.

Participants who have reported 'Very satisfied' or 'Satisfied' on each of the CoolSculpting participant questionnaires (upper arms and inner thighs) for question #1 (overall satisfaction) will be categorized as 'Satisfied.' The numbers and proportions will be summarized and the 95% CI of the proportions will be provided.

Fat reduction at 12 weeks compared to baseline will be summarized descriptively.

The numbers and proportions of participants with AEs, SAEs, ADEs, and SADEs will be summarized. The numbers and proportions of participant-reported pain scores (0 to 10 scale) will be summarized.

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[redacted]

List of In-text Tables

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
ADE	adverse device event
AE	adverse event
AT	as-treated
BMI	body mass index
CE	Conformité Européenne
CI	confidence interval
CRF	case report form
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
ISO	International Organization for Standardization
NIFR	non-invasive fat reduction
PP	per-protocol
SADE	serious adverse device event
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TMF	trial master file
UADE	unanticipated adverse device effect

4 INTRODUCTION

4.1 Background

CoolSculpting® is a non-invasive, clinically proven fat-reduction treatment that selectively targets adipocytes using a patented cooling technology. The CoolSculpting mechanism of action works by cooling the subcutaneous tissue (cryolipolysis procedure) that preferentially targets adipocytes which leads to controlled elimination of adipocytes (Manstein 2008, Zelickson 2009). Adipose tissue appears more preferentially sensitive to cold injury than skin and other tissues (eg, skin, muscle, and nerve) and the crystallization of cytoplasmic lipids in adipocytes occurs at temperatures well above the freezing point of water (Epstein 1970, Beacham 1980, Manstein 2008).

In the USA, the CoolSculpting system first received US FDA clearance in 2010 for non-invasive fat reduction (NIFR) in the flank followed by clearance for the abdomen in 2012 (Bernstein 2014). Further approvals were gained for visible fat bulges in the submental and submandibular area, thigh, along with bra fat, back fat, underneath the buttocks (also known as “banana roll”), and upper arm.

The CoolSculpting System was CE marked for fat layer reduction in 2009 and was initially approved in Canada in 2008. The clearance went to general fat layer reduction, without a specified treatment area. Up to now, the CoolSculpting system has gained clearance/approval in more than 70 countries.

The current CoolSculpting applicators (CoolAdvantage family, CoolMini, and CoolSmooth Pro) are however not cleared in China where the flanks and abdomen are the only approved body areas. Submissions to the Chinese regulatory authorities are therefore being planned to seek clearance for these applicators as well as to extend the number of body area indications to include the submental and submandibular areas, inner and outer thighs, and upper arms.

In order to increase the probability of success of achieving regulatory approval from the Chinese authorities for these applicators and body areas (given the majority of participants in the CoolSculpting clinical program and the subsequent reported CoolSculpting commercial experience were Caucasian), further CoolSculpting clinical data in Chinese participants are required.

The purpose of this study is to collect meaningful clinical data for the use of CoolSculpting in participants of Chinese descent (to be conducted in Canada) using the current CoolAdvantage and CoolAdvantage Petite applicators approved outside of China for the upper arm and inner thigh body areas.

In Canada, the Allergan CoolSculpting System is licensed (License #78510) and approved for:

- Fat layer reduction through cold-assisted lipolysis
- Minimizing pain and thermal injury during laser and dermatological treatments
- Acting as a local anesthetic for procedures that induce minor local discomfort

The CoolSculpting System can also provide localized thermal therapy (hot or cold) to minimize pain for post-traumatic and/or post-surgical pain and to temporarily relieve minor aches and pains and muscle spasms. The optional massage function can also be used for temporary:

- Relief of minor muscle aches, pains, and spasms
- Improvement in local circulation

4.1.1 Studies using CoolAdvantage applicators for the upper arms and inner thighs

There have been 2 clinical publications outlining the safety and efficacy of CoolAdvantage applicators for the upper arms. There have been no studies outlining the safety and efficacy of CoolAdvantage applicators for the inner thighs. However, there are 2 studies reporting the use of CoolFit, a legacy CoolSculpting applicator, for the inner thighs. The results of these studies are summarized below.

Rivers 2018 reported the efficacy and safety of using CoolAdvantage applicators in the upper arms of 15 subjects using clinical photography, ultrasound, caliper measurements, and subject satisfaction. In this single-center, open-label interventional study, subjects received simultaneous bilateral arm cryolipolysis treatments with up to two treatment cycles per arm conducted in a single session. Results were assessed 12 weeks after treatment. There was 83% correct identification (by a panel of 3 blinded physicians trained in dermatology or plastic surgery) of clinical photography before and after treatment. Ultrasound measured a mean fat layer reduction of 2.5 mm (SD = 2.4 mm, 95% CI = 1.6 to 3.3 mm) and caliper measurements demonstrated a mean fat layer reduction of 1.3 mm (SD = 1.42 mm, 95% CI = 0.6 to 2.1 mm) after cooling treatment. In addition, 87% of subjects were satisfied, 80% would recommend cryolipolysis to a friend, and 80% felt their appearance had improved after having the procedure. During treatment the average pain score was 1.3 ± 0.9; immediately after device removal pain was 1.4 ± 2.0, and prior to discharge it was 1.0 ± 1.2. At follow-up visits 1, 4, and 12 weeks post-treatment, all subjects reported a pain score of 0. Clinical assessment of the treatment sites was performed immediately post-treatment and at the follow-up visits. Immediately post-treatment, the most common AEs within the treatment area were numbness, erythema, and bruising. By the 4-week follow-up visit, all of these AEs had resolved except for mild numbness in the treatment zone reported by 73% of subjects. At the 12-week final visit, all AEs had resolved spontaneously. There were no reported device- and/or procedure-related complications, including paradoxical adipose hyperplasia.

