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Statistical Analysis Plan

A Pilot Study to Evaluate Safety and Effectiveness of Poly-l-lactic acid (PLLA) for the Improvement in Appearance of Cellulite

Sponsor	:	Q-Med AB
Protocol Number	:	43CASA2006
Protocol Version	:	2.0
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Plan Version	:	1.0
Plan Date	:	29 November 2022
Study Device	:	Sculptra
Indication	:	Cellulite

Signature Page

The signatures below indicate that these individuals have reviewed this project-specific Statistical Analysis Plan and consent to this document as governing the tasks outlined within. The signatures below also indicate that the processes and quality standards set forth by this Statistical Analysis Plan are approved for use in this study.

Name	***Title*,** **Organization**	**Signature**	**Date**
PPD	PPD	PPD	30 November 2022
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Document History

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Table of Contents

1 Abbreviations and Definitions

Abbreviations	Definitions
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CaHA	Calcium Hydroxylapatite
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
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HA	Hyaluronic Acid
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
in	Inches
IQR	Interquartile Range
IUD	Intrauterine Device
kg	Kilogram
lbs	Pounds
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
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NSAID	Non-Steroidal Anti-Inflammatory Drugs
PI	Principal Investigator
PLLA	Poly-l-lactic Acid

PP	Per Protocol Analysis
PT	Preferred Term
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
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TEAE	Treatment Emergent Adverse Event
WHO-DD	World Health Organization Drug Dictionary

2 Introduction

This statistical analysis plan (SAP) describes the planned statistical analysis and reporting of the clinical study protocol titled "A Pilot Study to Evaluate Safety and Effectiveness of Poly-l-lactic acid (PLLA) for the Improvement in Appearance of Cellulite" dated on 21 June 2021.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The purposes of this SAP are to:

- Outline the types of analyses and presentations of data that will form the basis for drawing conclusions to the study objectives and hypotheses outlined in the protocol
- Explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices for Good Statistical Practice

All analyses described in this plan are considered *a priori* analyses in that they have been defined prior to locking the study database. The planned analyses identified in this SAP may be included in clinical study reports (CSR), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Protocol version 2.0 issued on 21 June 2021:
  - MA-47276_43CASA2006_Protocol_d2_21JUN2021.pdf
- Electronic Case Report Forms (eCRF):
  - 43CASA2006 Sculptra cellulite_EXPANDED CRFs_Annotated_v4.0_15 Dec 2021.pdf
- ICH Guidance on Statistical Principles for Clinical Trials (E9)

The reader of this SAP is encouraged to also read the clinical study protocol and other identified documents for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

3 Study Objectives and Endpoints

3.1 Study Objectives

1. To evaluate the safety of Sculptra for the improvement in appearance of cellulite in the posterior thighs.
2. To evaluate the effectiveness of Sculptra for the improvement in appearance of cellulite in the posterior thighs.

3.2 Study Endpoints

3.2.1 Safety Endpoints

1. Incidence, intensity, time to onset and duration of adverse events (AEs) collected throughout the study period.
2. Incidence, intensity, time to onset and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days from each treatment.
3. Pain assessment using a CCI [redacted] immediately post treatment and 30 minutes post treatment.

3.2.2 Primary Effectiveness Endpoint

Percentage of responders, defined as having at least “Improved” on both thighs according to the Global Aesthetic Improvement Scale (GAIS), as assessed live by the Treating Investigator, at Month 9.

3.2.3 Secondary Effectiveness Endpoints

1. Percentage of responders, defined as having at least “Improved” according to the Global Aesthetic Improvement Scale (GAIS), as assessed live by the Treating Investigator for each posterior thigh separately, at Month 1, 2, 6 and 12.
2. Percentage of responders, defined as having at least “Improved” according to the Global Aesthetic Improvement Scale (GAIS), as assessed by photography by the subject at Month 1, 2, 6, 9 and 12 for each posterior thigh separately.

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4 Study Overview

4.1 General Study Design and Plan

This is a prospective, early feasibility study to evaluate the safety and effectiveness of Sculptra for the improvement in appearance of cellulite in the posterior thighs.

