CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 43CASA2006

Title Page

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

Clinical Trial Number (CTN): 43CASA2006

SPONSOR:
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Statements of compliance

The study should be conducted in compliance with the clinical trial agreement, the clinical study protocol, good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2020 should be followed. The International Conference on Harmonization (ICH) guideline for GCP (E6 (R2)) should be followed as applicable for medical device. The study should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki[1].

[1](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-princsples-for-medical-researchinvolving-human-subjects/)

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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Further details on all participating Investigators and the complete administrative structure of the study are found in the study files.

SPONSOR SIGNATURES

The Clinical Study Protocol is electronically signed in the document management system within the Q-Med AB quality management system by the representatives listed below.

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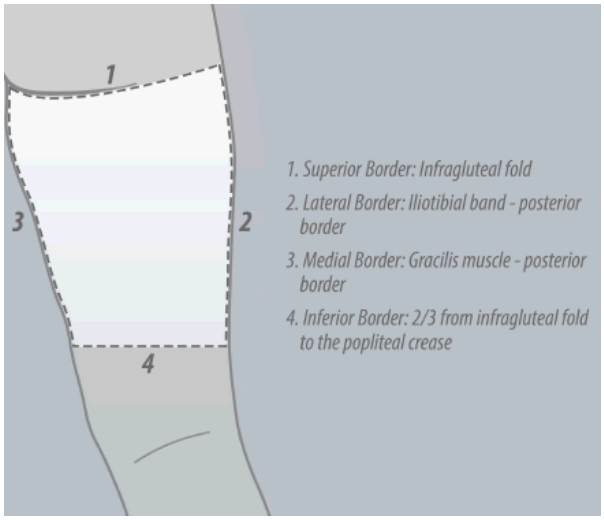
SYNOPSIS

Clinical Study Title:	A Pilot Study to Evaluate Safety and Effectiveness of Poly-l-lactic acid (PLLA) for the Improvement in Appearance of Cellulite.
Clinical Trial Number:	43CASA2006
Country Involved and Planned Number of Study Centers:	Country: Canada No. of Study Centers: Two study centers.
Clinical Study Design:	This is a prospective, pilot study to evaluate the safety and effectiveness of *Sculptra*™ for the improvement in appearance of cellulite in the posterior thighs. *Sculptra* will be reconstituted with 17 mL SWFI with the addition of 1 mL 2% lidocaine hydrochloride. Eligible subjects will be treated with *Sculptra* in three sessions spaced one month (+2 weeks) apart. Safety and effectiveness data will be collected for up to 12 months following the initial treatment. The study visits are illustrated in the Clinical Study Flow Chart in Figure 1, and a Schedule of Assessments is provided in Figure 2. Study procedures and assessments are summarized in Section 7.
Indication:	Improvement in appearance of cellulite in the posterior thighs.
Total Number of Subjects (Planned):	Approximately 30 women will be enrolled.
Safety Objectives and Endpoints:	Objective: To evaluate the safety of *Sculptra* for the improvement in appearance of cellulite in the posterior thighs. 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. CCI [redacted]
Primary Effectiveness Objective and Endpoint:	Objective: To evaluate the effectiveness of *Sculptra* for the improvement in appearance of cellulite in the posterior thighs. 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.

Secondary Effectiveness Objective and Endpoints:	Objective: To evaluate the effectiveness of *Sculptra* for the improvement in appearance of cellulite in the posterior thighs. 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. CCI [redacted]
Subgroup Analysis	Not applicable
Clinical Study Duration:	First subject first visit (FSFV) – Last subject last visit (LSLV): 15 months • 3 months enrollment • 12 months follow-up from baseline One month is defined as 4 weeks in the study
Inclusion Criteria:	The subjects must meet 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. CCI [redacted] 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.
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 liporeduction 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. Varicous 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.
Investigational Product:	*Sculptra*, a sterile, freeze-dried, injectable poly-l-lactic acid (PLLA) available in 367.5 mg dose vials including 150 mg PLLA. *Sculptra* is to be reconstituted to 17 mL per vial using SWFI, with the addition of 1 mL 2% lidocaine hydrochloride.
Comparator/Placebo Product:	Not applicable
Treatment area:	Posterior thighs. In this study, the study product will be administered in the treatment area delimited within the following anatomical borders: Superior border: Infragluteal fold Lateral border: Illotibial band – posterior border Medial border: Gracilis muscle – posterior border Inferior border: 2/3 from infragluteal fold to the popliteal crease. 
Treatment regimen:	Three treatment sessions spaced one month (+ 2 weeks) apart. 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. Maximum recommended dose per session: 6 vials (3 vials per thigh), up to 54 mL per thigh. The study product is to be injected in the deep dermis or subdermal region (i.e. subcutaneously), evenly spread over the entire treatment area. One vial per third of the area in each thigh (100 cm^2) is recommended.
Mode of administration:	Injections should be made using a 25 Gauge (G) 1.5 inch needle into the deep dermis or subdermal region (i.e.subcutaneously) , evenly spread over the entire

	treatment area with a fanning, asterisks or short linear threading technique with a distance of 1-2 cm using 0.05–0.1 mL per injection point. One vial per third of the area in each thigh (100 cm^2) is recommended. In some areas with marked lipoatrophy, a linear retrograde technique with cross sticks can be done in order obtain better correction of the skin depression. The reconstituted study product contains lidocaine, but additional topical or local anesthesia may be used at the discretion of the Treating Investigator before the treatment. If additional anesthesia is used, potential local anesthesia toxicity should be taken into consideration. The maximum allowable safe dose of lidocaine is 3-4.5 mg/kg. Post treatment care: Gentle massage in the treatment area to smoothen out the product is recommended. Subjects should avoid vigorous exercise or vigorous massage for 3 days after injection.
Statistical Method:	<u>Effectiveness assessments:</u> Continuous endpoints will be summarized using descriptive statistics, e.g. mean, median, standard deviation, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level. CCI [redacted]
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.
Interim Analysis:	n/a

CLINICAL STUDY FLOW CHART

Figure 1 Clinical Study Flow Chart

43CASA2006 N=30 subjects		
Visit 1 ↓	Day -30 to Day 1	Screening
Visit 2a ↓	Day 1 – Baseline	1st Treatment
Visit 2b ↓	72 hours post-treatment	Telephone Contact
Visit 3a ↓	Month 1	2nd Treatment (optional)
Visit 3b ↓	72 hours post-treatment	Telephone Contact
Visit 4a ↓	Month 2	3rd Treatment (optional)
Visit 4b ↓	72 hours post-treatment	Telephone Contact
Visit 5 ↓	Month 6	Follow-up
Visit 6 ↓	Month 9	Follow-up
Visit 7	Month 12	Follow-up/Early termination

SCHEDULE OF ASSESSMENTS

Figure 2 Schedule of Assessments

Activity	*Screening*	*Baseline 1st Treatment*	*Telephone Contact*	*Month 1 2nd Treatment (optional)*	*Telephone Contact*	*Month 2 3rd Treatment (optional)*	*Telephone Contact*	*Month 6 Follow-up*	*Month 9 Follow-up*	*Month 12 Follow-up /Early termination*
	Visit 1[1]	**Visit 2a**[1]	***Visit 2b***	***Visit 3a***[4]	***Visit 3b***[6]	**Visit 4a**[4,9]	***Visit 4b***[6]	**Visit 5**	**Visit 6**	**Visit 7**
	(≤ 30 days of Baseline)	Day 1	72 hours (±24 hrs) after 1st treatment	One month (+2 weeks) after 1st treatment	72 hours (±24 hrs) after 2nd treatment	One month (+2 weeks) after 2nd treatment	72 hours (±24 hrs) after 3rd treatment	Month 6 (±2 weeks) after Baseline	Month 9 (±2 weeks) after Baseline	Month12 (±2 weeks) after Baseline
Informed consent	X									
Inclusion/Exclusion criteria	X	X[3]								
Demographic data (date of birth, height, weight, gender, ethnicity, race and Fitzpatrick Skin Type	X							X[7]	X[7]	X[7]
Medical History	X									
Prior therapies	X									
Concomitant therapies/procedures	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)		X	X	X	X	X	X	X	X	X
Urine pregnancy test[2]	X	X[3]		X[3]		X[3]				X
Photography, incl 3D imaging		X[3]		X[3]		X[3]		X	X	X
Sculptra administration		X		X[4]		X[4]				
Device deficiencies		X		X[5]		X[5]				
Dispense subject diary (injection related events)		X		X		X				
Review subject diary completion			X	X	X	X	X	X		
Collect subject diary				X[3]		X[3,6]		X[6]		
Device palpability		X		X		X		X	X	X
Ultrasound		X[3]							X	X
Treating Investigator assessments										
Global Aesthetic Improvement Scale (GAIS)				X[3]		X[3]		X	X	X