Carruthers 2017 reported the efficacy and safety of the prototype CoolCup (CoolAdvantage) applicator in the upper arms of 30 subjects using clinical photography and ultrasound. In this multi-center, open-label interventional study, each subject received one cooling cycle to each arm that was assessed 12 weeks after treatment. There was an overall 85.2% ($p < 0.0001$) correct identification of clinical photography by at least 2/3 of blinded reviewers trained in dermatology or plastic surgery. Ultrasound measured a mean fat layer reduction of 3.2 mm, with a SD of 2.7 mm. The intra-treatment pain scores for all 60 arms treated were averaged and the overall average pain score was 1.0, with a SD of 1.2. By the 12-week post-treatment visit, all subjects reported a pain score of 0. Immediately after treatment, the most common side effects within the treatment area were erythema, edema, numbness, and tingling. By the 12-week post-treatment

visit, all side effects had resolved without intervention except for some cases of numbness in the treatment area. The treatment area numbness for these subjects was not clinically significant, did not disrupt normal activities, and spontaneously resolved without intervention. Including the aforementioned prolonged numbness, there were a total of 10 device- and/or procedure-related AEs. Four subjects reported prolonged numbness (bilateral numbness in 3 subjects, unilateral in 1 subject) with a duration longer than 12 weeks. One subject reported bilateral mild erythema that resolved 15 days post treatment. One subject reported minor tingling in the fourth and fifth fingers of her left hand immediately after device removal, which resolved within approximately 20 minutes post-treatment.

Zelickson 2015 reported the efficacy and safety of CoolFit applicators on the inner thighs of 45 subjects. In this multi-center, open-label interventional study, each subject received a single treatment cycle to the inner thigh that was assessed at 8 and 16 weeks after treatment. Clinical photography taken at baseline and at 16 weeks was assessed by 3 blinded independent physicians. Before and after photography was correctly identified in 91% of cases. A statistically significant 0.9 cm reduction of mean circumference was detected at 16 weeks compared to baseline ($p < 0.005$) and ultrasound measurements showed a mean fat layer reduction of 2.8 mm (95% CI = 2.23 to 3.27 mm, SD = 2.3 mm, range = + 3.4 mm to – 9.0 mm). At 16 weeks, subject satisfaction was 93%, 89% would recommend the treatment to a friend, 91% were likely to have a second procedure, and 84% noticed visible fat reduction in their inner thighs after one treatment. All side effects were transient and typical, such as erythema, mild swelling, and numbness. The longest time to full resolution for each of these side effects was 8 days for erythema, 12 days for mild swelling, and 132 days for mild numbness. There were no SAEs related to the device or procedure.

Boey 2014 reported the efficacy and safety of a prototype flat cup applicator (CoolFit) in the inner thighs of 11 subjects. In this single-center, open-label pilot study, each subject received a single treatment cycle to the inner thigh that was assessed at 8, 16, and 24 weeks. The contralateral thigh was an untreated control. Clinical photography taken at baseline and at 28 weeks was assessed by 2 blinded independent physicians and was correctly identified in 86% of cases. Normalized ultrasound measurements comparing baseline to 16 weeks post-treatment demonstrated a 20% reduction following treatment. Participant surveys at 16 weeks revealed 91% were satisfied and 82% felt inner thigh cryolipolysis was comfortable. Side effects in the treatment area, such as numbness and tenderness, were typical and self-resolving by the 8-week follow-up evaluation. No skin-related side effects were reported, such as blistering, persistent erythema, or hyperpigmentation.

4.1.2 CoolSculpting Studies in Asian Participants

It has been reported that 4 studies have assessed CoolSculpting in Asian participants (Putra 2019).

Suh 2018 reported the efficacy and safety of the CoolMini applicator applied to the submental space of 10 Korean subjects. In this single-center, open-label interventional study, each subject received 2 treatment cycles in one session that was assessed after 8 weeks. At 8 weeks, caliper measurement of the submental fat thickness reduced in 9 out of 10 participants, with an average reduction at 4 mm (23.2%). In ultrasound evaluation, there was a reduction of submental fat in

9 subjects at an average of 35.2%. The side effects were transient and tolerable. All participants showed mild erythema and edema, but no reported incidences of purpura, pain, paresthesia, and post-inflammatory hyperpigmentation.

Wanitphakdeedecha 2015 reported the efficacy and safety of CoolFit applicators in the upper arms and inner thighs of 20 Thai female subjects. In this single-center, open-label interventional study, 17 subjects completed the study following a single CoolSculpting treatment to their arms and/or inner thighs that were assessed after 3 and 6 months. There were average circumference reductions at the 3- and 6-month follow-up visits of 0.41 cm (0.87%) and 0.72 cm (1.52%), respectively. Subjects satisfaction surveys showed that most of the subjects were rated to have 1% to 25% improvement at the 3- and 6-month follow-up visits after treatment, respectively. There was no statistically significant difference between the satisfaction at the 3- and 6-month follow-ups ($p = 0.835$). Adverse reactions of 34 treatments included pain, erythema, dysesthesia, and purpura on the treated area. Intra-and post-procedural pain was described as mild to moderate by most of the subjects. The pain score was measured by visual analogue scale of 0 to 10; the mean pain score rated by subjects was 7 (ranging from 1 to 10). Post-inflammatory hypopigmentation, scarring, and paradoxical adipocyte hyperplasia were not observed.

Lee 2013 reported the use of cryolipolysis to reduce fat tissue in the thighs of 14 premenopausal Korean subjects. In this single-center study, CoolSculpting was performed on the left inner thigh for 60 minutes using a Cooling Intensity Factor of -73 mW/cm^2 with radiofrequency applied to the right inner thigh (control sham procedure). The primary endpoint was the difference in the femoral amount measured by computerized tomography from baseline to 12 weeks after treatment. In this study there was an observed 19.5% reduction of fat tissue for CoolSculpting compared to 28.2% reduction for radiofrequency. No major AEs were noted; 4 of 14 subjects experienced pain, whilst 3 of 14 participants reported moderate bruising. The authors concluded they could not show any difference in the reduction of fat following CoolSculpting or radiofrequency and postulated weight gain, inflammation post treatment and study design as postulated reasons for showing no difference.