The study will be conducted at one study center in Canada. Approximately 30 women with intent to undergo treatment to improve appearance of cellulite will be enrolled and will receive a single regimen of Sculptra. A single regimen consists of three injection sessions with one-month (+2 weeks) intervals. The first treatment will be administered on Day 1/Baseline visit, the second treatment at Month 1, and the third treatment at the Month 2 visit. Treatment will stop when optimal correction has been achieved and subsequent visits will be follow-up visits.

Sufficient amount of study product, as determined by the Treating Investigator, should be injected to achieve optimal correction, defined as the best correction that could be achieved as agreed upon by the Treating Investigator and the subject. Treatment will stop when optimal correction has been achieved and all subsequent visits will be follow-up visits. The maximum recommended dose per session is six (6) vials, three (3) vials per thigh. The maximum volume injected per thigh is up to 54 mL.

Treatment visits will be followed by a safety follow-up phone call 72 ± 24 hours after each treatment. All subjects will have follow-up visits at Month 6, 9 and 12. All visits and assessments are outlined in the Schedule of Assessments in Figure 2 of the study protocol.

4.2 Inclusion-Exclusion Criteria

4.2.1 Inclusion Criteria

The subjects must meet all of the following criteria to be eligible for the study:

1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent.
2. Immune-competent adult women 18 years of age and older.
3. Body Mass Index (BMI) ≥18.5 and ≤25.
4. Subjects with intent to undergo treatment to improve appearance of cellulite in the posterior thighs.

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6. Subject that in the opinion of the PI could benefit from treatment to improve appearance of cellulite.
7. Postmenopausal for at least 1 year or (if the subject is of childbearing potential) agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test at the screening visit and prior to all injection visits. Acceptable forms of effective birth control methods include:
    a. Combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 28 days prior to the Baseline visit
    b. Hormonal or copper intrauterine device (IUD) inserted at least 28 days prior to the Baseline visit
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository
    d. Bilateral tubal ligation prior to the Baseline visit
    e. Vasectomized partner (in monogamous relationships) for at least 3 months prior to the Baseline visit
    f. Strict abstinence (at least one month prior to the baseline visit and agrees to continue for the duration of the study or use acceptable form of birth control).
8. Negative urine pregnancy test for females of childbearing potential at screening and all injection visits.

4.2.2 Exclusion Criteria

The presence of any of the following exclusion criteria will exclude a subject from enrollment in the study:

1. Known/previous allergy or hypersensitivity to any of the Sculptra constituents.
2. Known/previous allergy or hypersensitivity to lidocaine and other local anesthetics, e.g. amide type anesthetics, or topical anesthetics or nerve blocking agents.

3. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions.
4. Previous treatment/procedure in or near the treatment area:
    a. Previous permanent implant, filler, lifting threads, or autologous fat in the treatment area, regardless of time.
    b. Previous semi-permanent implants exemplified by Calcium Hydroxylapatite (CaHA), poly l-lactic acid (PLLA) in treatment area, regardless of time.
    c. Previous Hyaluronic acid (HA) filler or collagen filler in the treatment area within 12 months.
    d. Previous energy based aesthetic procedures (e.g. laser, intense pulsed light, radiofrequency and endermology) in the treatment area within 6 months.
    e. Previous mechanical (e.g. dermabrasion, needling) or chemical aesthetic procedures (e.g. chemical peel) in the treatment area within 6 months.
    f. Previous treatment with cryotherapy, lipolytic treatments or lipореduction massage in the treatment area within 6 months.

