NCT03909100

Study ID: CMO-MA-PLS-0602

Title: International CoolSculpting: Prospective, Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen and/or Flanks (iCool)

Statistical Analysis Plan Date: October 6, 2018

1.0 TITLE PAGE

STATISTICAL ANALYSIS PLAN

International CoolSculpting: Prospective, Multiple-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen and/or Flanks (iCOOL)

Final: Version 1.0

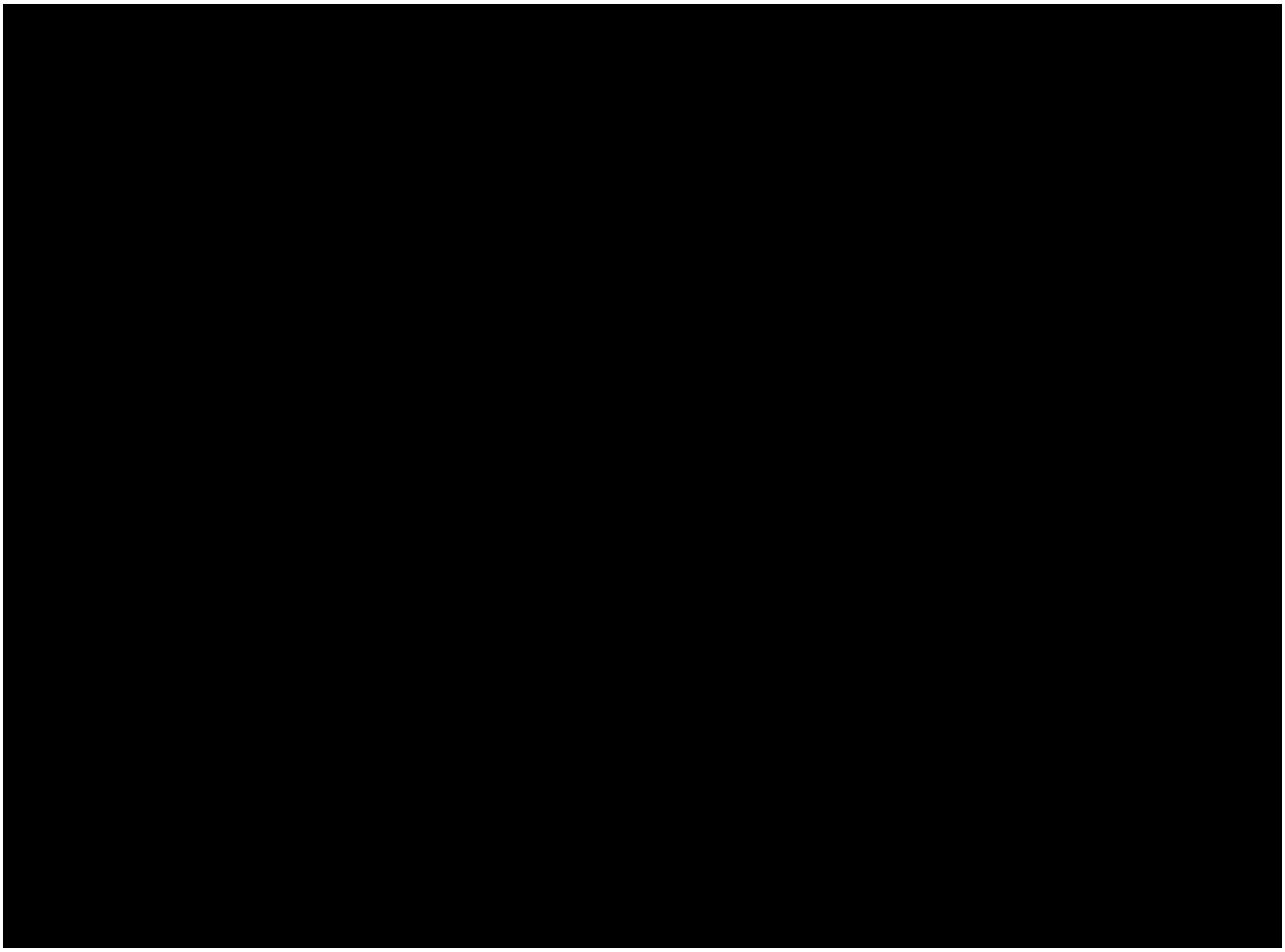
Protocol Number:	CMO-MA-PLS-0602
Development Phase:	Post-Marketing
Product Name:	CoolSculpting®
Study Statistician:	[redacted]
Sponsor:	Allergan Sales, LLC 5 Giralda Farms Madison, NJ 07940 USA +1-714-246-4500 +1-800-347-4500

