Effective date: 2021-03-24 11:04

Effective

: 5.0

**A randomized, evaluator-blinded, no-treatment controlled, multicenter study to evaluate the effectiveness and safety of Sculptra Aesthetic for correction of cheek wrinkles**

Study products: Sculptra® Aesthetic

Clinical trial number (CTN): 43USSA1812

Sponsor: Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala, Sweden
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**Confidentiality Statement**
This investigational plan contains confidential information belonging to Q-Med AB. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and neither disclose it to any third parties (except where required by applicable law) nor use it for any other purpose than in relation to the clinical study described herein.

Effective date: 2021-03-24 11:04

Effective

: 5.0

**Investigators and Study Administrative Structure**

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| Sponsor: | Q-Med AB<br>Seminariegatan 21<br>SE-752 28 Uppsala, Sweden<br>Telephone: +46 18 474 90 00 |
| Medical expert: | PPD |
| Global Head of Clinical Development: | PPD |
| Sponsor's Clinical Project Manager : | PPD |
| Sponsor's Statistician: | PPD |

Further details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a Clinical Investigational Plan (CIP) amendment.

Effective date: 2021-03-24 11:04

Effective

: 5.0

**Sponsor Signatures**

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

**Head of Clinical Scientists and Clinical Standards, Q-Med AB**

PPD

**Medical Expert, Q-Med AB**

PPD

**Statistician, Q-Med AB**

PPD

Effective date: 2021-03-24 11:04

Effective

: 5.0

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**Synopsis**

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| **Title of study:** | A randomized, evaluator-blinded, no-treatment controlled, multi-center study to evaluate the effectiveness and safety of Sculptra Aesthetic for correction of cheek wrinkles. |
| **Study population:** | Women or men over 21 years of age with the intent to undergo correction of cheek wrinkles. |
| **Countries involved, number of sites/country:** | United States, up to 13 sites |
| **Number of subjects:** | 150 subjects |
| **Study Design** | This is a prospective, randomized, evaluator-blinded, no-treatment controlled study. Approximately 150 subjects will be randomized (2:1) to either treatment with Sculptra Aesthetic (Treatment Group) or no treatment (Control Group), 100 subjects to treatment with Sculptra Aesthetic and 50 subjects to no treatment. At least 15 subjects will be Fitzpatrick skin type (FST) IV, and a least 14 will be FST V-VI.<br><br>Effectiveness and safety data will be collected for up to 12 months following the initial treatment.<br><br>All subjects will be offered to participate in an open extension study beginning after successful completion of this study. Subjects in the no-treatment control group will be offered treatment with Sculptra Aesthetic in the extension study. Subjects in the treatment group will continue to be followed for additional data collection as described in the extension study protocol. |
| **Primary Effectiveness Objective and Endpoint:** | To evaluate the effectiveness of Sculptra Aesthetic versus a no-treatment control in the correction of cheek wrinkles.<br>CCI [redacted] |
| **Secondary Effectiveness Objective(s) and Endpoint(s):** | To evaluate the effectiveness of Sculptra Aesthetic versus a no-treatment control in the correction of cheek wrinkles.<br><br>Endpoints:<br>CCI [redacted] |

Effective date: 2021-03-24 11:04

Effective

Version: 5.0

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| | 3. Improvement rate based on the Independent Photographic Reviewer's assessment using random pairings of baseline and month 12 photographs.<br><br>*<u>Treatment group:</u> An improved subject is defined as a subject for whom the Independent Photographic Reviewer correctly identified the month 12 photograph in the pair of pre- and post-treatment photographs at rest.*<br><br>*<u>Control group:</u> An improved subject is defined as a subject for whom the Independent Photographic Reviewer identified any of the photographs in the pair as post-treatment at rest.*<br><br>4. Percentage of subjects having at least "Improved" according to the Global Aesthetic Improvement Scale (GAIS) on both sides of the face combined, as assessed live by the subject and the Treating Investigator separately, at all visits following the Baseline visit for the Treatment Group and at month 7, 9 and 12 for the Control Group.<br><br>5. Percentage of subjects responding in each response category for each question in the subject satisfaction questionnaire at all visits following the Baseline visit for the Treatment Group.<br><br>6. Change from baseline in subject satisfaction using the Satisfaction with Cheeks FACE-Q questionnaire with Outcome Rasch transformed total scores as well as proportion of subjects in each response category for each of the individual questions at all visits following the Baseline visit for the Treatment Group and at month 7, 9 and 12 for the Control Group.<br><br>7. Time to return to social engagement after treatment using subject diaries for 28 days after each treatment. |
| CCI [redacted] | CCI [redacted] |
| **Safety Objectives and Endpoints:** | To evaluate the safety of Sculptra Aesthetic in the correction of cheek wrinkles.<br><br>Endpoints:<br><br>1. Incidence, intensity, time to onset and duration of adverse events collected throughout the study period.<br><br>2. Incidence, intensity and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days from each treatment. |