CCI [redacted]

1) *Screening and baseline visits may occur on the same day, if visits occur the same day assessments will not be duplicated*
2) *Females of childbearing potential*
3) *Pre treatment*
4) *If treatment is not performed this is a follow up visit*
5) *Only applicable if treatment is performed at this visit*
6) *If applicable (i.e. if treatment was performed at the previous visit)*
7) *Weight only*
8) *Immediately post treatment and 30 minutes post treatment.*
9) *For subjects that did not receive the optional treatment at Month 1, this is a follow up visit.*

Note: One month is defined as 4 weeks in the study

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BMI	Body Mass Index
CaHA	Calcium Hydroxylapatite
CMC	Sodium CarboxyMethylCellulose
CSP	Clinical Study Protocol
CTA	Clinical Trial Agreement
eCRF	electronic Case Report Form
CRO	Contract Research Organization
FSFV	First Subject First Visit
G	Gauge
GAIS	Global Aesthetic Improvement Scale
CCI	[redacted]
HA	Hyaluronic acid
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IFU	Instructions for use
IUD	Intrauterine Device
IB	Investigator's Brochure
IPL	Intense Pulsed Light
LSLV	Last Subject Last Visit
CCI	[redacted]
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PLLA	Poly-l-lactic acid
RA	Regulatory Authority
REB	Research Ethics Board
CCI	[redacted]

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1. GENERAL INFORMATION

The clinical study shall not commence until written approval/favorable opinion from the Research Ethics Board (REB) and Health Canada, the Regulatory Authority (RA).

2. BACKGROUND INFORMATION

2.1 Medical Background, Indication and Population description

Cellulite is a topographic and localized skin condition that is commonly found on the posterolateral thighs, buttocks, and abdomen. It is often identified by a dimpled or orange-peel appearance of the skin's surface [1]. The presence of visible cellulite is associated with histologic changes in the dermis, adipose tissue, and septae, compared with unaffected skin [2]. It is commonly accepted that the pathophysiology of cellulite is linked to a thickening and shortening of the septal network, along with fat lobules and a flaccid structural weakening at the adrenal subcutaneous interface [3, 4]. Simultaneously, adipose cells expand with weight gain or water absorption, and in doing so herniate into the dermis, creating skin dimpling and the characteristic appearance of cellulite [5].

Cellulite is related to collagen and elastic tissue degeneration in dermis and hypodermis associated with fat deposition [4, 6]. Collagen is a naturally occurring and abundant protein in the body that helps to give the skin strength and elasticity. With age, collagen production in the body decreases resulting in the visible signs of aging [7], such as an increase in skin laxity, which is a significant aggravating factor of cellulite [8].

The lack of efficacy from strategies that target adipose tissue suggests that alterations in adipose tissue are not the primary etiology of cellulite [2], despite that a higher degree of dimples is observed with increasing Body Mass Index (BMI) [9]. Age-related changes in dermal thickness is not necessarily considered to be the primary cause [2], but rather hormonal influences [6, 10]. Cellulite may worsen during high estrogen states, including pregnancy, nursing, and chronic use of oral contraceptives[11]. Further, weight gain and obesity can worsen the appearance of existing cellulite [9, 11].

Numerous treatments such as diet, physical activity, massage, topical products, liposuction, subcision, lasers, radiofrequency (RF) and ultrasound technologies have been proposed to treat cellulite, as well as carboxytherapy and cryolipolyis [3, 4, 6, 10], all with varying efficacy [5]. However, the results that most of these treatments offer can be modest at best, temporary in longevity [12] , do not target the underlying structural causes, or require very advanced surgical training [13]. There is little or no evidence to support effectiveness of some of the treatments or evidence to produce the long-term effect of neocollagenesis that would theoretically correct the fat undulation associated with collagen and elastic tissue degeneration in the dermis and hypodermis [3, 11], although most treatment options show improvement of cellulite in the majority of patients. In order to increase the overall result, a combination of several methods can be used to generate an 'amplifying effect' [4].

CCI

Approximately 30 women will be enrolled and treated with *Sculptra* in the posterior thighs in this pilot study. The Sponsor intends to use the information gathered in this pilot to initiate a pivotal study using *Sculptra* for the improvement in appearance of cellulite in the posterior thighs provided the results are favorable.

2.2 Relevant previous data

2.2.1 Non-clinical documentation

Please refer to the Investigator's Brochure (IB) for a description of performed non-clinical studies with *Sculptra*.

2.2.2 Clinical documentation

Please refer to the IB for a description of performed clinical studies with *Sculptra* relevant for treatment of cellulite.

2.3 Risks and benefits

CCI [redacted].

Risks with *Sculptra* as with any other injectable implant include infections, perforation of blood vessels, trauma to nerves and lumps. The most common reported adverse events (AEs) after *Sculptra* treatments are formation of papules and nodules, swelling, mass/induration, of which most resolve with time.

Infection, and damage to body structures such as nerves or blood vessels at the injection site, have also been reported. Rare but serious AEs associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures.

For intravascular complications or embolic events, the treating physician should provide prompt medical attention and follow relevant clinical practice guidelines [15] for handling these symptoms. The treating physician should also review the Intravascular Injection Treatment Protocol [16] provided separately as a supportive tool.

Lidocaine can, in rare cases, give allergic reactions, and therefore subjects with known allergy or hypersensitivity to local anesthetics should not be included in the study.

The potential risks related to treatment with *Sculptra* have been assessed and evaluated in accordance with requirements in the ISO 14971 standard and sponsor's established risk management procedures. Based upon the evaluation, risks are considered minimal given the area of injection, depth of injection and volume of product used.

Additional information about reported AEs and anticipated risks are included in the study Instructions for use (IFU) and IB.

Given the anticipated low level of acceptable AEs in connection with the injection, it was determined the risk-benefit assessment for use of *Sculptra* in this study with the specified reconstitution and injection procedures for improvement in appearance of cellulite appears to offer a clinical benefit at reasonable risk.

3. STUDY OBJECTIVES AND ENDPOINTS

This investigation is an early feasibility study to investigate the safety and effectiveness of *Sculptra* for a new indication, the improvement in appearance of cellulite in the posterior thighs, with the objective of an expanded label indication.

3.1 Study Objectives

The effectiveness objective is to evaluate the effectiveness of *Sculptra* for the improvement in appearance of cellulite in the posterior thighs.

3.1.1 Primary objectives and endpoints

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.

3.1.2 Secondary objectives and 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.

3.1.3 Safety objectives and endpoints

The safety objective is to evaluate the safety of *Sculptra* for the improvement in appearance of cellulite in the posterior thighs.

The safety endpoints are:

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.

3.2 Appropriateness of measurements

The aim of this study is to investigate the aesthetic improvement of cellulite appearance. The primary endpoint chosen is GAIS assessment by Investigator. The GAIS a widely used and accepted measure within the aesthetic filed. In utilizing GAIS, Investigators can evaluate and report clinically meaningful aesthetic improvement.

CCI [redacted]

Effectiveness evaluation in dermal filler clinical studies includes a combination of clinician- and subject-reported outcomes. As these are aesthetic devices and elective procedures, the incorporation of the subject perspective is critical to a study for the benefits associated with dermal fillers.

The prospective subject and clinician play a central role in determining what aesthetic treatment is right, especially when there are many alternatives.

3.3 Clinical Hypothesis

This study has been designed to demonstrate safety and investigate effectiveness of *Sculptra* for the improvement in appearance of cellulite in the posterior thighs.

4. STUDY DESIGN

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 two study centers in Canada. Approximately 30 women with intent to undergo treatment to improve appearance of cellulite will be enrolled and treated with *Sculptra* in three sessions spaced one month (+2 weeks) apart. Subjects will be treated at baseline, Month 1 and Month 2 including a safety follow-up phone call 72 ± 24 hours after each treatment. All subjects will have a follow-up visits at Month 6, 9 and 12. All visits and assessments are outlined in the Schedule of Assessments in Figure 2.

Stopping rule:

Enrollment and injections at a study center will be temporarily halted if an SAE occurs for a vascular embolic event that leads to skin necrosis, vision loss, or stroke and is determined by the Investigator to be directly or possibly related to the investigational device or injection procedure.

The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:

- was unanticipated
- directly related to the study product or device injection procedure and
- presents an unreasonable risk to study subjects,

the study will be terminated, and the Investigators notified. The REB and RA will also be notified if the study is prematurely terminated due to safety concerns.

If the SAE does not meet the above criteria, then enrollment in the study will continue provided all other safety criteria have been met.