Confidentiality Statement

STATISTICAL ANALYSIS PLAN

Signature Page

Protocol Number: CMO-MA-PLS-0602



2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

3D	three-dimensional
AE	adverse event
ADE	adverse device effect
BMI	body mass index
[redacted]	[redacted]
CSQ	Cryolipolysis Satisfaction Questionnaire
[redacted]	[redacted]
CI	confidence interval
eCRF	electronic case report form
CI	confidence interval
PT	Preferred Term
SAE	serious adverse event
SADE	serious adverse device effect
SOC	System Organ Class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the effectiveness and safety data as outlined and/or specified in the most recent protocol amendment of Study CMO-MA-PLS-0602 (version dated 20 Nov 2019). Specifications of tables, figures, and data listings are contained in a separate document.

Study CMO-MA-PLS-0602 is a multi-country, multi-center, non-randomized, open-label, single-arm, medical device post-marketing study in healthy volunteers with age ≥ 22 and ≤ 65. All participants will undergo CoolSculpting® treatments(s) in an outpatient clinical setting. A treatment is comprised of timed segments of tissue cooling followed by massage.

The length of this study will be up to 20 weeks, not including the ≤ 7 days screening visit. Signed informed consent from the participants will be obtained before any study-related procedures are performed. All participants will be assigned a participant number sequentially based on the order in which the study participant is enrolled into the study. Participants meeting the inclusion criteria will be assigned to receive up to 2 treatment sessions 8 weeks apart and final follow-up 12 weeks after the final treatment (measured at week 12 for participants who receive 1 treatment session, or week 20 for 2 treatment sessions). 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.

No interim analyses are planned for this study.

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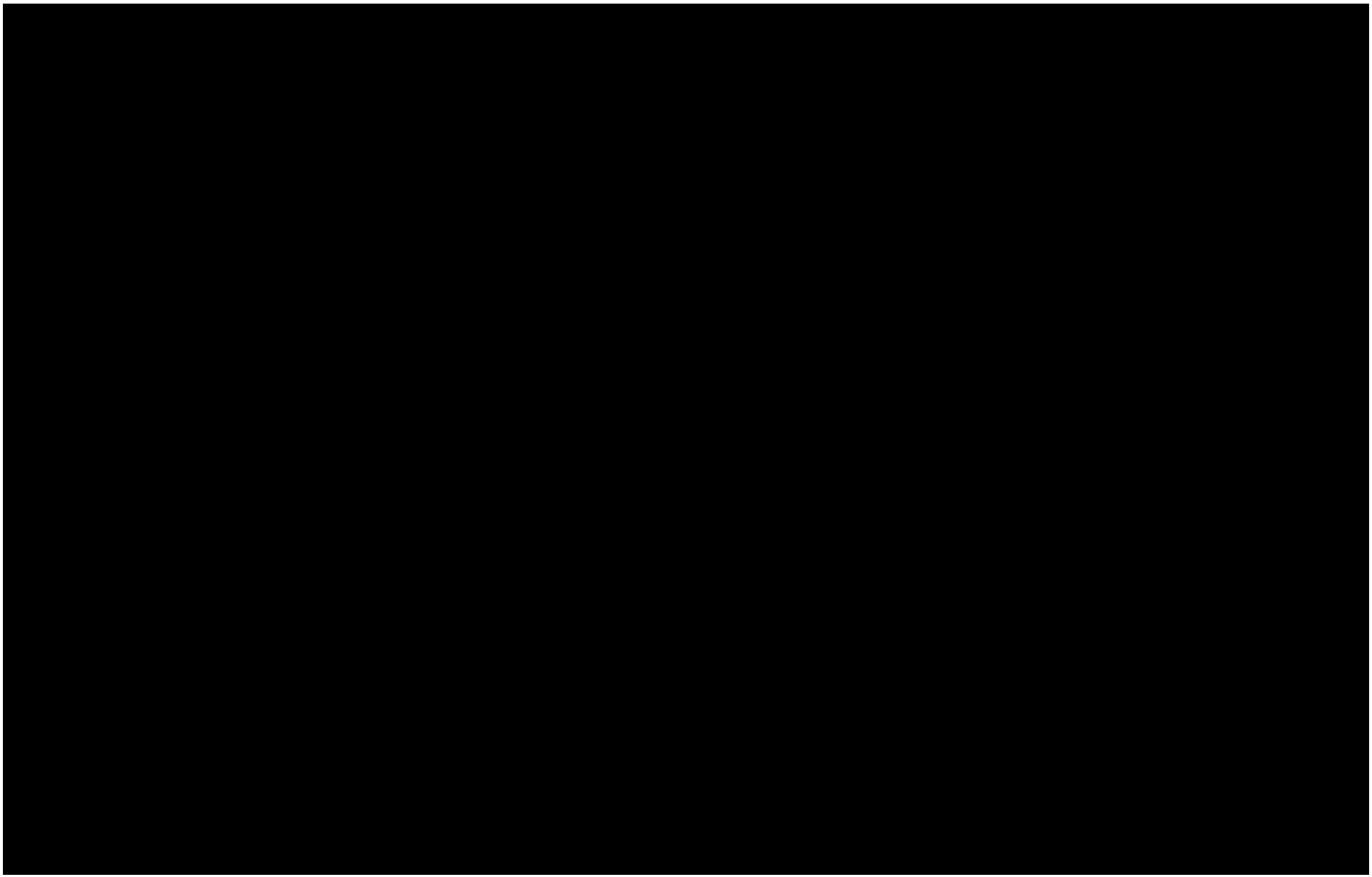