Effective date: 2021-03-24 11:04

Effective

: 5.0

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| | 3. Safety assessment by a qualified staff member at all visits according to predefined methods at baseline and at all follow-up visits for the Treatment Group and the Control Group:<br>□ Cheek firmness, symmetry and function<br>□ Device palpability (baseline assessment excluded)<br>□ Mass formation<br>□ Cheek sensation<br>□ Visual Function Assessments |
| **Clinical Study Duration:** | The planned clinical study duration (from First Subject First Visit (FSFV) to Last Subject Last visit (LSLV)) is approximately 17 months<br>The planned duration of recruitment (from FSFV to Last Subject First Visit (LSFV)) is approximately 6 months.<br>*One month is defined as four weeks in the study.* |
| **Duration of Subject Participation:** | Clinical study participation for each subject may be up to approximately 13.5 months from screening to final follow-up visit. |
| **Inclusion criteria:** | The subjects must meet the following criteria to be eligible for the study:<br>1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent.<br>2. Women or men over 21 years of age.<br>3. Intent to undergo correction of cheek wrinkles on both sides of the face and a Galderma [redacted] score of Moderate or Severe on EACH side of the face, as assessed on Day 1 by the Blinded Evaluator as well as the Treating Investigator, but agreement on score is not required. The [redacted] score for each side of the face does not need to be equal; however, the difference between the two sides should be limited to 1 grade.<br>4. Female subjects must be postmenopausal for at least 1 year; if the subject is a female of childbearing potential, she 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: |

Effective date: 2021-03-24 11:04

Effective

: 5.0

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| | 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<br><br>b. Hormonal or copper intrauterine device (IUD) inserted at least 28 days prior to the Baseline visit<br><br>c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository<br><br>d. Bilateral tubal ligation prior to the Baseline visit<br><br>e. Vasectomized partner (in monogamous relationships) for at least 3 months prior to the Baseline visit<br><br>f. Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form of birth control). |
| **Exclusion criteria:** | The presence of any of the following exclusion criteria will exclude a subject from enrollment in the study:<br>1. Known/previous allergy or hypersensitivity to any of the Sculptra Aesthetic constituents.<br>2. Known/previous allergy or hypersensitivity to lidocaine and other local anesthetics, e.g. amide-type anesthetics or topical anesthetics agents.<br>3. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions.<br>4. Previous tissue augmenting therapy, contouring or revitalization treatment in the face, except the lips, with any of the following filler prior to Baseline visit:<br>a. Collagen, Hyaluronic Acid – 12 months<br>b. Calcium Hydroxyapatite (CaHa), Poly L- Lactic Acid (PLLA) or permanent (non-biodegradable)- Prohibited<br>5. Previous treatment/procedure in the face in the previous 6 months that, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or |

Effective date: 2021-03-24 11:04

Effective

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| | exposes the study subject to undue risk by study participation, e.g.:<br><br>a. Resurfacing (laser, photomodulation, light, radiofrequency, ultrasound, chemical peel, dermabrasion, or other ablative/non- ablative procedures)<br><br>b. Needling or mesotherapy<br><br>c. Cryotherapy<br><br>d. Neurotoxin injections<br><br>e. Lipolytic injections (e.g. dexycholic acid or other lipolytic substances)<br><br>f. Dental work, such as root canals or sinus surgery<br><br>or is planning to undergo any of these procedures affecting the treatment area, at any time during the study.<br><br>6. Presence of any disease or lesions near or on the area to be treated, e.g.<br><br>a. Inflammation, active or chronic infection in or near the treatment area<br><br>b. Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes zoster/ herpes simplex and acanthosis<br><br>c. Scars or deformities<br><br>d. Cancer or precancerous condition (e.g. actinic keratosis or actinic cheilitis)<br><br>7. History of severe elastosis and/or excessive sun exposure that in the opinion of the Treating Investigator, could affect the safety and effectiveness outcome of the study.<br><br>8. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation (e.g. aspirin or other NSAIDs), Omega-3, or vitamin E within 14 days before treatment. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.<br><br>9. Treatment with chemotherapy, immunosuppressive agents (inhaled corticosteroids allowed), immunomodulatory therapy (e.g. monoclonal antibodies or antiviral treatment for HIV or Hepatitis C) within 6 months before treatment. |