4.1 Overall Design

4.2 Study rationale and justification for design

Aesthetic treatments to correct cellulite have become an increasingly common request and have driven the growing demand for a new, effective and minimally invasive procedure. The desire for smoothening and improving the appearance of dimpled skin has traditionally been met with subcision of fibrous septa, infrared light, laser, radiofrequency, cellulite creams and massage, for example. The use of *Sculptra* for treatment to improve appearance of cellulite represents a minimally invasive procedure to achieve aesthetic improvement in the posterior thighs.

CCI [redacted]

This study is designed to investigate the feasibility in treatment to improve clinical appearance of cellulite in the posterior thighs using *Sculptra*. *Sculptra* stimulates collagen build over time and multiple treatment sessions at least 4 weeks apart is recommended by leading experts [17]. Based on previously performed clinical studies and post-market surveillance data, most AEs occur within two to three weeks of an injection session. In addition to the on-site follow-up visits throughout the study, at which subjects will be questioned by study center personnel about AEs, a subject diary to capture the most common injection-related events for 28 days following each treatment will be utilized in the study to facilitate reporting. The effectiveness peak may be seen up to 12 months after the initial treatment based on previous studies using *Sculptra* in facial areas. The 12-month duration of the study has been set to ensure the vast majority of AEs and the effectiveness peak is captured within the follow-up period.

4.3 Number of subjects and study centers

Approximately 30 women will be included across two study centers in Canada.

4.4 Study duration

The planned clinical study duration from First Subject First Visit (FSFV) to Last Subject Last Visit (LSLV) is approximately 15 months. A subject will be involved in the study for up to 13 months, including a screening phase of up to 30 days and follow-up time after last injection. End of study is when enrollment has reached the target number of subjects and all subjects have completed the last study visit.

4.5 Study visits description and procedures

All study visits and assessments are outlined in the Schedule of Assessments in Figure 2.

4.5.1 Visit 1, Screening (Day -30 to Day 1)

The screening visit and baseline visit (Day 1) may be performed on the same day. The following activities and screening assessments will be performed within 30 days prior to baseline.

- Obtain Informed Consent prior to conducting any study specific procedure.
- Assess eligibility: Review inclusion/exclusion criteria.
- Obtain demographic data: date of birth, height, weight, gender, ethnicity, race and Fitzpatrick Skin Type (FST).
  - FST is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet light.[18] [19]. For determination of the FST, see Table 1 below.
  - Height may be self-reported, weight is to be measured at clinic.
- Record the subject's medical history (including any prior dermatological procedures or implants).
- Record the subject's prior and concomitant therapies.
- Perform Urine Pregnancy test for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for treatment.
- Schedule the baseline and treatment visit (Day 1) if performed on a different day than screening.

Table 1 Fitzpatrick Skin Types (FST)

Skin type	Skin color	Skin characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

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4.5.2 Visit 2a, Baseline and First treatment (Day 1)

The screening visit and baseline visit (Day 1) may be performed on the same day. If Screening visit and Baseline visit are not performed on the same day, the following should be repeated:

- Review for changes in concomitant therapies.
- Re-confirm eligibility criteria.
- Perform Urine Pregnancy test for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for treatment.

Once the subject is deemed eligible by the Treating Investigator, the following procedures should be completed:

- Obtain pre-treatment Photography.
- Perform pre-treatment ultrasound.
- Assess severity of depressions and undulations associated with cellulite using the GCTS - Treating Investigator.
- *Sculptra* administration.
- CCI .
- Evaluate the subject for post-treatment AEs - Treating Investigator.
- Evaluate for device deficiencies - Treating Investigator.
- Dispense diary and instruct subject on daily Diary completion. Remind subject to bring the Diary to the next study center visit.
- Evaluate the subject for device palpability – Treating Investigator.
- Inform subject about the follow-up telephone call 72-hours (±24 hrs) after the visit.
- Schedule the next visit 1 month (+2 weeks) after baseline.

4.5.3 Visit 2b, Follow up 72-hour telephone call (±24 hours)

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the study center for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the diary completion and reported events since receiving treatment. Remind subject to complete the diary daily and bring it to the next on-site visit.

4.5.4 Visit 3a, Second treatment (1 month (+2 weeks) after Baseline

- Review for changes in concomitant therapies.
- Collect and review subject diary.
- Obtain pre-treatment Photography (2D and 3D).
- Assess GAIS – Subject and Treating Investigator.

CCI

- Assess severity of depressions and undulations associated with cellulite using the GCTS - Treating Investigator.
- Assess whether optimal treatment result has been obtained (as agreed by the Treating Investigator and Subject). If a second treatment is to be performed, confirm eligibility criteria:
  - Perform Urine Pregnancy test for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for treatment
  - No treatment should be given in the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

For subjects who receive a second treatment:

- *Sculptra* administration.
- CCI .
- Evaluate the subject for post-treatment AEs - Treating Investigator.
- Evaluate for device deficiencies - Treating Investigator.
- Dispense diary and instruct subject on daily Diary completion. Remind subject to bring the Diary to the next study center visit.
- Evaluate the subject for device palpability – Treating Investigator.
- Inform subject about the follow-up telephone call 72-hours (±24 hrs) after the visit.
- Schedule the next visit 1 month (+2 weeks) after second treatment.

4.5.5 Visit 3b, Follow up 72-hour telephone call (±24 hours)

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the study center for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the diary completion and reported events since receiving treatment. Remind subject to complete the diary daily and bring it to the next on-site visit.

4.5.6 Visit 4a, Third treatment (1 month (+2 weeks) after second treatment

- Review for changes in concomitant therapies.
- Collect and review subject diary.
- Obtain pre-treatment Photography (2D and 3D).
- Assess GAIS – Subject and Treating Investigator.

CCI

- Assess severity of depressions and undulations associated with cellulite using the GCTS - Treating Investigator.
- Assess whether optimal treatment result has been obtained (as agreed by the Treating Investigator and Subject). If a third treatment is to be performed, confirm eligibility criteria:
  - Perform Urine Pregnancy test for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for treatment.
  - No treatment should be given in the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

For subjects who receive a third treatment:

- *Sculptra* administration.
- CCI .

- Evaluate the subject for post-treatment AEs - Treating Investigator.
- Evaluate for device deficiencies - Treating Investigator.
- Dispense diary and instruct subject on daily Diary completion. Remind subject to bring the Diary to the next study center visit.
- Evaluate the subject for device palpability – Treating Investigator.
- Inform subject about the follow-up telephone call 72-hours (±24 hrs) after the visit.
- Schedule the next visit at Month 6 (2 weeks) after second treatment.

4.5.7 Visit 4b, Follow up 72-hour telephone call (±24 hours)

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the study center for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the diary completion and reported events since receiving treatment. Remind subject to complete the diary daily and bring it to the next on-site visit.

4.5.8 Visit 5, Follow up Month 6 (±2 weeks) after Baseline

- Obtain weight.
- Review the subject's concomitant therapies.
- Obtain Photography (2D and 3D).
- Evaluate the subject for AEs - Treating Investigator.
- Collect and review subject diary (only applicable for subjects who received a third treatment).
- CCI
- Evaluate the subject for device palpability – Treating Investigator.
- Assess GAIS – Subject and Treating Investigator.

CCI

4.5.9 Visit 6, Follow up Month 9 (±2 weeks) after Baseline

- Obtain weight.
- Review the subject's concomitant therapies.
- Obtain Photography (2D and 3D).
- Evaluate the subject for AEs - Treating Investigator.

- CCI
- Evaluate the subject for device palpability – Treating Investigator.
- Assess GAIS – Subject and Treating Investigator.

4.5.10 Visit 7, Follow up Month 12 (±2 weeks) after Baseline/Early termination

- Obtain weight.
- Review the subject's concomitant therapies.
- Perform Urine Pregnancy test for all females of childbearing potential.
- Obtain Photography (2D and 3D).
- Evaluate the subject for AEs - Treating Investigator.
- CCI
- Evaluate the subject for device palpability – Treating Investigator.
- Assess GAIS – Subject and Treating Investigator.

4.6 Procedures/Reasons for Subject Discontinuation

Each subject should be advised in the Informed Consent Form (ICF) that the subject has the right to withdraw from the study at any time, for any reason, without prejudice. Subjects may also be discontinued from this study if the investigator determines that it is in the subject's best interest to do so and may be withdrawn at the investigator discretion at any time.