Shek 2012 reported clinical effectiveness and participant satisfaction of a novel cryolipolysis device (ZELTIQ®) for body contouring after 1 treatment and after 2 treatments to the flanks and abdomen in a commercial setting. Twenty-one Chinese subjects received a single treatment lasting 60 minutes and 12 subjects received 2 treatments lasting 60 minutes each (an average of 3 months apart). The thickness of fat at the treatment site was measured using a caliper and standardized clinical photos were taken at baseline and 2 months post-treatment. There was significant abdominal caliper improvement of 14.67% ($p < 0.0001$) from baseline in the first group of subjects and after both treatments in the second group of subjects; for the abdomen (14% - 1st treatment [$p < 0.0001$], 7.2% - 2nd treatment [$p = 0.02\%$]); flanks (13.4% - 1st treatment [$p=0.003\%$], 4.3% - 2nd treatment [$p=0.084\%$]). Eighty-one percent of subjects were rated to have moderate to good improvement. Subjectively, 80% felt satisfied to very satisfied, and the remaining were indifferent. Eighty-six percent would have considered non-invasive cryolipolysis performed on another part of their body and would consider recommending this treatment to family and friends.

4.2 Rationale

The current CoolSculpting applicators (CoolAdvantage family, CoolMini, and CoolSmooth Pro) are not cleared in China where the flanks and abdomen are the only approved body areas. This study, to be conducted in Canada, will collect meaningful clinical data for the use of CoolSculpting in participants of Chinese descent using CoolAdvantage and CoolAdvantage Petite applicators for the upper arms and inner thighs. Furthermore, it will help support a regulatory submission to the Chinese authorities where submissions are being planned to seek clearance for these applicators and extend the number of body area indications.

4.2.1 Benefit and Risks

4.2.1.1 Benefits

NIFR in the treatment area is anticipated to provide an aesthetic benefit and the use of this non-invasive system will eliminate the need for an invasive procedure that requires anesthesia or recovery time.

4.2.1.2 Risks

Although this study presents minimal risks to the participant, 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 AEs 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 (eg, 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; and
- localized sensory changes (eg, numbness, tingling) at the treatment area spontaneously resolving **without medical intervention within 12 weeks** of the procedure.

If the severity of these anticipated effects causes disruption to the participant's daily activities, then they will be evaluated as a potential adverse effect.

Potential Adverse Effects

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	Skin damage from burns may be due to hot or cold. 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 participant 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 (ie, lasting longer than 12 weeks).
Sensory Alteration Requiring Medical Intervention	Sensory changes (pain, burning, stinging, hypersensitivity) with a severity warranting medical intervention.
Vasovagal Symptoms	The occurrence of symptoms of anxiety, light-headedness, dizziness, nausea, sweating, near syncope, or syncope (fainting).
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 pad or applicator pressure
Subcutaneous Induration	Hardness within the treatment area, either as general firmness or discrete nodules.
Paradoxical Hyperplasia	Visibly enlarged tissue volume within the treatment area which may develop 2-5 months after treatment.
Hernia	Creation or exacerbation of hernia. Hernia is defined as a protrusion of an organ or the fascia of an organ through the wall of the cavity that normally contains it.
Treatment Area Demarcation	Treatment area demarcation: excessive fat removal in the treatment area causing unwanted indentation
Other	Any other untoward medical event determined by the investigator to be an adverse event, regardless of the relationship to the device or treatment.

5 STUDY OBJECTIVE AND ENDPOINTS

5.1 Objectives

The objective of this study is to evaluate the safety and effectiveness of the Allergan CoolSculpting system using CoolAdvantage and CoolAdvantage Petite applicators for NIFR of the upper arms and inner thighs in participants of Chinese descent.

5.2 Endpoints

Primary Endpoint:

- Correct identification of baseline versus 12-week treatment images of the upper arms by at least two out of three blinded, independent reviewers. Success will be defined as at least 75% correct identification of the pre-treatment images.

Secondary Endpoints:

1. Correct identification of baseline versus 12-week treatment images of the inner thighs by at least two out of three blinded, independent reviewers.
2. Participant response of 'satisfied' or 'very satisfied' for question 1 (overall satisfaction) on the following CoolSculpting participant questionnaires at the 12-week visit:
    a. Upper arms
    b. Inner thighs
3. Fat reduction using caliper measurements at 12-weeks compared to baseline for the following areas:
    a. Upper arms
    b. Inner thighs