    OR is planning to undergo any of these procedures affecting the treatment area, at any time during the study.
5. Previous surgery in or near the treatment area, including but not limited to buttock lift or liposuction.
6. Scar or skin coloring/bleaching/tattoo that obscures evaluation of the treatment area.
7. Intends to initiate a weight loss program during the study.
8. Presence of any disease or lesions near or on the area to be treated, e.g.
    a. Inflammation, active or chronic infection in or near the treatment area
    b. Psoriasis, eczema, herpes zoster and acanthosis
    c. Cancer or precancerous condition (e.g. actinic keratosis)
    d. Varicose veins, severe stretchmarks or severe cellulitis
    e. Severe skin laxity, flaccidity, sagging
    f. Skin condition in the treatment area that in the Investigator's opinion could interfere with the safety or effectiveness of the study product or injection procedure.
9. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation (e.g. aspirin or other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)), Omega-3, or Vitamin E within 14 days before treatment. Note: Omega-3 and Vitamin E are acceptable as part of a standard multivitamin formulation.
10. Treatment with systemic retinoids within 6 months of the Baseline visit, chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies or antiviral treatment for Human Immunodeficiency Virus (HIV) or Hepatitis C). Systemic corticosteroids (inhaled corticosteroids are allowed) within 3 months before treatment.
11. Use of topical corticosteroids, topical prescription retinoids or cellulite cream in the treatment area within 1 month of the Baseline visit.
12. History of cancer or previous radiation near or on the area to be treated.
13. HIV positive or active hepatitis.
14. History of or active collagen diseases such as systemic lupus erythematosus, rheumatic arthritis, polymyositis, dermatomyositis, skin or systemic scleroderma.
15. Tendency to form keloids, hypertrophic scars, or any other healing disorder.
16. Woman who is pregnant (confirmed by positive urine pregnancy test/serum pregnancy test), breast feeding or intend to become pregnant over the duration of the study.
17. Any medical condition that, in the opinion of the Treating Investigator, would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease, history of disc hernia or lower back pain that may interfere with the outcome of the study).
18. Other condition preventing the subject from entering the study in the Treating Investigator's opinion, e.g. subjects not likely to avoid other cosmetic treatments in

the treatment area, subjects anticipated to be unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.

19. Study center personnel, close relatives of the study center personnel (e.g. parents, children, siblings, or spouse), or employees and close relatives of employees at the Sponsor company.
20. Participation in any interventional clinical study within 30 days of screening.

4.3 Subject Randomization

This is a non-randomized, open-label, single-arm study.

4.4 Sample Size

The sample size of approximately 30 subjects is not based on a statistical calculation. The selected number of subjects is regarded as enough for an evaluation of safety and effectiveness in this pilot study.

5 General Considerations

5.1 Presentation

Individual subject data obtained from electronic case report forms (eCRFs), central laboratories, local laboratories, external sources, and derived data will be presented in data listings by subject. All data listings that contain an evaluation date will contain a relative study day.

All outputs will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Council for Harmonisation recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, effectiveness, and safety parameters. Tabulations will be organized by using columns for each visit, and rows for each parameter where appropriate.

For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For continuous variables, the number of subjects, mean (arithmetic), standard deviation (SD), median, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise specified, will be as follows: mean and median to 1 more decimal place than the raw data and SD to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate. Confidence Intervals (CIs) will be provided and will be rounded to 1 more decimal place than the raw data, unless otherwise specified in the table shell.

For ordinal variables, the summary procedures for both categorical and continuous variables will be followed where appropriate.

5.2 Data Conventions

The precision of original measurements will be maintained in summaries, when possible.

For tables where rounding is required, rounding will be done at the final stage of the calculation to the nearest round-off unit. For example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX + 1 (e.g., 97.5 will round up to 98), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97).

Percentages based on frequency counts will be based on available data, and denominators will generally exclude missing values, unless otherwise stated. For frequency counts of categorical variables, categories whose counts are zero will be displayed for completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the corresponding table with a count of 0. Percentages based on frequency counts of eCRF collections (e.g., demographic categories) will be presented as a whole number (no decimal places), and nonzero values less than 0.5% will be presented as "<1%." Values less than 100% but that round up from 99.5% to 100% will be presented as ">99%."

5.3 Timing of Analyses

The statistical analyses will be performed at the end of the study, after the database has been cleaned and locked. However, an interim review of selected effectiveness data will be performed after all subjects have done their month 6 visit, see Section 5.10.

5.4 Analysis Populations

Study populations definitions are provided below. The numbers of subjects in each population and reasons for exclusion will be summarized.

5.4.1 Safety Analysis Set

All safety analyses will be carried-out in the Safety Analysis Set (SAF), consisting of all subjects who were injected in at least one thigh.

5.4.2 Full Analysis Set

The primary effectiveness analysis population will be the Full Analysis Set (FAS), defined as all subjects who were injected in both thighs.

5.4.3 Per Protocol Analysis Set

If there are any clinical study protocol (CSP) deviations considered to have substantial impact on the primary effectiveness outcome, a per protocol (PP) analysis set excluding those subjects may be defined.