5.1 OBJECTIVES

Primary Objective

The primary objective is to evaluate overall patient satisfaction for non-invasive fat reduction in CoolSculpting® participants.

Secondary Objectives

1. To evaluate overall satisfaction for non-invasive fat reduction in abdomen alone, flank alone, and abdomen and flanks in CoolSculpting® participants.

2. To evaluate overall satisfaction for non-invasive fat reduction in CoolSculpting® participants by number of treatment cycles.

3. To evaluate overall satisfaction for non-invasive fat reduction in CoolSculpting® participants by BMI (normal: 18.5 to <25, overweight: 25 to ≤30).

4. To evaluate change in volume of fat after CoolSculpting® treatment(s) using 3D photography.

5. To determine the frequency of AEs, including SAEs; and ADEs including SADEs.

[redacted]

1. [redacted]

[redacted]

[redacted]

[redacted]

6.1 PARTICIPANT POPULATIONS

6.2 ENROLLED POPULATION

The enrolled population will consist of all participants who sign the informed consent form.

6.3 EVALUABLE POPULATION

The evaluable population will consist of all participants who sign the ICF, have at least one of the procedures conducted, and also report the CSQ Item #1 at 12 weeks after the final treatment (measured at Week 12 for participants who receive 1 treatment session and at Week 20 for participants who receive 2 treatment sessions).

6.4 SAFETY POPULATION

The safety population will consist of all participants who have at least one of the procedures conducted.

6.5 OTHER POPULATIONS

Not applicable.

6.6 DATA COLLECTED BUT NOT ANALYZED

Not applicable.

7.1 PARTICIPANT DISPOSITION

The number of participants who are in the enrolled population and the number and percentage of participants who are in the safety population and evaluable population will be summarized.

The number and percentage of participants who complete the study and who prematurely discontinue from study will be presented for enrolled population; furthermore, the number and percentage of participants discontinued prematurely from study will be presented by the primary reason for discontinuation as collected on the eCRF. Reasons for pre-mature discontinuation from the study include:

- Physician decision
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problems
- Withdrawal by subject
- Lost to follow up
- Other

8.1 DEMOGRAPHICS AND OTHER BASELINE DATA

8.2 DEMOGRAPHICS

Demographic parameters will be summarized descriptively for the safety and evaluable populations. Demographic parameters include age, age group (22-29, 30-39, 40-49, 50-59, 60-65), sex, and race (White, Black, Asian – Chinese, Asian – Japanese, Asian – Korean, Asian - Other, Arab/Middle Eastern, Other, Choose not to answer). Age will be calculated in years from year of birth to the informed consent date.