Effective date: 2021-03-24 11:04

Effective

. . 5.0

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| | 10. Use of topical corticosteroids or topical prescription retinoids (in the treatment area) within 1 month of the Baseline visit or systemic retinoid treatment within 6 months of the Baseline visit.<br><br>11. Previous surgery including plastic surgery, lifting threads, tissue grafting or tissue augmentation with permanent implants, silicone or fat, or tattoo, affecting the treatment area.<br><br>12. History of cancer or previous radiation near or on the area to be treated.<br><br>13. HIV positive or active hepatitis.<br><br>14. History of or active collagen diseases such as systemic lupus erythematosus, rheumatic arthritis, polymyositis, dermatomyositis, skin or systemic scleroderma.<br><br>15. Tendency to form keloids, hypertrophic scars, or any other healing disorder.<br><br>16. Presence of piercing, beard or facial hair that could interfere with study evaluation.<br><br>17. Abnormal result on functionality, sensation, symmetry, mass formation or palpation assessments in the treatment area.<br><br>18. Abnormal result on extraocular muscle function test or confrontational visual field assessment.<br><br>19. Presence of a dental, oral, or facial condition which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment, e.g. has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities.<br><br>20. 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.<br><br>21. 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 that may interfere with the outcome of the study).<br><br>22. Other condition preventing the subject from entering the study in the Treating Investigator's opinion, e.g. subjects failing baseline safety assessments, 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. |

Effective date: 2021-03-24 11:04

Effective

: 5.0

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| | 23. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), or employees and close relatives of employees at the Sponsor company.<br><br>24. Participation in any interventional clinical study within 30 days of screening. |
| **Investigational product:** | Sculptra Aesthetic is a sterile, freeze-dried, injectable poly-L-lactic acid (PLLA) with excipients. Each vial of dry powder contains:<br>150 mg PLLA<br>90 mg sodium carboxymethylcellulose<br>127.5 mg of non-pyrogenic mannitol<br>The contents in one vial will be reconstituted prior to use by the addition of 8 mL of sterile water for injection (SWFI) at the investigational site.<br>Immediately prior to injection, 1 mL of 2% lidocaine will be added to make a total volume of 9 mL. |
| **Reference therapy:** | No treatment. |
| **Treatment regimen and location of treated area:** | Each subject in the treatment group will receive a single regimen of Sculptra Aesthetic. A single regimen consists of up to four (4) injection sessions with 1-month (+5 week) intervals. Sculptra Aesthetic will be administered using a 25G (gauge) needle using the bolus, fanning, cross-hatching, linear threading injection technique or other techniques at the discretion of the Treating Investigator. Injections will be made subdermally, i.e. in the subcutaneous and supraperiosteal region. A maximum of 18 mL (2 vials) of Sculptra Aesthetic will be administered per treatment session with a maximum of 9 mL (1 vial) per cheek, evenly distributed within the treatment area.<br>The treatment area is within the following borders:<br>□ Superior border - from top of tragus to top of alar crease<br>□ Medial border - from top of the alar crease, along the nasolabial fold (NLF) to the inferior border of the mandibular ramus<br>□ Inferior border - from medial border at mandibular ramus to angle of mandibular ramus<br>□ Lateral border - from angle of mandibular ramus to top of tragus |
| **Effectiveness Assessment(s):** | 1. Cheek wrinkles by Blinded Evaluator using [redacted]<br>2. Cheek wrinkles by Treating Investigator using [redacted]<br>3. Global aesthetic improvement by Treating Investigator and Subject using GAIS. |