The withdrawal criteria are:

- **Medical Reasons** — If the subject suffers from a medical condition and/or AE that, in the judgment of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons should document the specific condition for withdrawing the subject.
- **Withdrawal by Subject:** — Includes consent withdrawal, subject relocation, schedule conflicts. A subject can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorized representative at any time for any reason.
- **Lost to follow-up:** — If a subject does not return for a scheduled visit, reasonable effort shall be made to contact that subject, confirm with three documented phone calls and a certified letter (delivery receipt requested) without answer before declaring the subject lost to follow-up.
- **Other:** — This category is to be used for a subject who discontinues due to a reason other than as specified in the pre-defined categories above. Explain the reason for discontinuation.

The reason and date for withdrawal should be documented in the subject's source documents and in the electronic case report forms (eCRF)s. When possible, an explanatory comment should be added to further explain the reason for the withdrawal. If withdrawal of a subject occurs during a regular study visit, the eCRF for that specific visit shall be completed as far as possible.

If withdrawal of a subject occurs between regular study visits, the subject should when possible (irrespective of the reason for withdrawal) be scheduled for a termination visit to document subject outcome for the secondary endpoints.

If a subject is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses. Subjects who receive product and are withdrawn or discontinued from the study will not be replaced. For AEs still ongoing at the time of withdrawal, see section 7.2.6.

5. STUDY POPULATION

Approximately 30 women with intent to undergo treatment to improve appearance of cellulite in the posterior thighs will be included in this study.

5.1 Clinical Study Population Characteristics

5.1.1 Inclusion criteria

The subjects must meet 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.

5. CCI [redacted]

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.

5.1.2 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 liporeduction 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. Varicous 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.

5.1.3 Medical history

History of relevant surgical events and medical conditions should be documented (including any prior dermatological procedures or implants) in the eCRF using medical terminology.

5.1.4 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

5.1.4.1 Recording

Prior and concomitant therapies are to be recorded on the appropriate form in the eCRF. Concomitant therapies are to be recorded, reviewed, and updated at each visit. Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition.

5.1.4.2 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (Section 5.1.4.3), all therapies are authorized.

5.1.4.3 Prohibited concomitant therapies

The following therapies are prohibited during the study because they may interfere with the effectiveness and/or safety assessments of the study product(s) and/or injection procedure:

- Anticoagulants or inhibitors of platelet aggregation that have the ability to prolong bleeding times (e.g. aspirin, NSAIDs [20]), Omega-3 or Vitamin E should not be used within 14 days before any treatment to avoid increased bruising or bleeding at injection sites. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.
- The study product contains lidocaine, but additional local anesthesia may be used. Lidocaine should however be used with caution in subjects receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g. certain antiarrhythmics, as the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies or antiviral treatment for HIV or Hepatitis C). Systemic corticosteroids within 3 months before treatment. Inhaled corticosteroids are allowed.

- Topical corticosteroids, topical prescription retinoids or cellulite cream in the treatment area within 1 month of the Baseline visit
- Planned aesthetic surgery in the thigh or gluteal area.
- Tissue augmenting therapy, contouring or revitalization treatment with fillers, fat-injections, collagen, CaHa, PLLA or lifting threads, tissue grafting, tissue augmentation with permanent implants, silicone or fat in the thigh area.
- Needling, mesotherapy, lipolytic injection, liporeduction massage, intense pulsed light (IPL), radiofrequency, endermology, ultrasound, cryotherapy, laser or light treatment, photo modulation, chemical peeling, dermabrasion or other ablative/non-ablative procedures are prohibited in the thigh area.
- Tattoo or skin bleaching in the posterior thigh.
- Participation in any interventional clinical study.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, the Sponsor should be notified, time permitting, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical study, the Sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical study.

5.2 Subject Identification Number

Prior to any study procedures being conducted, the subject must sign the ICF. Each subject will be assigned a subject number that will be allocated in ascending order within each study center. A screen failure is a subject who signed the ICF but never enrolled (i.e. received treatment) in the study. For screen failures, the subject source documents should indicate which assessments have been made and the reason why the subject was determined to be a screen failure. A screen failure should not be re-entered in the study. For the duration of the clinical study, each subject will be identified using the subject number for all documentation and discussion.

6. STUDY INTERVENTION

6.1 Description of the Investigational Device

6.1.1 Investigational device

The term “study product” refers to *Sculptra*. The study product will be provided by Sponsor.

Sculptra is an injectable implant that contains microparticles of PLLA, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family. *Sculptra* is reconstituted prior to use by the addition of Sterile Water for Injection (SWFI), USP to form a sterile non-pyrogenic suspension. Each vial of dry powder contains:

- 150 mg poly-L-lactic acid (PLLA)
- 90 mg sodium carboxymethylcellulose (CMC)
- 127.5 mg mannitol

6.1.2 Reference product

Not applicable.

6.1.3 Additional products and materials

Needles for injection, 25G 1.5-inch BD needles, will be supplied by the Sponsor. The needle is approved for use in Canada.

The following will be supplied by the study centers:

- Sterile Water for Injection (SWFI), USP, 20 mL
- Single-use 5 mL sterile syringes
- Single-use 20 mL sterile syringes
- Fluid Dispensing Connector
- Single-use 1 mL sterile syringe
- 18 G sterile needles
- Single-use 3-5 mL (depending on Investigator's preference) sterile syringes
- Antiseptic
- Lidocaine HCl 2%

(Note: The reconstituted study product contains lidocaine, but additional topical or local anesthesia may be used at the discretion of the Treating Investigator before the treatment. If additional anesthesia is used, potential local anesthesia toxicity should be taken into consideration. The maximum allowable safe dose of lidocaine is 3-4.5 mg/kg. Type of anesthesia, administration route, product name, and quantity used must be recorded in the eCRF.)

6.2 Packaging and Labelling

Sculptra is supplied as a sterile freeze-dried preparation for injection in a clear glass vial, which is sealed by a penetrable stopper, covered by an aluminum seal with a flip-off cap. Each carton of *Sculptra* contains one vial.

Each vial of *Sculptra* is packaged for single use only.

Labelling will be performed according to Health Canada, Food and Drugs Act (FDA), Part 3 of the Medical Devices Regulations section 86 on labelling. The carton will be labelled with lot number, expiration date, CTN number, name of the device, name of manufacturer and the following:

"Investigational Device. To be used by Qualified Investigators only."

"Instrument de recherche. Réservé uniquement à l'usage de chercheurs compétents"

Detailed product information is provided in the study IFU.

6.3 Instructions for Use and Administration

The study product is reserved for use by Treating Investigators who are experienced in treating cellulite in the posterior thigh area and who have been trained in the appropriate injection techniques. Training will be provided by the Sponsor.

Before treatment the subject will be informed about the expected post-treatment events that should be recorded in the subject diary and potential risks involved with the treatment and when to contact the Investigator in case of emerging symptoms.

The investigator must be trained on, and have at hand, the relevant clinical practice guidelines [15] and the actions to be taken if intravascular complications or embolic events occur. The treating physician should also review the Intravascular Injection Treatment Protocol [16] provided separately as a supportive tool in the Investigator file.

Detailed information regarding the treatment procedure, treatment regimen and post-treatment care including subject instructions are provided below and in the IFU.

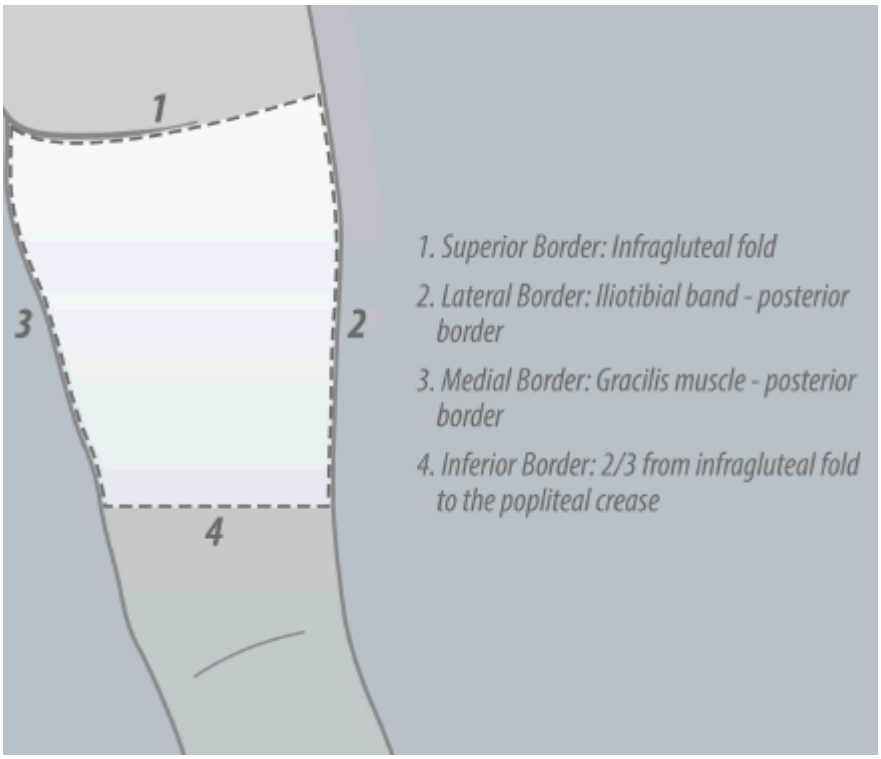
6.3.1 Treatment procedure

Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections should be observed at all times including the use of disposable gloves during the injection procedure. The treatment site should be cleaned with a suitable antiseptic solution.