5.5 Baseline Definition

Baseline is defined as the last non-missing assessment prior to the first injection of the study device (including unscheduled assessments) in the study.

5.6 Derived and Transformed Data

Variables requiring calculation will be derived using the following formulas:

- Responder rate (%) regarding GAIS will be calculated as (number of subjects (or thighs) being at least improved/number of subjects reporting at the specified visit)*100.

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- Time to onset of an AE will be derived as the start date minus the date of most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment.

- Duration of an AE will be derived as the stop date minus the start date + 1. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment. Completely missing stop date will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of AEs that were ongoing at the end of the study will be given.

  Time to return to daily activities after treatment will be derived as the subject diary date/time with the first "Yes" for "Did you feel comfortable returning to daily activities today?" minus the date/time of the corresponding treatment session injection start time, and will be represented in days. Time to feeling comfortable returning to daily activities will be calculated for each diary (treatment session) separately.

  Subjects who never report feeling comfortable during each session period will have their response date and time censored at the date and time of their last diary entry in each period.

- Time to onset of pre-defined expected post-treatment events collected using subject diaries will be derived as the first recorded event date minus the date of most recent treatment.

- Days – A duration expressed in days between 1 date (date1) and another later date (date2) will be calculated using the following formula:
  duration in days = date2 – date1 + 1

- Months – A duration expressed in months is calculated as the number of days divided by 365.25/12 (approximately 30.4)

- Years – A duration expressed in years is calculated as the number of days divided by 365.25

- Change from baseline – Change from baseline will be calculated as:
  Change = post baseline value – baseline value

5.7 Subgroups

No subgroups are defined for this study.

5.8 Visit Windows

All endpoints will be summarized and analyzed by nominal visit as recorded on the CRF. Data collected at unscheduled visits will be listed only, with the exception of baseline data (see Section 5.5).

Study dates outside of visit windows as described in the Schedule of Assessments presented in the Study Protocol will be considered protocol deviations. Methodology for summarizing out-of-window visit durations are described in Section 6.3.1 of this SAP.

5.9 Missing Data

As a general principle, no substitutions will be made for missing data. All analyses will be based on available data. Exceptions are the start and stop dates of AEs and therapies (described below). The imputed dates will be used to determine whether an AE is treatment-emergent and whether a therapy is prior or concomitant. Listings of AEs and therapies will present the actual partial dates; imputed dates will not be shown.

5.9.1 Imputation of Adverse Event Start and Stop Dates

Start date:

- If start date is completely missing, start date is set to date of most recent treatment.
- If (1) year is present and month and day are missing or (2) year and day are present and month is missing:
    - If year = year of most recent treatment, then set month and day to month and day of most recent treatment.
    - If year < year of most recent treatment, then set month and day to December 31st.
    - If year > year of most recent treatment, then set month and day to January 1st.
- If month and year are present and day is missing:
    - If year = year of first dose and
        - If month = month of most recent treatment, then set day to day of most recent treatment.
        - If month < month of most recent treatment, then set day to last day of month.
        - If month > month of most recent treatment, then set day to 1st day of month.
    - If year < year of most recent treatment, then set day to last day of month.
    - If year > year of most recent treatment, then set day to 1st day of month.

Stop date:

If the outcome of the AE was ongoing or unknown, then the rules outlined below will not be applied.

- If stop date is completely missing, stop date is set to date of study discontinuation/end of study date.
- If (1) year is present and month and day are missing or (2) year and day are present and month is missing:
    - If year = year of study discontinuation, then set month and day to month and day of study discontinuation.
    - If year < year of study discontinuation, then set month and day to December 31st.
    - If year > year of study discontinuation, then set month and day to December 31st.
- If month and year are present and day is missing:
    - If year = year of study discontinuation/end of study date and

- If month = month of study discontinuation/end of study date, then set day to day of study discontinuation date.
- If month < month of study discontinuation/end of study date, then set day to last day of month.
- If month > month of study discontinuation/end of study date, then set day to 1st day of month.

- If year < year of study discontinuation/end of study date, then set day to last day of month.If year > year of study discontinuation/end of study date, then set day to 1st day of month.