8.3 BASELINE CHARACTERISTICS

Baseline characteristics will be summarized descriptively for the safety and evaluable populations. Baseline characteristics include weight, height, Fitzpatrick Skin Type (I, II, III, IV, V, VI), body mass index (BMI), and BMI category (18.5 - <25, 25 - ≤30); where BMI is calculated as weight [kg]/(height [m])^2.

8.4 MEDICAL AND SURGICAL HISTORIES

Abnormalities in participants' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or newer. The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized for the Safety Population.

The summary table by SOC and PT will be presented with SOC in alphabetical order and in decreasing frequency within each SOC. If more than one medical and surgical history term is coded to the same preferred term for the same participant, the participants will be counted only once for that preferred term.

8.5 PRIOR AND CONCOMITANT MEDICATIONS

Prior medication is defined as any medication taken before the date of the first study treatment. *Concomitant medication* is defined as any medication taken on or after the date of the first study treatment. World Health Organization (WHO) Drug Dictionary, Global B3 version 201903 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

The number and percentage of participants with use of prior medications will be summarized by WHO drug class and preferred drug name for the Safety Population. Similarly, the number and percentage of participants with use of concomitant medications will be summarized by WHO drug class and preferred drug name for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Formulations (including salts, esters, etc.) containing the same active ingredient will be pooled under the coded drug name of the base compound. Medications containing multiple active ingredients of different coded drug names will be reviewed during the course of the study and may be pooled under a single coded drug name for analyses.

8.6 PROTOCOL DEVIATIONS

The number and percentage of participants with important protocol deviations will be summarized for all participants. Deviations related to the following categories will be included:

- Inclusion or exclusion criteria
- Withdrawal criteria
- Treatment
- Concomitant medications

Protocol deviations will be reviewed and documented before database lock.

9.1 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.2 EXTENT OF EXPOSURE

For each treatment area, the treatment duration in each treatment cycle will be calculated as the number of minutes from the time of treatment cycle start to the treatment cycle end; the treatment duration in a treatment session is the sum of the treatment durations from all treated cycles. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented by treatment session cycle and by treatment area.

In addition, descriptive statistics will be presented for combined treatment sessions; and similarly, for combined upper and lower abdomens, combined right and left flanks, and for all treatment areas combined. The treatment duration for the combined treatment areas is defined as sum of the treatment durations from the corresponding treated areas, regardless of overlapped duration.

Number and percentage of participants with treatment interrupted or discontinued along with the reason will be presented by treatment session and by treatment area.

9.3 MEASUREMENT OF TREATMENT COMPLIANCE

The study investigators are responsible for performing the study in compliance with the protocol. The treatment compliance will not be applicable in the study.

10.1 EFFECTIVENESS ANALYSES

The effectiveness analyses will be based on the evaluable population. Baseline is defined as the last non-missing assessment before the first cycle of treatment.

In addition to the entire evaluable population, summaries will be provided for the following cohorts:

- Participants with 1 treatment session
- Participants with 2 treatment sessions

Some effectiveness parameters are also measured or reported at 8 weeks post treatment session #1. Descriptive summaries will be provided for this visit similar as for the effectiveness endpoints at the final visit.

10.2 PRIMARY ANALYSIS

The primary endpoint of the study will be the overall participant satisfaction based on CSQ Item question #1 at 12 weeks after the final treatment (measured at week 12 for participants who received 1 treatment session, week 20 for 2 treatment sessions) for non-invasive fat reduction in CoolSculpting participants, including participants who receive treatment in the abdomen alone, flanks alone, or both abdomen and flanks.