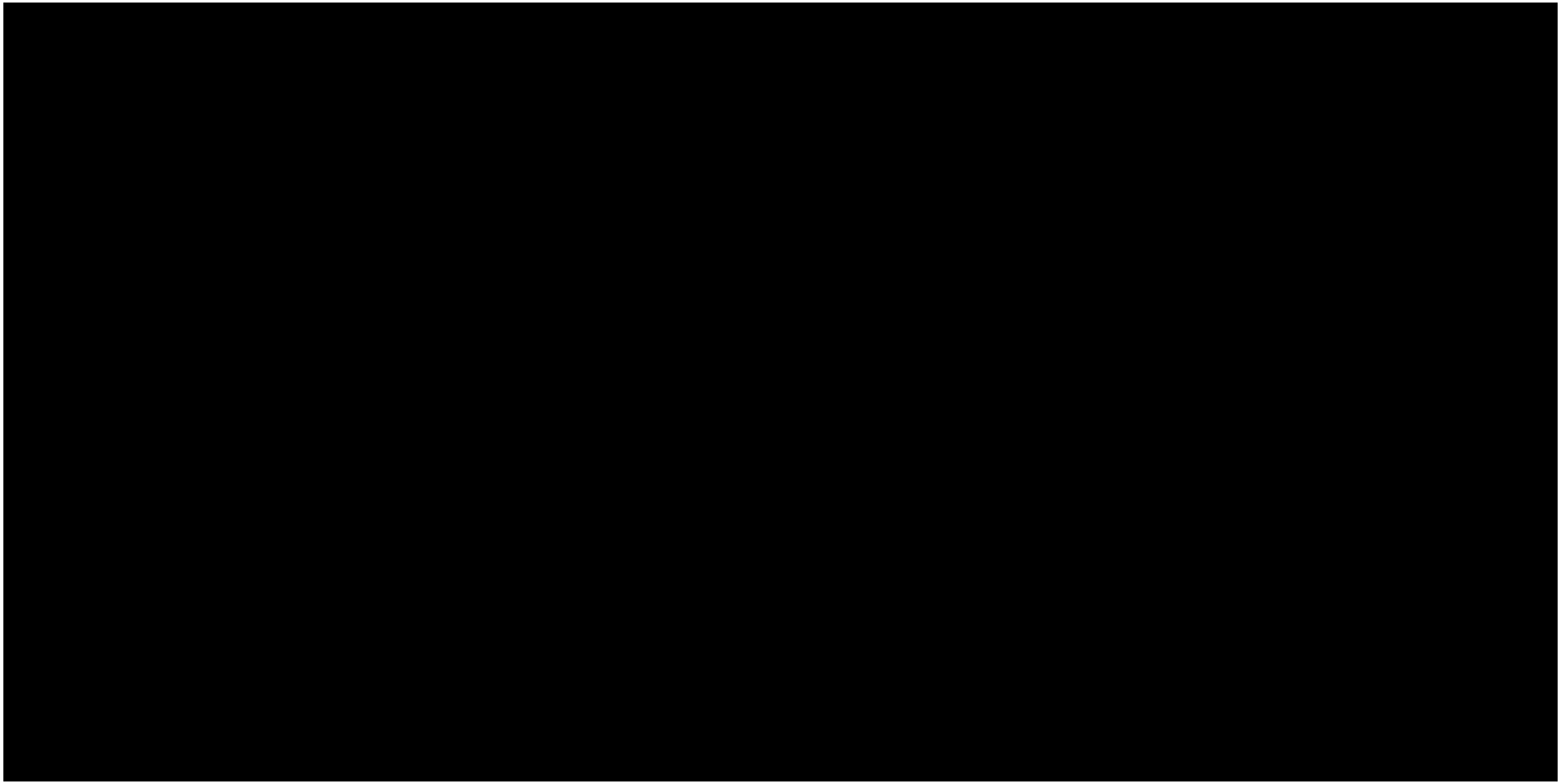
Safety Endpoints:

- AEs, including SAEs; and ADEs, including SADEs.
- [redacted]

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan: Description

Study MED-MA-PLS-0633 is a multi-center, prospective, open-label, nonrandomized, interventional cohort, medical device post marketing study. The Schedule of Assessments is provided in Table 1.



6.2 Discussion of Study Design

The background and rationale that led to the study design are described in Section 4.1 and Section 4.2.

6.3 Selection of Study Population

6.3.1 Number of Planned Participants

Approximately 42 participants will be enrolled at approximately 2-3 sites.

Refer to the statistical considerations on which the numbers are based in Section 9.1.

6.3.2 Inclusion Criteria

To be eligible for study entry, participants must satisfy all of the following criteria:

1. Participant (healthy volunteers) has read and signed the study written ICF.
2. Male or female participant ≥ 18 years of 1st or 2nd generation, non-mixed race, Chinese descent.
3. Participant has clearly visible and palpable fat on the left and right lower aspects of the upper arms and/or left and right inner thighs, which in the investigator's opinion is appropriate and may benefit from the treatment.
4. Participant has not had weight change fluctuations exceeding 4.5 kg (or 5% of body weight) in the preceding month.
5. Participant has a BMI of ≥ 18.5 to ≤ 30. A BMI is defined as weight in kilograms divided by height in meters squared (kg/m^2).
6. Participant agrees to maintain weight (ie, within 5% of body weight) by not making any changes in diet or exercise routine during the course of the study.
7. Participant agrees to have photographs taken of the treatment area(s) during the scheduled time periods.

[redacted]

6.3.3 Exclusion Criteria

Participants will be excluded from the study if one or more of the following criteria are applicable:

1. Participant has a history of an invasive fat reduction procedure (eg, liposuction, surgery, lipolytic agents, etc), or implants in or immediately adjacent to the area of intended treatment.
2. Participant has a history of prior surgery or scar tissue on the arms and/or inner thighs related to the area being considered for treatment.
3. Participant has a known history of cryoglobulinemia, cold urticaria, cold agglutinin disease, or paroxysmal cold hemoglobinuria.
4. Participant has a known sensitivity to cold or has any condition with a known response to cold exposure that limits blood flow to the skin, such as cold urticaria, Raynaud's disease, or Chilblains (pernio).
5. Participant with a clinically significant bleeding disorder, or concomitant use of oral or subcutaneous anticoagulants, or is taking any medication that in the investigator's opinion may significantly increase the participant's risk of bruising.
6. Participant with a history of carpal tunnel syndrome, compartment syndrome, or deep vein thrombosis in the upper or lower extremities.
7. Participant is currently taking or has taken diet pills or weight control supplements within the past 6 months.
8. Participant has any dermatological conditions, such as moderate to excessive skin laxity, infection, open wound, or scars in the location of the treatment sites that may interfere with the treatment or evaluation (stretch marks are not an exclusion).
9. Participant has an active implanted device such as a pacemaker, defibrillator, drug delivery system, or any other metal-containing implant within or adjacent to the area being considered for treatment.
10. Participant is pregnant or intending to become pregnant in the next 3 months.
11. Participant is lactating or has been lactating in the past 6 months.
12. Participant is unable or unwilling to comply with the study requirements.
13. Participant is currently enrolled in a clinical study of any unapproved investigational device, investigational product, or any other type of medical research judged not to be scientifically or medically compatible with this study.

14. Participant has any other condition or laboratory value that would, in the professional opinion of the investigator, potentially affect the participant's response or the integrity of the data or would pose an unacceptable risk to the participant.
15. Participant has had a NIFR and/or body contouring procedure in the area(s) of intended treatment within the past 12 months.
16. Participant needs to administer, or has a known history of subcutaneous injections, into the area(s) of intended treatment (eg, cortisone, heparin, insulin) within the past 6 months.
17. Participant with known sensitivity or allergy to fructose, glycerin, isopropyl alcohol, or propylene glycol.
18. Participant with impaired peripheral circulation in the area to be treated.
19. Participant with neuropathic disorders such as post-herpetic neuralgia or diabetic neuropathy.
20. Participant with impaired skin sensation.
21. Participant with a history of hernia in or adjacent to the treatment area(s) site.
22. Participant with a skin condition such as eczema, dermatitis, or rashes in the area to be treated.
23. Participant diagnosed with a systemic fibrosing disease or fibrosis in the area intended or adjacent to the area to be treated.