5.9.2 Imputation of Prior and Concomitant Therapies Start and Stop Dates

Start date:

- If start date is completely missing, start date will be imputed with the informed consent date.
- If year is present and month and day are missing, set month and day to January 1.
- If year and day are present and month is missing, set month and day to January 1.
- If year and month are present and day is missing, set day to the 1st day of month.

Stop date:

- If end date is completely missing, end date will not be imputed and therapy will be assumed to be ongoing.
- If year is present and month and day are missing, set month and day to December 31st.
- If year and day are present and month is missing, set month and day to December 31st.
- If year and month are present and day is missing, set day to the last day of month.

5.10 Interim Analyses and Data Monitoring

When all subjects have completed the Month 6 visit, effectiveness data from all subjects up to the Month 6 visit will be reviewed. CCI [redacted] No cleaning or partial lock of data will be performed for this data review, and no formal report will be written to summarize the review. Only subject data listings will be used together with the photographs.

The results of this interim analysis will be kept within a minimum number of persons, including the Sponsor biostatistician, clinical data analyst, clinical project manager, and approximately 3 people from the Aesthetic project leadership.

5.11 Multi-Center Studies

Study center will not be considered as an explicative factor in the statistical analyses.

5.12 Multiple Testing

Due to the proof-of-concept purpose of this trial, no alpha-level adjustment for multiplicity will be applied.

6 Summary of Study Data

6.1 Subject Disposition

The disposition of subjects will be presented in tables and/or figures as appropriate. The number and percentage of screened, treated, completed, and withdrawn subjects (including reasons for withdrawal) will be presented, as well as number of subjects in each analysis population set.

Subject disposition by study center will be tabulated.

A by-subject listing of inclusion into analysis sets and exclusion reasons, and study completion information including reason for study treatment discontinuation or early withdrawal from study, if applicable, will be presented.

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed, along with the relevant comments recorded on the eCRF (i.e., the Exit Form).

6.2 Screen Failures

Screen failures will be summarized by study center and inclusion/exclusion criteria not met, as appropriate.

6.3 Protocol Deviations

Subjects with CSP deviations will be listed individually, including subject number and observed deviation.

Depending on the seriousness of the deviation, subjects might be excluded from the PP population, which shall be documented prior to database lock. Since PP will be used for the primary analysis at Month 9 only, the focus will be on deviations occurring before and on Month 9 visit day, as they might compromise the primary endpoint. For this study, the protocol deviations that will exclude subjects from PP are identified (but not limited to) in Table X below.

		Deviation
GENERAL		
		Visit out-of-window
	*	Follow-up at Month 9 after baseline performed earlier than 2 weeks before, or later than 4 weeks after the scheduled visit
EFFECTIVENESS		
		Primary effectiveness endpoint
	*	No baseline photo is available
	*	GAIS by treating investigator missing at Month 9 after baseline

		Deviation
		Treatment
	*	Not both thighs treated
OTHER		
		Inclusion/exclusion criteria
	*	Violate any inclusion or exclusion criteria considered to have substantial effect on the primary effectiveness endpoint
		Concomitant medication/procedures
	*	Take any prohibited concomitant medication/procedures considered to have substantial effect on the primary effectiveness endpoint

6.3.1 Out of Window Visit Duration

When a subject performs a planned study visit outside of the protocol-specified visit windows, the subject has an out of window study visit, which is considered a type of protocol deviation for this study. Knowing a subject's Screening visit and Baseline visit and using the protocol-specified visit windowing, one can calculate a subject's target study visit window date range for each planned study visit. Then, by comparing a subject's actual study visit date to the target study visit window date range, one can calculate the days over/under the actual study visit was in relation to the target study visit date, or study visit out of window duration. The duration, in days, a study visit is out of window will be summarized overall and by visit. Duration will be split into the following below categories. Duration categories will include both days before and days after the target planned visit date.

- +/- 1-2 days
- +/-1 3-7 days
- +/- 8-20 days
- +/- 21 or more days.

The number and percentage of subjects within each out of window duration category will be presented descriptively.

6.4 Demographic and Baseline Variables

Subject demographics and other baseline characteristics measured prior to treatment will be summarized descriptively for the SAF and FAS.