The study product contains lidocaine hydrochloride, but additional topical or local anesthesia or an ice pack may be used at the discretion of the Treating Investigator to further reduce pain on injection. If (topical or local) anesthetic or ice is used, the area should be cleaned after anesthetic is removed. The use of anesthetic or ice should be recorded in the source documentation and in the eCRF.

The boundaries of the treatment area are the infragluteal fold superiorly, the illotibial band laterally, the gracilis muscle medially and 2/3 from infragluteal fold to the popliteal crease inferiorly, see Figure 3.

Figure 3 Treatment area



The study product shall be reconstituted according to instructions in the IFU.

Injections should be made using a 25 Gauge (G), 1.5 inch needle into the deep dermis or subdermal region (i.e. subcutaneously), evenly spread over the entire treatment area, with a fanning, asterisks or short linear threading technique with a distance of 1-2 cm using 0.05–0.1 mL per injection point. In some areas with marked lipoatrophy, a linear retrograde technique with cross sticks can be done in order obtain better correction of the skin depression.

One vial per third of the area in each thigh (100 cm^2) is recommended.

The needle should be changed when blunt. The number of needles used shall be recorded in the eCRF.

6.3.2 Treatment regimen (dose and interval)

Eligible subjects 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. 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 will not be performed if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

6.3.3 Post-treatment care

The injected sites could be gently massaged by the treating Investigator to conform to the contour of the surrounding tissues. Topical cooling may be applied to reduce initial swelling and bruising. After the injection, some common injection-related reactions might occur. These reactions include erythema, swelling, pain, itching, bruising or tenderness at the implant site. Typically, resolution is spontaneous within one week after injection into the skin.

Subjects should be advised not to do vigorous exercise or have vigorous massage within 3 days after injection and to avoid exposing the treated area to heat (sunbathing, ultraviolet-lamp exposure, sauna, steam baths, etc.) until any signs of initial swelling and redness have resolved.

6.4 Supplies Management

6.4.1 Product accountability

The study products will be released to the PI or his/her authorized designee after study approvals have been received from the REB and RA and the Clinical Trial Agreement (CTA) has been signed by all parties.

The PI must ensure that the study products are kept in a secure location, with access limited to those authorized by the PI.

The study product must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the PI maintains accurate product accountability records, i.e. documentation of the physical location of all study products, deliveries, and return of study product between the Sponsor and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all

study product received from the Sponsor; including the product name, date received, lot number, expiration date, and amount received. In addition, dispensing logs shall be maintained including the product name, lot number, expiry date, dispense date, the number of vials used, the subject receiving study product, and number of vials left in stock at the study center.

When the study is completed, all unused or expired study product at each study center shall be returned to the Sponsor for destruction *or* be destroyed locally at the study center, with proper documentation, after agreement with the Sponsor. Any malfunctioning study products shall be reported as described in Section 7.2.10.

Product deliberately or accidentally destroyed during shipment or at a study center shall be accounted for and documented. Used syringes, vials, needles, and any opened unused material must be discarded immediately after the treatment session and must not be reused due to risk for contamination of the unused material and the associated risks including infections according to standard procedures at the study center. Disposal of hazardous material, i.e. syringes and needles, must conform to applicable laws and regulations.

All study product(s) sent to the PI will be accounted for and no unauthorized use is permitted.

6.4.2 Storage of Study Product

Sculptra powder should be stored at controlled room temperature (15-30°C) away from heat. Upon reconstitution, *Sculptra* should be used immediately. Do not freeze.

6.4.3 Dispensing and Return

Not applicable, the treatment will be administered by the Treating Investigator at the study center and be documented in the accountability records.

6.4.4 Treatment compliance

Not applicable, the treatment will be administered by the Treating Investigator at the study center and be recorded in the eCRF.

6.4.1 Case report form recordings

The following should be recorded in the eCRF:

- Date and time of completed injection
- Amount of study product per thigh and session,
- Needle size and number of needles used
- Injection technique used
- Treatment area
- Additional local or topical anesthesia

6.5 Randomization

Not applicable, all eligible subjects consenting to participate in the study will receive study product.

6.6 Blinding

Not applicable.

6.7 Post-trial provisions

In time, the implant will be degraded in the body and additional treatments will be necessary to maintain the aesthetic result.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1 Efficacy Assessments

The methods for collecting effectiveness data are described in this section. To minimize inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline assessments complete all corresponding follow-up evaluations.

The methods for collecting effectiveness data are:

- Photography
- Time to return to daily activities after treatment will be assessed using subject diaries.
- Global aesthetic improvement by Treating Investigator and Subject using GAIS.

7.1.1 Photography

Photographs will be taken in a standardized way to document the condition at baseline, for effectiveness assessments as indicated in Figure 2 Schedule of Assessments, and to document AEs in the treated area. The subject will be standing and wearing a standardized photographic garment.

Camera equipment will be provided by the Sponsor or their designee. Study center personnel designated to take photographs shall be thoroughly trained in the equipment and techniques before study start. The same photographic equipment and standardized setting must be used at each visit (e.g. distance, light, position). Instructions for photography are provided in a separate photography manual.

7.1.2 GAIS

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 in Table 2 GAIS.

Table 2 GAIS

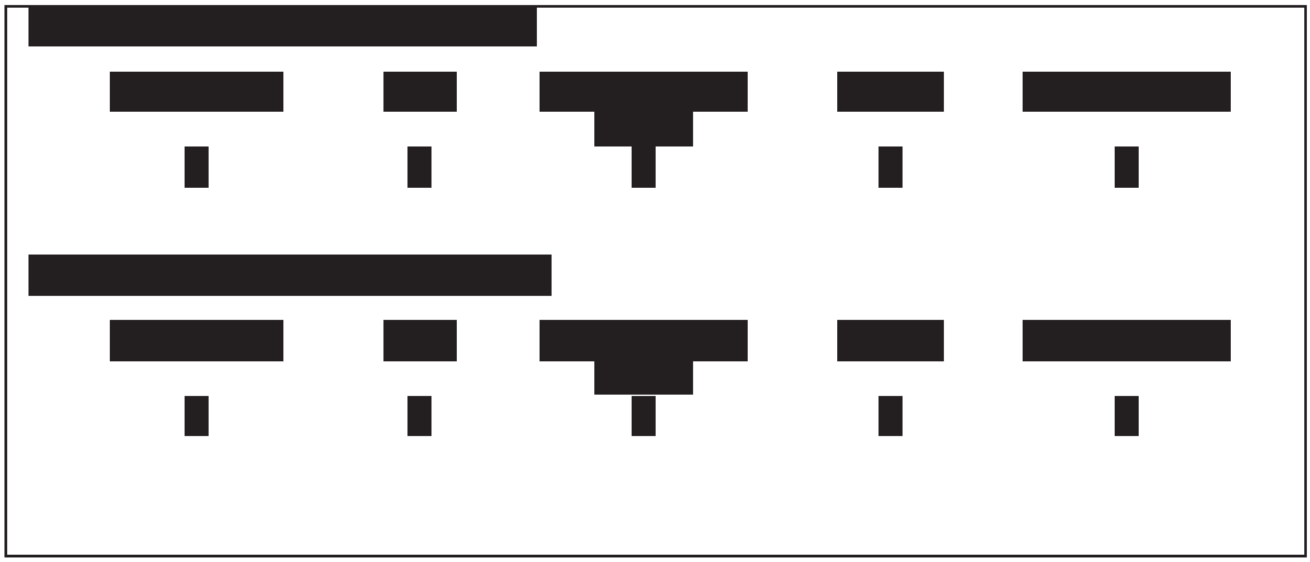
Rating (Treating Investigator and subject)	Description (only for Treating Investigator)
Very much improved	Optimal aesthetic result for the implant for this subject.
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
Improved	The appearance 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.