6.3.4 Removal of Participants from Therapy or Assessments

Notification of early participant discontinuation from the study and the reason for discontinuation will be provided to the sponsor and will be clearly documented on the appropriate CRF.

Reasons for discontinuation from the study may include the following:

- Completed
- Other
- Physician decision
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor

- Technical problems
- Withdrawal by subject

Participants who do not comply with the protocol or who withdraw consent will not be replaced. Participants who stop study treatment for any other reason will not be replaced. Participants are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the CRF.

Participants withdrawing from the study will be encouraged to complete the same final evaluations as participants completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for participants who completed the study.

Reasonable efforts will be made to contact participants who are lost to follow-up. These efforts must be documented in the participant's file.

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the CoolSculpting procedure or the company occur, making further treatment of participants impossible. In this event, the investigator(s) will be informed of the reason for study termination.

Pregnancy

Female participants will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator, who fills out a provided pregnancy surveillance form. The form needs to be sent to the sponsor within 24 hours of awareness of a confirmed pregnancy to the following email address:
CoolSculptingProductSurveillance@allergan.com

Once pregnancy is confirmed, the participant will be immediately withdrawn from the study. Upon discontinuation from the study, only those procedures that would not expose the participant to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a participant is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery using the second page of the pregnancy surveillance form.

Full details will be recorded on the withdrawal page of the CRF.

6.4 CoolSculpting System

6.4.1 CoolSculpting Description

Participants will undergo a CoolSculpting treatment in an outpatient clinical setting. A treatment is comprised of timed segments of cooling. Treatments will be administered according to the User Manual CoolSculpting System that has been prepared for specific countries. The

CoolSculpting System, also labelled as the ZELTIQ System or the ZELTIQ Breeze System, is a non-invasive cooling device that applies controlled cooling to a treatment site on the participant's skin.

6.4.2 Identity of CoolSculpting System

The CoolSculpting System is comprised of a control unit, a surface or vacuum applicator, and supplies such as cards, foam borders, gel pads, liners, pre-treatment skin wipes, and securement systems. The applicators, foam borders, gel, gel pads, liners, pre-treatment skin wipes, and securement systems are participant-applied parts.

During a treatment, the operator applies a gel/gel pad and applicator to the participant's skin. The vacuum applicator draws tissue into the applicator cup and holds the tissue against the cooling surfaces of the applicator. The operator starts the treatment. Sensors in the cooling surfaces of the applicator monitor the skin surface, providing feedback that controls the rate of heat flux. The gel/gel pad protects the skin by providing thermal coupling at the interface between the cooling surfaces of the applicator and the skin. The card provides cycles and profiles for use with the system.

The CoolSculpting System operates at temperatures below 0°C, which can freeze tissue. Therefore, the system monitors tissue during cooling and employs multiple safety features, including the Freeze Detect system, to minimize the risk of damage to tissue. In spite of these multiple safety features, on rare occasions, a possible freeze condition may occur that can be detected by the Freeze Detect System.

The Freeze Detect system is comprised of several features, including thermal sensors and proprietary algorithmic software. Freeze Detect is an integral part of the CoolSculpting System and is automatically employed when a treatment is initiated. When the Freeze Detect system detects a possible freeze condition, it stops the treatment and displays a Z409 message. If this message is received, remove the applicator and gel pad or gel, and assess the tissue before taking further action. The current recommended practice is to wait at least 24 hours before retreating the area relating to a Z409 error message. Failure to follow instructions could result in injury to the participant, including first- or second-degree burns. Second-degree burns or complications of second-degree burns may result in hyperpigmentation.

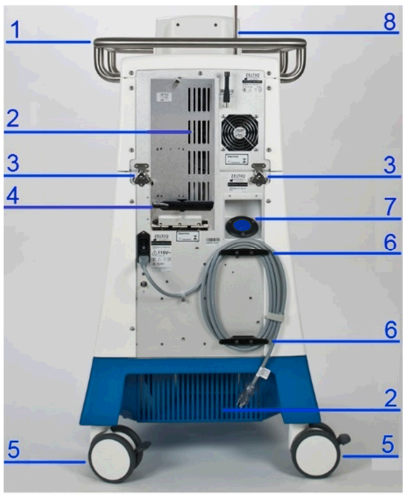
6.4.2.1 Control Unit

Control Unit - Front View

Components - Front View

1. Rail: When the applicator is resting on top of the control unit, the rail helps keep the applicator in place. In addition, the rail is used as a handle to move the system.
2. Vents: Vents provide airflow that reduces heat build-up inside the control unit. Ensure all vents are free from obstructions when the control unit is in operation.
3. Drawer: The drawer provides storage space for supplies and user documentation.
4. Casters and Locks: The control unit has four casters that swivel. Each caster has a lock. Always engage the locks on all four casters before you use the control unit.
5. Screen: The screen displays system controls, information about the status of the system, information about the treatment, and messages for the operator.

Control Unit - Rear View



Components: Control Unit, Rear View

1. Rail: When the applicator is resting on top of the control unit, the rail helps keep the applicator in place. In addition, the rail is used as a handle to move the system.
2. Vents: Vents provide airflow that reduces heat build-up inside the control unit. Ensure that all vents are free from obstructions when the control unit is in operation.
3. Latches: The latches lock the upper and lower modules of the control unit together.
4. Antenna: The antenna and data modem send data to Allergan (availability and use of the data modem are subject to regional limitations).
5. Casters and locks: The control unit has four casters that swivel. Each caster has a lock. Always engage the locks on all four casters before you use the control unit.
6. Cleats: When the power cord is not in use, wrap it loosely around the cleats.
7. Chiller tank cap: The chiller tank cap provides access to the chiller tank for checking the coolant level and adding coolant.
8. Support Arm: Drape the applicator cable over the support arm to minimize drag on the connections and to keep the cable out of your way. Use the Velcro® straps to secure the cable to the support arm.