Demographic variables will include the following:

1. Age at informed consent
2. Sex
3. Race
4. Ethnicity

Other baseline characteristics will include the following:

5. Weight (lbs)

6. Height (in)
7. Body mass index (BMI) (kg/m^2)
8. CCI
9. Fitzpatrick Skin Type Score

A by-subject listing will also be provided.

6.5 Medical History and Concurrent Diseases

Verbatim terms on eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using Medical Dictionary for Regulatory Activities terminology (MedDRA) version 24.1 or later.

Medical history and concurrent diseases will be summarized by SOC and PT for the SAF. Summaries will be ordered by descending order (based on total) of incidence of SOC and PT within each SOC. A by-subject listing will also be provided.

6.6 Prior and Concomitant Therapies

Prior therapies are defined as therapies that have been used within 30 days preceding the screening visit or within the timelines specified in the Inclusion/Exclusion criteria, and then stopped prior to the screening visit.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the course of the study, or
- any new therapies received by the subject since the screening visit

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version Sept. 2021 or later and will be classified according to the default Anatomical Therapeutic Chemical (ATC) classification system code (up to 4 levels), WHO-DD Drug Name, and PT.

Prior and concomitant medications will be summarized for the SAF by the ATC Class Level 3 category (or Level 2 if there is not an applicable Level 3 category) and PT. Subjects may have more than one medication per ATC category and PT. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications at that specific level. A by-subject listing will also be provided.

Prior and concomitant procedures/non-pharmacological treatments will be mapped to PTs using MedDRA version 24.1 or later.

Prior and concomitant procedures will be summarized by PT for the SAF. Summaries will be ordered by descending order (based on total) of incidence of PT. A by-subject listing will also be provided.

6.7 Study Device Exposure

Eligible subjects will receive a single regimen of Sculptra. A single regimen consists of up to three injection sessions with one-month (+2 weeks) intervals. The first treatment will be administered on Day 1/Baseline visit, the second treatment at Month 1, and the third treatment at the Month 2 visit. Sufficient amount of study product, as determined by the Treating Investigator, should be injected to achieve optimal correction, defined as the best correction that could be achieved as agreed upon by the Treating Investigator and the

subject. Treatment will stop when optimal correction has been achieved and subsequent visits will be follow-up visits. The maximum recommended dose per session is six (6) vials, three (3) vials per thigh. The maximum volume injected per thigh is up to 54 mL.

Treatment exposure will be summarized for the SAF by visit as well as in total, including number of needles used, total volume injected per thigh, injection depth, injection technique, and post-injection procedures. A by-subject, by-thigh listing will also be provided and will include additional procedure information (e.g., the use of anesthetic or ice).

7 Effectiveness Analyses

7.1 General Considerations

All effectiveness analyses will be based on the FAS as described below.

7.2 Primary Effectiveness Analyses

The 7-graded GAIS will be used to assess the aesthetic improvement of cellulite by the Treating Investigator and the subject. The Treating Investigator will assess the aesthetic improvement live by comparing to a photograph taken at the baseline visit before the first treatment. The subject will assess the aesthetic improvement by comparing a photograph taken before the first treatment at the baseline visit to a photograph from the current visit. The overall treatment area will be assessed for the right and left posterior thigh separately. The Treating Investigator and the subject will, independently of each other, respond to the question: “How would you describe the aesthetic improvement today compared to the photograph taken before treatment?” by using the respective categorical scale below.

Table 1. Global Aesthetic Improvement Scale

Rating (Treating Investigator and subject)	**Description (only for Treating Investigator)**
Very much improved	Optimal aesthetic result for the implant for this subject.
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
Improved	The appearance is improved from the initial condition.
No change	The appearance is essentially the same as baseline.
Worse	The appearance is worse than the initial condition.
Much worse	Marked worsening in appearance from the initial condition.
Very much worse	Obvious worsening in appearance from the initial condition.

For the primary effectiveness endpoint, a responder is defined as a subject who is assessed as improved or better (Improved, Much improved, Very much improved) on the GAIS for both thighs at the same visit.

The GAIS assessment by Treating Investigator will be presented in a frequency table by visit and thigh (Left, Right). Further, a contingency table of dichotomous (at least Improved; No

change or worse) response by thigh (Left, Right, Both) will be provided for each evaluator for each visit. The proportion of responders will be presented, together with a 95% binomial confidence interval for that proportion. This result at the Month 9 visit will represent the primary effectiveness endpoint. In addition, the proportion of responders (both sides combined) over time will be visualized in a graph.