The CSQ consists of 3 versions: CSQ-Abdomen, CSQ-Flank, CSQ-Abdomen and Flank; Participants with abdomen only treatment will be administered only the CSQ-Abdomen. Participants with flank only treatment will be administered only the CSQ-Flank version. Participants with both abdomen and flank treatments will be administered all 3 versions (CSQ-Abdomen, CSQ-Flank, and CSQ-Abdomen and Flank)); however, only CSQ-Abdomen and Flank will be used for the primary analysis. In each version, the CSQ Item question #1 is “Rate your overall satisfaction with the fat reduction procedure on the treated area”, with the following categories:

- Very satisfied
- Satisfied
- Neither satisfied nor dissatisfied
- Dissatisfied
- Very dissatisfied

‘Very satisfied’ and ‘Satisfied’ will be categorized as a new category, ‘Satisfied’.

The number and percentage of participants will be presented by category at 12 weeks after the final treatment, regardless of the CSQ version.

Furthermore, the 95% confidence interval on the proportion by category at 12 weeks after the final treatment, regardless of the CSQ version will be calculated using normal approximation method.

10.3 SECONDARY ANALYSES

All secondary endpoints will be measured at Week 12 for participants who received 1 treatment session and at Week 20 for participants who received 2 treatment sessions. The following analyses will be provided:

- Proportion of participants by treated area(s) (abdomen, flanks, and both abdomen and flanks) with "satisfied" or "very satisfied" on the CSQ Item #1.
- Proportion of participants by number of treatment cycles who received 1 or 2 treatment sessions with "satisfied" or "very satisfied" on CSQ Item #1.
- Proportion of participants with "Satisfied" or "Very Satisfied" on CSQ Item #1 by BMI categories (18.5 - < 25, 25 - ≤ 30)
- Mean change in volume of fat from baseline as measured by 3D photography.

The count and percentage of participants with the same categories as the primary endpoint for CSQ Item #1 will be summarized and the 95% CIs for the percentages will be calculated.

Descriptive summary statistics of change in volume of fat from baseline will be provided by visit.

11.1 SAFETY ANALYSES

The safety analyses will be based on the safety population.

11.2 ADVERSE EVENTS

Adverse events (AEs) will be collected throughout the study beginning with the first treatment visit. Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 22.0 or newer. AEs, AE severity, and causality are defined in the protocol (Section 11.1).

An AE will be considered a treatment-emergent (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the treatment start date and time. An AE is considered an ADE if the AE with a reasonable possibility (Possible, Probable, or Causal relationship) that the device caused the event. An AE is considered a study procedure related AE if the AE with a reasonable possibility (Possible, Probable, or Causal relationship) that the procedure caused the event.

Overall summary of TEAEs, SAEs, ADEs, SADEs, study procedure related AEs, TEAEs leading to study discontinuation, and deaths will be presented as total and by treatment session. AEs/ADEs occurred on or after the date of treatment sessions 1 and before the date of treatment session 2 are counted for treatment session 1; AEs/ADEs occurred on or after the date of treatment sessions 2 are counted for treatment sessions 2.

The number and percentage of participants will be summarized by System Organ Class (SOC) and Preferred Term (PT), with or without by severity, as total and by treatment session as follows:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- ADEs by SOC and PT
- ADEs by SOC, PT, and severity
- Study Procedure Related AE by SOC and PT
- Treatment-emergent Serious AEs (SAEs) by SOC and PT
- Serious ADEs (SADEs) by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT

The AE summary tables by SOC and PT will be presented with SOC in alphabetical order and in decreasing frequency within each SOC.

If more than 1 AE is coded to the same preferred term for the same participant, the participants will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

In addition, deaths, SAEs (including SADEs) and TEAEs leading to study discontinuation will be listed separately.

11.3 CLINICAL LABORATORY PARAMETERS

Listing for pregnancy test results will be provided.

[redacted]

12.1 SUBGROUP ANALYSIS

The following subgroup analyses for the primary and secondary effectiveness endpoints will be provided:

1. Subgroup analysis for Chinese participants. Chinese participants are defined as participants with race of Asian – Chinese per study CRF.
2. Subgroup analysis for Asian participants. Asian participants are defined as participants with race of Asian – Chinese, Asian – Japanese, Asian – Korean, or Asian – Other, per study CRF.
3. Subgroup analysis for number of cycles (in 1 or 2 treatment sessions) used per body area per treatment session for satisfied (very satisfied, satisfied) vs neither satisfied/dissatisfied vs unsatisfied (dissatisfied, very dissatisfied).
4. Subgroup analysis for each site and each country.