6.4.2.2 Applicator

The applicator delivers controlled cooling to the treatment site.

The applicator consists of the applicator connector, the applicator cable, and the applicator head.

The applicator is used with supplies provided by Allergan.

6.4.3 Packaging and Labelling

Clinical study materials will be labelled according to the country's regulatory requirements.

6.4.4 Method of Assigning Participants to Treatment Groups

At screening, after the participant has signed the ICF, the participant will be assigned a participant number sequentially based on the order in which the participant is screened into the study. This participant number will serve as the participant identification number on all study documents.

6.4.5 Blinding

This is an open-label study. Blinding will only be employed for photograph review by an independent panel of physician reviewers with expertise in the areas of dermatology and/or plastic surgery.

6.4.6 Prior and Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study. Diet pills or weight control supplements are not permitted (see exclusion criterion # 7 in Section 6.3.3).

6.4.7 Treatment Compliance

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, protocol deviation, or protocol exemption, as defined below.

Protocol Violation

A violation is any non-adherence to the protocol that may result in significant additional risk to the participant (eg, enrollment of a participant who does not meet the study criteria). A protocol violation can also be an event of non-adherence to GCPs that may impact participant safety (eg, failure to obtain proper consent before performing study procedures). Violations should be reported to the study sponsor and the IRB within 5 working days if they occur.

Protocol Deviation

A deviation is any non-adherence to study procedures that does not result in additional risk to the participant (eg, participant missed a visit). Protocol deviations are not required to be reported to the IRB; however, they must be recorded on the study CRFs and may be reported and reviewed in conjunction with the progress report as part of the annual review process.

7 TIMING OF STUDY PROCEDURES

Participants will provide written informed consent before any study-related procedures are performed.

The planned study assessments are provided in Section 6.1.1.

[redacted]

[redacted]

[redacted]

8 EFFECTIVENESS AND SAFETY ASSESSMENTS

The planned schedule of assessments is provided in Section 6.1.1.

8.1 Effectiveness Assessments

8.1.1 Photography

A series of baseline and follow-up photographs of the treatment areas will be taken using standardized set up, lighting, and camera settings to ensure consistency. The participants' faces will not be on the photographs. No other identifiable participant information will be recorded on the photographs. Where participant identifiable markings are seen within the treatment area, the images containing these markings will not be used for the purpose of publications but kept as part of the study record in the TMF. The photographs may be cropped or re-sized for comparison purposes but otherwise will not be re-touched or altered in any way. Image files will be stored electronically by Allergan in addition to Quantificare and indexed by participant identifier. Copies of participant photographic data will be filed at the clinical site.

Photos will be reviewed by a blinded independent panel of physician reviewers with expertise in the areas of dermatology and/or plastic surgery. All photographs will be blinded by removing the participant identification and dates of the photographs. The reviewers will be presented with two series of photographs for each treatment area, the pre-treatment and the post-treatment series, and asked to select the series representing the pre-treatment photographs. The order in which the photographs are presented will be randomized by participant. The order in which the pre- and post-treatment series are presented will also be randomized. The reviewers will be asked to select the baseline photograph series for each treatment area and record their data on individual data collection forms provided by the Sponsor.

8.1.2 Participant Satisfaction

Participant satisfaction data will be collected via written questionnaires at the final 12-week follow-up visit. These questionnaires have been developed based on questions used in previous CoolSculpting studies and modified to pertain to specific body areas treated (upper arms and inner thighs). One or two questionnaires will be provided depending on the body areas treated (upper arms and/or inner thighs). For the upper arm participant satisfaction questionnaire, see Section 15.3.1. For the inner thigh participant satisfaction questionnaire, see Section 15.3.2.

8.1.3 Caliper Measurement

Caliper measurements of the treatment areas will be taken at pre-treatment and at 12-weeks post final treatment. After the treatment area is identified and marked, the thickness of the fat layer will be measured using a caliper at the middle of the fat bulge. For each treatment area, 3 measurements will be taken and recorded. The average of the three measurements will be calculated. The location of where measurements are taken will be recorded on a transparency sheet or equivalent, along with reference points using the participant's body landmarks (such as a mole, skin pigmentation, etc). This transparency may be used at the post treatment visit to locate the measurement sites. In addition, to further ensure the quality and consistency of the

measurements, the same staff member should perform the caliper measurements for each participant. For further details on caliper measurements, please see Section 15.4.

8.2 Safety Assessments

Throughout the course of the study, all AEs will be monitored and reported on an AE CRF, including seriousness, severity, action taken, and relationship to study treatment. If AEs occur, the first concern will be the safety of the study participants.

Safety will be monitored by documentation of AEs and clinical assessment of the treatment sites. Post-treatment sensory changes outside of treatment areas will also be documented and assessed.

8.2.1 Adverse Events

Throughout the course of the study, all AEs will be reported and monitored on an AE CRF, including event name, duration, seriousness, relatedness, severity, action taken, and outcome. If AEs occur, the first concern will be the safety of the study participants. AEs and device deficiencies are to be recorded on the corresponding CRF for the participant upon the site becoming aware of said event. Additionally, SAEs and UADEs will be reported using SAE forms within 24 hr of awareness.

AEs will be collected throughout the study once there is a signed ICF. At each visit, the investigator or designated study staff will solicit and assess the participant for AEs. Previously recorded AEs and changes in therapy/concomitant medications are to be updated as necessary. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate CRF.

Adverse Event Definition

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 participants, users, or other persons, if related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. Disease signs and symptoms that existed before the study treatment are not considered AEs unless the condition recurs after the participant 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 once the participant has signed the ICF. At each post-baseline visit, the investigator will begin querying for AEs by asking each participant 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 eCRF.

Adverse Device Event

An ADE is defined in accordance with ISO 14155 as "an adverse event related to the use of an investigational medical device." This definition includes any AEs 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.