All GAIS results will be listed by subject, thigh, and evaluator.

If the PP population contains less than 90% of the FAS population, the primary analysis will be repeated using the PP population.

7.3 Secondary Effectiveness Analyses

Considering the explorative nature of the secondary endpoints, all the inferential results obtained on them will be descriptively interpreted.

7.3.1 Global Aesthetic Improvement Scale (GAIS)

The tables described in section 7.2 for the primary effectiveness endpoint at the specified visits will also be used to represent secondary effectiveness endpoint #1. The proportion of improved thighs will be presented, together with a 95% binomial confidence interval for that proportion, for each thigh separately and also for both thighs combined at Month 1, 2, 6, 9 and 12. In addition, the proportion of improved thighs (both sides combined) over time will be visualized in a graph.

Similar tables will also be presented for the GAIS assessment by subject. These tables will be used to summarize secondary effectiveness endpoint #2.

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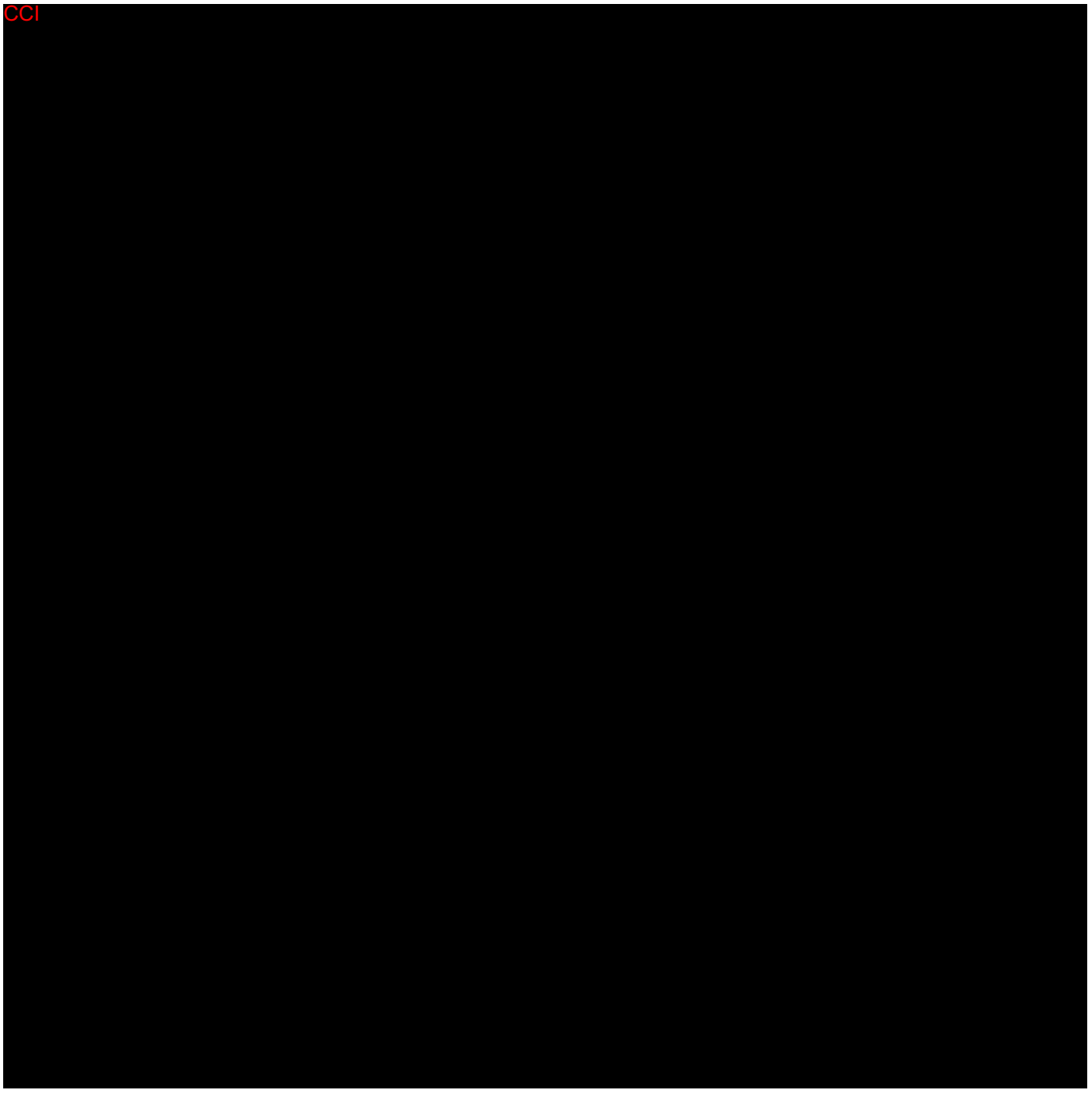