Figure 4CCI

GALDERMA	Title **43CASA2006 CSP Sculptra cellulite**	Doc id **MA-47276**

Effective date: 2021-06-21 06:13

CCI



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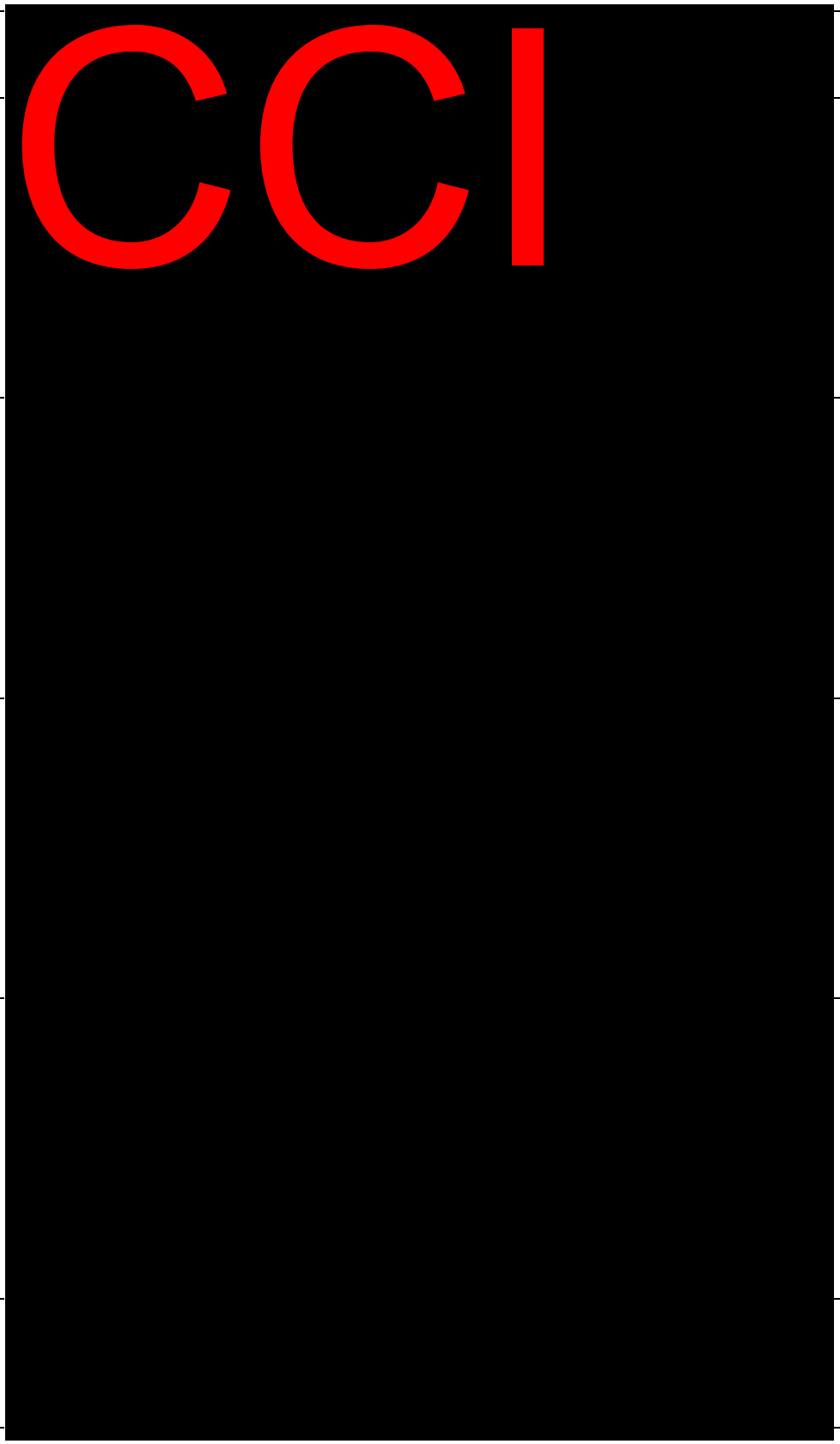

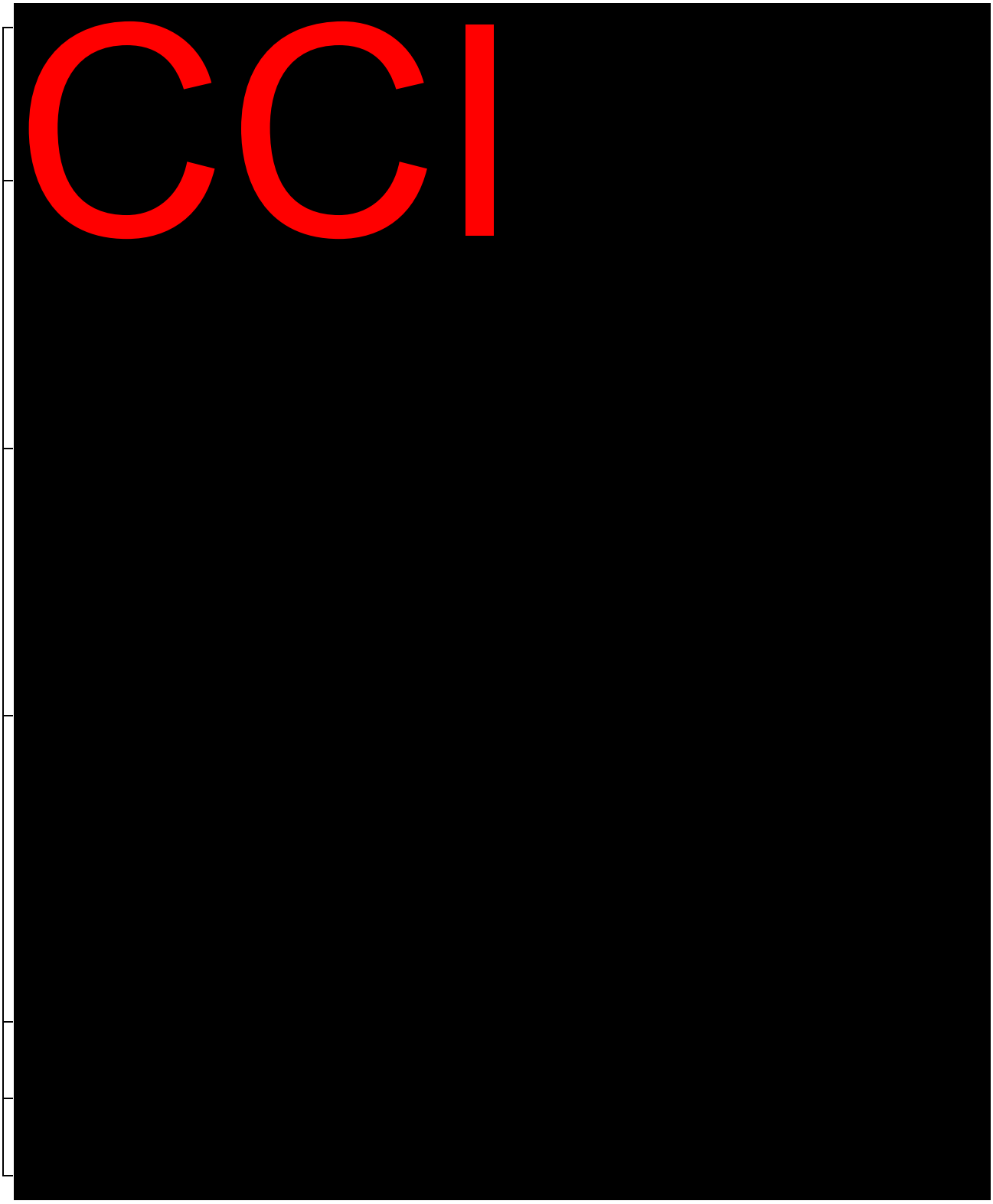

7.1.5 Volume analysis, surface contour, skin texture/roughness and circumference of the thigh assessments using 3D imaging

Volume analysis (surface relief changes), surface contour, skin texture/roughness and circumference of the thigh will be assessed using CCI and software. The assessment should be made for each thigh separately. 3D imaging should be performed at baseline, Month 6, Month 9 and Month 12. Camera equipment will be provided by the Sponsor or their designee. Further details regarding the 3D imaging procedure will be specified in a separate user guide. Study centers should follow the maintenance instructions from the equipment manufacturer and keep records of maintenance in the investigator file.

7.1.6 Ultrasound

Dermal thickness will be assessed using ultrasound as indicated in the Schedule of Assessments in Figure 2. The assessment should be made for each thigh separately. Ultrasound equipment will be supplied by the Sponsor or their designee to the study centers. Further instructions regarding the equipment and procedure will be specified in a separate user guide.