Device Deficiency or Complaints

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

If a device deficiency occurs, the investigator will notify Allergan using the CRF. Device deficiencies shall be documented throughout the study and appropriately managed by Allergan. The Clinical Trial Site will enter all the information regarding device deficiency into the appropriate CRFs. Device deficiencies associated with AEs will also require completion of SAE forms. Allergan shall review all device deficiencies and determine and document in writing whether they could have led to a SADE. These shall be reported to the regulatory authorities and IRBs as required by Federal regulations.

Assessment of Severity

Severity is a clinical determination of the intensity of an AE. The severity assessment for a clinical AE will be assigned a category by the investigator as follows:

Mild	An AE that is easily tolerated by the participant, causes minimal discomfort, may require only minimal treatment and does not interfere with everyday activities.
Moderate	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed, but poses no significant or permanent risk of harm.
Severe	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Relationship to a device refers to a determination of the relationship (if any) between an AE and the device. A causal relationship is present if the investigator determines that there is a reasonable possibility that the AE may have been caused by the device.

An AE could be considered procedure-related when, in the judgment of the investigator, it is reasonable to believe that the event is associated with the procedure, regardless of the relationship to the study device. Procedure-related causes that contribute to the occurrence of the

event can be attributed to other products, surgical techniques, or medications required specifically for the procedure.

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the device and/or study procedure. Causality should be assessed using the categories presented in the following table:

Not related	Clinical event of which the relationship to the device and/or procedure can be excluded, such as if the event has an incompatible time relationship to study procedure and/or use of the device, involves a body part or organ not expected to be affected by the device or procedure, could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study device, and is not due to use error.
Unlikely	Clinical event whose time relationship to use of the device and/or study procedure makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible	Clinical event with a reasonable time relationship to the use of the device and/or study procedure, but that could also be explained by concurrent disease or other drugs or chemicals. Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	Clinical event with a reasonable time relationship to the use of the device and/or study procedure, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Causal relationship	Clinical event with plausible time relationship to the use of the device and/or study procedure, is a known side effect of the product category the device belongs to or of similar devices and procedures; follows a known response pattern to the medical device; involves a body-site or organ that the device or procedures are applied to and/or influence; harm is due to error in use, and that cannot be explained by concurrent disease or other drugs or chemicals.

Follow-up of Adverse Events

All investigators should follow up with participants with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the CRF.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages. The following data should be documented for each AE in the appropriate CRF fields:

- Description of the symptom event.
- Classification of 'serious' or 'not serious.'
- Severity.
- Date of first occurrence and date of resolution (if applicable).
- Action taken.
- Causal relationship.
- Outcome of event.

8.2.1.1 Serious Adverse Events

Serious Adverse Event Definition

An SAE is defined as an AE that:

- led to death
- led to serious deterioration in the health of the participant, that either resulted in
    - a life-threatening illness or injury; or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization; or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
    - if a participant becomes pregnant, then spontaneous abortion, fetal distress, fetal death, or a congenital abnormality or birth defect is considered an SAE

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the participant or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Serious Adverse Device Effect (SADE)

All device or surgical related SAEs must be entered into the EDC system within 24 hours of being notified of the event. The sponsor will be notified by EDC system once the SAE electronic form has been submitted.

- The relationship of the clinical event to the devices and procedure should be reported on the Form and will be determined by the investigator.
- Following evaluation of each SAE, the responsible ethics committee will be notified as appropriate based on national regulations.
- All SAEs that occur from the time the ICF is signed through to their final study visit must be reported to the sponsor. In addition to entering the information into the EDC system, the investigator must:
- Notify the sponsor immediately (within 24 hours) by emailing the Allegan Product Surveillance team at: CoolSculptingProductSurveillance@allergan.com

The following SAE information should be provided:

- Description of the symptom event (including treatment dates, areas treated, event description, etc)
- Applicator(s) and Serial Number used during treatment
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event: report as much information within 24 hours regardless of the amount of information available, although the investigator is expected to provide as much information as possible.

Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the participant.

Provide the sponsor with a complete, written case history (AE report form) that includes a statement as to whether the event was or was not related to the use of the investigational device or procedure.

The sponsor (or its representative) will report all SAEs associated with the use of the study device to the regulatory agencies (Ethics Committee, Competent Authorities) as appropriate according to relevant standard operating procedures and to the national laws of the country where the trial is performed.

In every SAE, appropriate measures should be taken to treat/resolve and monitor the participant. The investigator should keep Allergan closely informed of the progress as related to the SAE. Any participants who are withdrawn from the study due to an AE shall still be followed until the outcome is resolved.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 6.3.4.

8.2.1.2 Unanticipated Serious Adverse Device Effect

Unanticipated Serious Adverse Device Effect Definition

An unanticipated serious ADE is a SADE effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

8.2.2 Warnings and Precautions

Unauthorized modification or repair of the control unit, its components, or supplies may result in unsafe conditions and/or impaired performance. No modification of this equipment is allowed without express authorization from Allergan. Any unauthorized modification or repair will void the warranty.

CoolSculpting System use has not been studied in children, those who are pregnant or lactating, or who have:

- Known sensitivity to cold such as cold urticaria, Raynaud's disease, or Chilblains (pernio)
- Known sensitivity or allergy to fructose, glycerin, isopropyl alcohol, or propylene glycol
- Impaired peripheral circulation in the area to be treated
- Neuropathic disorders such as post-herpetic neuralgia or diabetic neuropathy
- Impaired skin sensation
- Open or infected wounds
- Bleeding disorders or concomitant use of blood thinners
- Recent surgery or scar tissue in the area to be treated
- Hernia in or adjacent to the treatment site
- Skin conditions such as eczema, dermatitis, or rashes in the area to be treated

8.2.3 Other Laboratory Variables

Screening for pregnancy will be performed (urine β-HCG at the Screening and Treatment visits).

[redacted]

8.3 Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

SAEs and UADEs must be reported within 24 hours of knowledge of the event to the Sponsor at the following email address:

CoolSculptingProductSurveillance@allergan.com

A full reporting of the event shall be provided within 2 working days of the event. The Sponsor is then responsible for notifying the IRB, as required.

8.4 Data Safety Monitoring Board

Not applicable.

8.4.1 Appropriateness of Measurements

The effectiveness and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant.

9 STATISTICAL METHODS

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses.