8 Safety Analyses

All safety measures will be descriptively summarized for the SAF population.

8.1 Adverse Events

All adverse events (AEs) will be assigned to a PT and will be classified by Primary SOC according to MedDRA version 24.1 or later.

Any AE which started at or after the first administration of study treatment will be considered as Treatment Emergent Adverse Event (TEAE). If the start date is missing for an AE, the AE will be considered to be treatment emergent. Missing classifications concerning study treatment relationship will also be considered as treatment-related.

A summary of all AEs, will be provided, which will include:

- Number of subjects with at least one AE and number of events (in total as well as serious AEs)
- Number of subjects with at least one related AE and number of events (in total as well as serious AEs)
- Number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs)
- Number of subjects who did not have an AE

The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT, and maximum intensity. In addition, for related AEs the number of days to onset and the duration of event will be summarized by SOC and PT. Action taken for related AEs will also be summarized. Serious AEs will be listed as well as related AEs with late onset (>21 days after most recent treatment).

Non-related AEs will be summarized by SOC, PT, and maximum intensity.

Events that occurred before the first administration of study treatment are included as Medical History.

8.2 Subject Diary Data

A subject diary will be dispensed to all subjects for daily completion for 28 days beginning on injection day for each treatment with direct questioning for injection site responses: pain, tenderness, redness, bruising, swelling, itching and other. The presence and maximum intensity shall be assessed for the treated area:

Table 3. Grading for subject diary data

Category
None
Tolerable
Affects daily activities
Disabling

Number and percentage of subjects reporting each of the pre-defined, expected, post-treatment symptoms listed above, as collected in the 28 days diary, will be presented in total and by maximum intensity for each treatment session. Number of days with the event will be presented for each treatment session by category: 1, 2-7, 8-14, and 15-28 days. A by-subject listing will also be provided.

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8.4 Pregnancies

For all women of childbearing potential, including those currently using contraception, a urine pregnancy test will be performed at screening, all treatment visits (prior to treatment) and at the final study visit at Month 12. The test result must be negative for the subject to receive any treatment with study product and will be documented in source data and the eCRF. Pregnancy test results will be listed only.

8.5 Device Deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies will be listed only.

8.6 Device Palpability

Device palpability will be assessed at each scheduled visit post-treatment by a qualified staff member and will assess whether the palpability is the normal expected feel. An unexpected feel is to be recorded as an AE. Device palpability will be listed only.

9 Summary of Changes to the Protocol

None

10 Technical Details

All analyses in this SAP will be generated using SAS version 9.4 or higher, unless otherwise specified, and includes the following packages: Base SAS, SAS/STAT, SAS/GRAPH, SAS/Secure 168-bit, SAS/Secure Windows, SAS Enterprise Guide, SAS/ACCESS Interface to PC Files, SAS Workspace Server for Local Access, and High-Performance Suite.

11 References

[1] US Federal Register. International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. 16 September 1998. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

[2] American Statistical Association. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, 07 August 1999. http://www.amstat.org/profession/ethicalstatistics.html

[3] Royal Statistical Society. The Royal Statistical Society: Code of Conduct, August 1993. http://www.rss.org.uk/about/conduct.html

12 List of Planned CSR Tables, Listings, and Figures

Please reference document “43CASA2006 Statistical Analysis Plan TLF Shells v1.0” for the complete list of all tables, listings, and figures (TLFs) as well as corresponding mock shells. Minor changes made to the layout or formatting of the TLFs after SAP finalization will not necessitate a modification to the SAP.