For TEAEs and ADEs, the following summary tables will be provided as total and by treatment session for the subgroups (Chinese participants, Asian participants, number of treatment cycles, and country/site), respectively:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- ADEs by SOC and PT
- ADEs by SOC, PT, and severity

In addition, summaries on demographics, other baseline data (Sections 8.2, 8.3, and 8.4), exposure (Section 9.1), other effectiveness (Section 10.3), other safety data (Sections 11.2 and 11.3) will be provided for Chinese participants and Asian participants, respectively.

13.0 HEALTH OUTCOMES ANALYSES

Not applicable.

14.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

15.0 DETERMINATION OF SAMPLE SIZE

The sample size will be based on providing reasonable precision for the estimate of the overall satisfaction rate.

Previous studies conducted on participants undergoing flank or abdominal fat reduction using CoolSculpting products reported moderately high overall satisfaction rate. The mean overall satisfaction rate was 65.8% from the study (protocol: ZA15-004) based on 19 participants, and 63.3% from another study (Protocol: ZA10-001) based on 60 participants. The weighted average of rates from the 2 studies, which is 63.9%, is now used as the initial estimate of the mean overall satisfaction rate for this planned study. A sample size of 98 participants would provide a 10% margin of error (associated with 95% confidence interval) for the estimate of the 63.9% expected rate. Allowing a 10% dropout during the study period, approximately 108 participants will be needed for recruitment into the study.

16.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version [redacted]

17.1 DATA HANDLING CONVENTIONS

Descriptive summaries include:

- Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values.
- Categorical variables will be summarized by number and percentage of participants.

In general, data listing will be provided.

17.2 VISIT TIME WINDOWS

The analysis visit windows for effectiveness endpoints will be defined as follows

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Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 2	Last assessment for which the assessment date is less than the treatment start date
Treatment	Final treatment	The final evaluations will be done on or +14 days of week 12 for participants who receive 1 treatment session; on or +14 days of week 20 for participants who receive 2 treatment sessions	Latest non-missing assessment after treatment start date

If the assessment date (or visit date, if the assessment date is unavailable) is on or after the date of the first study treatment, the study day is calculated as: assessment date – date of the first study treatment + 1. If the assessment date (or visit date, if the assessment date is unavailable) is before the date of the first study treatment, the study day is calculated as: assessment date – date of the first study treatment. Therefore, a negative day indicates a day before the start of the study intervention.

If multiple assessments were taken within an analysis window, the assessment obtained on the day closest to the target day will be used; in the case of a tie, the assessment obtained on the later day will be used in the analysis.

17.3 [redacted]

[redacted]

17.4 MISSING DATE OF THE LAST STUDY TREATMENT

When the date of the last study treatment is missing for a participant in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available treatment record date will be used as the last treatment date.

17.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.6 MISSING CAUSAL RELATIONSHIP TO STUDY TREATMENT FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first study treatment, the month and day of the first study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first study treatment, the day of the first study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the first study treatment or if both years are the same, but the month of the incomplete start date is before the month of the first study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first study treatment or if both years are the same, but the month of the incomplete start date is after the month of the date of the first study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first study treatment, the date of the first study treatment will be assigned to the missing start date

- If the stop date is before the date of the first study treatment, the stop date will be assigned to the missing start date

17.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

17.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first study treatment, the month and day of the first study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first study treatment, the day of the first study treatment will be assigned to the missing day

- If the year of the incomplete start date is before the year of the first study treatment, or if both years are the same but the month of the incomplete start date is before the month of the first study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the first study treatment, or if both years are the same but the month of the incomplete start date is after the month of the first study treatment, the first day of the month will be assigned to the missing day

17.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last study treatment is missing, impute it as described in Section 16.4. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last study treatment, the month and day of the last study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last study treatment, the day of the last study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last study treatment or if both years are the same, but the month of the incomplete stop date is before the month of the date of the last study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last study treatment or if both years are the same, but the month of the incomplete stop date is after the month of the date of the last study treatment, the first day of the month will be assigned to the missing day

18.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There is no change to the most recent protocol amendment (version 3.0), dated 20 Nov 2019.

19.0 REFERENCES

Not applicable.