7.1.7 Return to daily activities

Time to return to daily activities after treatment will be assessed using subject diaries for 28 days after each treatment.

7.2 Safety Assessments

The methods for collecting safety data are described in this section and include:

The methods for collecting safety data are:

- Subject Diary data
- Laboratory assessments
- CCI
- Device palpability assessment
- Adverse Event reporting
- Device deficiency reporting

7.2.1 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 (grading for subject diary in Table 3) shall be assessed for the treated area.

Injection site responses that have not been pre-defined in the diary may also be recorded in the diary under “other”.

Diary data will be counted and displayed separately from other AE data. All pre-defined diary events ongoing at Day 28, shall be followed up until resolved.

Table 3 Grading for subject diary data

Category
None
Tolerable
Affects daily activities
Disabling

7.2.2 Laboratory assessments

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.

7.2.3 Pain assessment

Subjects will rate their pain using an CCI (Appendix 1) where 0 is no pain and 10 is the worst pain imaginable. Pain will be assessed immediately after treatment and 30 minutes after treatment at the initial treatment visit and at all follow-up visits.

7.2.4 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.

7.2.5 Adverse events

7.2.5.1 Definition of an adverse event (AE) (Medical Devices Regulation (MDR) article 2(57))

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons[I], in the context of a clinical investigation, whether or not related to the Investigational device.

This definition includes:

a) events related to the investigational product or the reference product

b) events related to the procedures involved

c) events that are anticipated as well as unanticipated

7.2.5.2 Definition of a serious adverse event (SAE) (MDR article 2(58))

An SAE is any AE that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1. a life-threatening[III] illness or injury, or

[I] For users or other persons, this definition is restricted to events related to the investigational product.

2. a permanent impairment of a body structure or body function, or
3. hospitalisation or prolonged hospitalization[III], or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
5. chronic disease

c) led to foetal distress, foetal death, or a congenital physical or mental impairment or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (see Section 7.2.5.5).

7.2.5.3 Recording instructions for adverse events

Each subject should be questioned about AEs at each study visit following the screening visit. All AEs, non-serious as well as serious, are to be reported as an AE in the eCRF.

The question asked should be: ”Since your last clinical visit; have you had any health problems?”. Information on AEs can also be obtained from signs and symptoms detected during each examination or from a laboratory test, observations made by the study center personnel, subject diaries, or spontaneous reports from the subjects or their relatives.

When an AE is related to a device deficiency (refer to Section 7.2.10), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form, provided in the investigator file, and in the eCRF.

Investigators, or other study center personnel, shall record all AEs in the eCRF, including:

a) Event term (recorded in standard medical terminology and avoiding abbreviations)
b) Affected area
c) Start date (first day with symptoms)
d) Stop date (last day with symptoms)
e) Intensity (mild, moderate, or severe according to definition in Section 7.2.5.4)
f) Seriousness (serious or not serious, according to definition in Section 7.2.5.2)
g) Causal relationship to study product or study product injection procedure (yes or no)
h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

The AE form/module in the eCRF must be signed and dated by the Investigator.

[II] The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

[III] Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

The pre-defined, expected post-treatment events shall be assessed separately, see Section 7.2.1. These events shall be collected daily by subjects in a diary for 28 days following each treatment.

7.2.5.3.1 Intensity

All AEs, non-serious as well as serious, are to be reported as an AE in the eCRF.

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

Mild: Awareness of symptoms or signs, but easily tolerated (acceptable*)*

Moderate: Enough discomfort to interfere with usual activity (disturbing)

Severe: Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.

7.2.5.3.2 Causal relationship and seriousness

Each AE, serious as well as non-serious, shall be assessed by the Investigator for causal relationship with the study product and its use (the injection procedure) and for seriousness (Yes or No) of the event.

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product?", and
- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

In addition, each SAE will be classified by both the Investigator and Sponsor separately, according to four different levels of causality:

1. **Not related** - Relationship to the device, comparator or procedures can be excluded when:
   - the event has no temporal relationship with the use of the investigational device, or the procedures related to investigational device;
   - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/ exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
   - the event involves a body-site or an organ that cannot be affected by the device or procedure;
   - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
   - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2. **Possible -** The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. **Probable** - The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. **Causal relationship** - the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
    - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has a temporal relationship with investigational device use/application or procedures;
    - the event involves a body-site or organ that
        - the investigational device or procedures are applied to;
        - the investigational device or procedures have an effect on;
    - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
    - the discontinuation of medical device application (or reduction of the level of activation/ exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
    - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
    - harm to the subject is due to error in use;
    - the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

7.2.5.4 Reporting of adverse events

AE reporting on each subject shall start upon first treatment. All other events that occur after the subject signs the ICF but before enrollment will be recorded in the subject's medical history. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

7.2.5.5 Reporting of serious adverse events

The Investigator shall report any **SAE** to the Contract Research Organization (CRO) **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via e-mail or submitted via the eCRF.

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- CTN 43CASA2006
- Subject identification (age, gender, subject number)
- Date when AE occurred
- Date when AE became serious
- Adverse event description
- Name of Investigator and original reporter (if other than Investigator)
- Name of study product
- Treatment specification

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the CRO immediately, but not later than 24 hours of awareness of the new data. Complete and adequate information on each SAE is required. All attempts to obtain this information, including dates for follow-up activities, must be documented by the Investigator.

Supporting documentation to be provided with the SAE report:

- Concomitant therapies form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

CCI [redacted] [redacted]

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed to the CRO. A copy of the fully completed SAE form shall be kept at the study center.

In addition, the PI shall **report SAEs to RA within 72 hours of discovery** and report SAEs to the responsible REB without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her REB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor is responsible for reporting to the RA according to national regulations.

Enrollment and injections at a study center will be temporarily halted if an SAE occurs for a vascular embolic event that leads to skin necrosis, vision loss, or stroke and is determined by the Investigator to be directly or possibly related to the investigational device or injection procedure, see stopping rules in section 4.1.

Following the initial SAE report from the Investigator to the CRO, the sponsor shall conduct an evaluation of the SAE and report the results of such evaluation to RA and to all reviewing ECs and participating investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter the Sponsor shall submit such additional reports concerning the effect as RA requests.

7.2.6 Follow-up of unresolved events ongoing at termination of the study

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure and ongoing at study end, shall be followed up after the subject's participation in the study is over. Such events shall be followed-up after the last study visit until resolved, assessed as chronic or stable, or subject is lost to follow up. Follow-up information shall be reported on the AE follow-up form.

7.2.7 Follow-up of events occurring after subject termination of the study

All AEs with a causal relationship to the study products or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor. The report should as a minimum include the information described in Section 7.2.5.3. The report can be sent via e-mail according to contact details specified in Section 7.2.5.5. The events shall thereafter be followed-up until resolved, considered chronic or stable, or subject is lost to follow up.

7.2.8 Anticipated adverse events

Information regarding anticipated AEs for *Sculptra* is included in the study specific IFU.

7.2.9 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period, the subject must be withdrawn from any following study treatment but should continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge and be submitted to the CRO according to contact details specified in section 7.2.5.5. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the exposure *in utero* report form to the Sponsor immediately but no later than 24 hours after the Investigators awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

7.2.10 Device deficiencies

7.2.10.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety[2], or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

7.2.10.2 Recording instructions for device deficiencies

In the event of a device deficiency. the Investigator shall send the completed clinical study complaint form to the CRO.

CCI [redacted] [redacted]

A **device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the CRO within 72 hours** after the Investigator's awareness (for contact information, see section 7.2.5.5). If the form is completed within an eCRF system, refer to the eCRF completion guidelines.

If the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the REB.

The deficient study product shall be kept by the study center until the Sponsor has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study center.

7.2.11 Stopping rule

Enrollment and injections at a study center will be temporarily halted if an SAE occurs for a vascular embolic event that leads to skin necrosis, vision loss, or stroke and is determined by the Investigator to be directly or possibly related to the investigational device or injection procedure.
The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:

- was unanticipated
- directly related to the study product or device injection procedure and
- presents an unreasonable risk to study subjects,

the study will be terminated, and the Investigators notified. The REB and RA will also be notified if the study is prematurely terminated due to safety concerns.

If the SAE does not meet the above criteria, then enrollment in the study will continue provided all other safety criteria have been met.

8. STATISTICAL DESIGN AND ANALYSIS

8.1 General

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system. Confidence intervals and p-values will be 2-sided and performed at a significance level of 5%.

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[2] Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

Continuous variables will be summarized using descriptive statistics, e.g. mean, median and standard deviation. Categorical variables will be presented in frequency tables with number and percent of observations for each level.