Data will be summarized based on the nature of the data. Categorical (eg, gender, independent photographic review) data will be tabulated by category. The mean, standard error, maximum, and minimum will be tabulated for continuous data (eg, age). The significance level will be two-sided 0.05 for all statistical tests.

9.1 Determination of Sample Size

In this study, both arms and thighs will be evaluated by independent raters. The independent raters' evaluations will be combined into one clinical judgement on each arm and thigh. The evaluations on arms and thighs will be considered as independent.

Rivers 2018 described that the rate of correct identification was 83%. Using 75% as the lower bound of the 95% CI, the ½-width of the 95% CI will be 8%.

Based on these assumptions, we will need 60 evaluable arms or 32 evaluable participants for the arm evaluations with the assumption that less than 10% of participants have only one arm evaluation available. The same number of participants for thigh evaluations will be needed.

With an assumption that only 80% of all subjects will have both arms and thighs treated, we will need 38 evaluable participants in total for the study. Adding a 10% attrition rate, we will need to enroll 42 participants in the study.

9.2 Populations for Analyses

1. PP population: The PP population will consist of all treated participants followed for 12 weeks and with weight change of no more than 5% of total body weight at the time the 12-week images are taken. Because a weight change of more than 5% will affect the images, the primary effectiveness analysis will be performed based on this study population. Participants who do not complete treatment on the upper arms and/or inner thighs will not be included in the effectiveness analyses.
2. AT population: The AT population will consist of all treated participants regardless of weight change, etc.
3. Safety population: The safety population will consist of all the treated participants with at least one safety evaluation after the treatment. This population should be identical to the AT population. All safety data analyses will be performed based on the safety population.

9.3 Statistical Analyses

9.3.1 Disposition, Baseline and Study Information

In general, disposition data, participant baseline and characteristics data, and concomitant therapy data will be summarized descriptively. The categorical variables will be presented with number and proportion while the continuous variables will be presented with mean, SD, median, minimum, and maximum.

9.3.1.1 Participant Disposition

The number of participants who have enrolled into the study, the number and percentage of participants who have had the procedure, the number and percentage of participants who have had all follow-up visits, and the number of participants who discontinued and the reasons for discontinuation will be summarized.

9.3.1.2 Participant Baseline and Characteristics

The demographics (age, sex, race [including determination of 1st or 2nd generation Chinese descent]) of participants will be summarized.

The summary on height, weight, and BMI will be also provided. The number and percentage of participants by BMI category (normal 18.5 to 25, overweight 25 to 30) will also be provided.

9.3.1.3 Concomitant Therapy

The concomitant therapy (drug and/or procedure) that a participant has during the study will be recorded and summarized.

9.3.1.4 Treatment Compliance

The treatment compliance will not be applicable in this study.

9.3.2 Effectiveness Analyses

The primary effectiveness analysis will be based on the PP population.

9.3.2.1 Primary Effectiveness Analysis

The number and proportion of participants with correct identification of baseline vs 12-week images of the upper arms by at least two out of three blinded, independent reviewers and the corresponding 95% CI of the proportion of participants with correct identification will be summarized.

9.3.2.2 Secondary Analyses

The number and proportion of participants with correct identification of baseline vs 12-week images of the inner thighs by at least two out of three blinded, independent reviewers and the

corresponding 95% CI of the proportion of participants with correct identification will be summarized.

Participants who have reported 'Very satisfied' or 'Satisfied' on each of the CoolSculpting participant questionnaires (upper arms and inner thighs) for question #1 (overall satisfaction) will be categorized as 'Satisfied.' The numbers and proportions will be summarized and the 95% CI of the proportions will be provided.

Fat reduction at 12 weeks compared to baseline will be summarized descriptively.

[redacted]

9.3.3 Safety Analyses

The numbers and proportions of participants with AEs, SAEs, ADEs, and SADEs will be summarized. The numbers and proportions of participant-reported pain scores (0 to 10 scale) will be summarized.

9.3.3.1 Subgroup Analyses

Subgroup analyses will be documented in the SAP.

9.3.4 Interim Analyses

No interim analyses are planned for this study.

9.4 Protocol Deviations

Major protocol deviations will be determined before database lock. Details will be outlined in the SAP.

10 QUALITY ASSURANCE AND QUALITY CONTROL

10.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion

10.2 Monitoring

Data for each participant will be recorded on a CRF. Data collection must be completed for each participant who signs an ICF and is administered study treatment.

In accordance with current GCP, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the independent ethics committee (IEC)/IRB, the sponsor's internal auditors, and representatives from regulatory authority's direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs

10.3 Data Management and Coding

The sponsor or sponsor's agent will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of sponsor or agent.

Study centers will enter data directly into an EDC system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

11 RECORDS AND SUPPLIES

11.1 Device Accountability

Not applicable.

11.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the sponsor and investigator's site.

12 ETHICS

12.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the participants, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the participants or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

12.2 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, and the applicable national and local laws and regulatory requirements.

12.3 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no participant undergoes any study-related examination or activity before that participant has given written informed consent to participate in the study.

The investigator or designated personnel will inform the participant of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The participant should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the participant will be given ample time to consider the study. Participants will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the participant ICF will be provided to the participant or their authorized representative.

It should be emphasized that the participant may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the participant is otherwise entitled. Participants who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s). The study

participants will be informed about this new information and reconsent will be obtained.

12.4 Participant Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, as well as that of any other applicable agency(ies), will be granted direct access to the study participants' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the participants to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the participant's identity will remain confidential.

13 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last participant), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all participant medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multi-center studies must not be published separately.

14 REFERENCES

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15 APPENDICES

15.1 Investigator Signature Page

Protocol Title: CoolSculpting® the Upper Arms and Inner Thighs in Participants of Chinese Descent (XinCOOL)

Protocol Number: MED-MA-PLS-0633

Confidentiality and Current GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant regulatory guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Allergan and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Allergan and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the participants' state of health will be regarded as confidential. No participants' names will be disclosed. All participants will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the participant before disclosure of participant information to a third party.

Information developed in this clinical study may be disclosed by Allergan, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

15.2 CoolSculpting Procedure Training Guides