8.2 Analysis populations

The following populations will be defined:

- Safety — Includes all subjects who were injected in at least one thigh
- Full Analysis Set (FAS) — Includes all subjects who were injected in both thighs

FAS is the primary population for all effectiveness analyses.

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

Safety analysis is performed based on the safety population set.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

8.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the FAS, using descriptive statistics.

8.4 Data Transformations

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.

CCI [redacted]

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. 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.

8.5 Efficacy analysis

8.5.1 Primary analysis

The GAIS assessment by the Treating Investigator at Month 9 will be presented in a frequency table. In addition, the proportion of improved subjects (assessed as at least improved on both thighs) will be presented together with a 95% confidence interval (based on the binomial distribution).

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

8.5.2 Secondary analysis

The GAIS assessment by the Treating Investigator will be presented in frequency tables. In addition, the proportion of improved thighs (assessed as at least improved) will be presented together with a 95% confidence interval (based on the binomial distribution). This will be done for each thigh separately and also for both thighs combined at Month 1, 2, 6, 9 and 12.

The GAIS assessment by the subject will be presented in frequency tables. In addition, the proportion of improved thighs (assessed as at least improved) will be presented together with a 95% confidence interval (based on the binomial distribution). This will be done for each thigh separately and also for both thighs combined at Month 1, 2, 6, 9 and 12.

8.6 Safety analysis

AEs will be coded according to MedDRA and summarized by system organ class (SOC), preferred term (PT). 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 using mean, SD, min, max and median. Action taken for related AEs will also be summarized. Serious AEs will be listed.

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

Number and percentage of subjects reporting each pre-defined, expected, post-treatment symptoms, as collected in the 28 days diary, will be presented in total and by maximum severity for each treatment session.

8.7 Handling of missing data

Study data will be presented on observed cases, i.e.no imputation of missing values will be performed. Exception: when calculating duration and time to onset for AEs where start date is missing. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment.

8.8 Interim analysis

No applicable as this is an open study.

8.9 Data monitoring committee

Not applicable.

8.10 Withdrawals and deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with CSP deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to database lock.

Deviations from the statistical plan will be documented in the clinical report.

8.11 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.

9. DATA MANAGEMENT

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the CSP and the CRF template. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

9.1 Protection of personal data

The study shall include collection and processing of personal data as specified in the Regulation European Union (EU) 2016/679 (General Data Protection Regulation, GDPR) and the regulation EU 2017/745

(MDR) on the protection of individuals with regard to the processing of personal data and on the free movement of such data, the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada. For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the Investigator are responsible for complying with all requirements pursuant to national legislation in which the Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The ICF shall contain information about what personal data to be collected in the study and that this will be kept confidential. The provided information shall be sufficient to enable all subjects to give their consent not only to the participation in the study, but also to the processing of personal data. Such information includes information regarding the purposes of the collecting, processing, data transfer to countries not having same high level of security for processing of personal data than Sweden and EU, and the length of time during which personal data will be stored. The subject shall have the right of access to stored personal data, and the right to correction of incorrect information.

If a subject decides to terminate the study prematurely, data collected before withdrawal of consent will be used in the evaluation of the study, however no new data may be collected.

Authorized representatives from the Sponsor, CRO or a RA may visit the study center to perform audits/inspections, including source data verification, i.e. comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

9.2 Data Collection

An electronic data capture application, compliant with regulatory requirements for software validation (US FDA 21CFR11) will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and shall be completed electronically for each screened subject (screening visit) and enrolled subjects (subsequent visits).

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data shall be entered directly from the source documents, which are to be defined at each study center before inclusion of the first subject.

Authorized study center personnel designated by the PI shall complete data collection. Appropriate training and security measures shall be completed with all authorized study center personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and shall not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study center as part of the Investigator file.

Any delegation of collection of data shall be specified and recorded.

9.2.1 Data entry

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator

shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

9.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her authorized designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or by its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorized designee. The appropriate study center personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study center personnel, time, and date is logged.

9.2.3 User identification

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records shall be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

9.2.4 Audit trail

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

9.2.5 Source documentation

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

The Investigator is responsible for maintaining adequate and accurate source documents. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary.

Source documents shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, shall be clearly identified with the CTN and subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

The PI/Institution shall permit study-related monitoring, audits, REB review, and RA inspections and shall provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed ICFs and detailed records

of study product accountability). The records shall be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records shall be documented and the Sponsor shall be informed in writing.

The Sponsor shall verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record or other relevant source.

9.3 Archiving / Record keeping

All records pertaining to the conduct of the study, including signed eCRFs, ICFs, study product accountability records, source documents, and other study documentation must be retained for as long as is specified in the CTA after study completion or longer if required by national legislation. Sponsor will inform the study centers as to when these documents no longer needs to be retained. Measures shall be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fireproof cabinet).

After study completion and database lock, electronic study data shall be provided by the CRO for archiving.

It is the PI's responsibility to inform the Sponsor in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

10. PROTOCOL DEVIATIONS

The PI is not allowed to deviate from the CSP. However, under emergency circumstances, deviations from the CSP to protect the rights, safety and well-being of the subjects may proceed without prior approval of the Sponsor and the REB and RA. Such deviations should be documented and reported to the REB and RA as soon as possible. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor (within 24 hours following detection) as well as the REB if required.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Personnel Training

The product is reserved for use by the PI or his/her authorized designee in accordance with local legislation, trained in the appropriate aseptic injection techniques and expected to follow the recommendations in the study specific IFU. Additional training on the reconstitution procedure and treatment in the posterior thigh area will be provided by the Sponsor.

11.2 Quality Control / Clinical Monitoring

Study center monitoring of the study will be arranged by the Sponsor according to GCP guidelines to verify that the rights and well-being of the subjects are protected, the reported data are accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved CSP, subsequent amendment(s), GCP and the applicable regulatory requirements.

Any CSP deviation shall be documented appropriately, verified, discussed, and collected by the monitor and appropriate actions will be taken. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those that occur under emergency circumstances, to the Sponsor as well as the REB if required by national regulations. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study.

11.3 Quality assurance / Audit / Inspections

The study center may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the PI and other relevant study center personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study center team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the signature and delegation log.

12. ETHICS

The clinical investigation shall not commence until written approval/favorable opinion from the REB and, if required, the relevant RA of the countries where the clinical investigation is taking place has been received.

12.1 Application to Research Ethics Board and Regulatory Authority

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CSP/CSP amendment(s) from the REB The study shall not begin until the required favorable opinion from the REB has been obtained. The PI shall file all correspondence with the REB in the Investigator file and copies of REB approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the REB or RA shall be followed.

The study requires application for approval from the RA. The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed. The Sponsor will provide the PI with a copy of the relevant document.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

12.2 Subject information and consent

The PI or his/her authorized designee must always use the REB-approved subject information and ICF and it must not be changed without prior discussion with the Sponsor and approval from the applicable REB.

It is the responsibility of the PI or his/her authorized designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study, e.g. explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the REB. The subject shall be informed that the participation is confidential and voluntary and that the subject has the right to withdraw from the study at any time, without any consequences to his/her

future medical care, treatment or benefits to which the subject is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the ICF and to consider participation in the study. Before any study-related activities are performed, the ICF shall be personally signed and dated by the subject and the PI or his/her authorized designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries. The data will not contain any information that can be used to identify any subject.

Photographs collected during the study will be analyzed and stored in a database by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study.

All signed ICFs shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated ICF and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study.

13. FINANCING, INDEMNIFICATION AND INSURANCE

The CTA outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CSP regarding certain rights and obligations, the CTA is the prevailing document. Q-Med AB's obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The Institution/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

14. SUSPENSION OR PREMATURE TERMINATION

The Sponsor will suspend or terminate the study when so instructed by the REB or RA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons, or for business reasons.

15. PUBLICATION POLICY

The PI's, Institution's, and Q-Med AB's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

The aim is to submit the results of this study for publication in the public database ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved[3]. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among

[3] Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org).

the authors that fulfil the above-mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

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SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL

CTN: 43CASA2006

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

I, the undersigned, have read and understand the Clinical Study Protocol (CSP) specified above, and agree on the contents. The CSP, the Clinical Trial Agreement (CTA) and the additional information given in the Investigator's brochure (IB) and the study specific Instructions for Use (IFU) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study center

GALDERMA	Title **43CASA2006 CSP Sculptra cellulite**	Doc id **MA-47276**

SIGNATURES PAGE

Date	Signed by
2021-06-17 21:51	PPD
Justification	Compiled by

2021-06-18 05:51	PPD
Justification	Approved by Technical Expert

2021-06-18 09:57	PPD
Justification	Approved by Owner

2021-06-21 06:13	PPD
Justification	Approved by Technical Expert