Effective date: 2021-03-24 11:04

Effective

. . 5.0

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| | 4. Improvement in cheek wrinkles by Central Independent Photographic Reviewer.<br>5. Subject's satisfaction after treatment using a Subject Satisfaction Questionnaire.<br>6. Subject's satisfaction using FACE-Q "Satisfaction with Cheeks".<br>7. Lifting effect of cheek using 3D imaging<br>8. Return to social engagement after treatment using subject diaries.<br>9. Dermal thickness using Ultrasound.<br>10. Radiance, skin tightness and jawline contour assessed live by Treating Investigator. |
| **Safety Assessment(s):** | 1. Adverse Event reporting: AEs will be obtained from signs and symptoms reported by the subjects or detected during each examination.<br>2. A subject diary will be dispensed to all subjects in the treatment group for daily completion for 28 days beginning on injection day for each treatment with direct questioning for pain, tenderness, redness, bruising, swelling, itching, lumps/bumps and "other". Subjects will be specifically asked to record any of the following symptoms in the other section; changes in vision (i.e. loss of vision, blurriness, double vision, pain in or around your eye, blindness, blind spots, problems moving your eyes), skin changing color around the eyelids, crusty or scabby skin around the eyelids, pain, headache, fever, dizziness, confusion, weakness or numbness in the arms or legs, changes to consciousness or alertness, difficulty speaking/ speech impairment and face droop.<br>3. Functionality, sensation, firmness, symmetry, mass formation and palpation tests according to pre-defined methods, at baseline and at each on-site follow-up visit.<br>4. Device deficiencies will be assessed at treatment visits.<br>5. Visual function assessments will be performed before and 30 minutes following injection and at all scheduled follow up visits. |
| **Statistical Methods:** | <u>Principles for the analysis</u><br>CCI [redacted]<br>For a significant result, the two-sided p-value of the comparison of responder rates between the treated and untreated subjects at month 12 using the Fisher's exact test needs to be smaller than 0.05. The estimates of the responder rate in each treatment group will be presented along with the difference in responder rates. Corresponding confidence intervals for both responder rates and difference in responder rates and p-value for difference in responder rates will also be presented. |

Effective date: 2021-03-24 11:04

Effective

: 5.0

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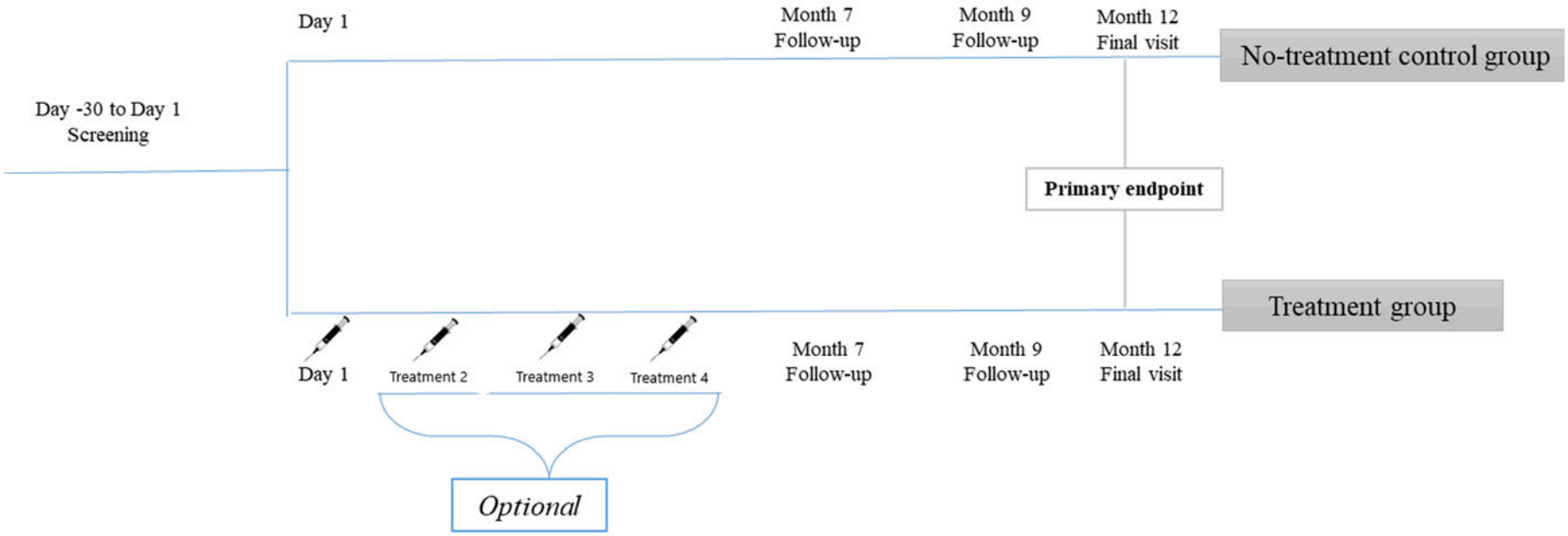
| | The secondary endpoints of [redacted]) as assessed live by the Blinded Evaluator will be analyzed in the same way. Results for the right and left side of the face separately as well as combined will be presented.<br><br>All other secondary effectiveness endpoints will be analyzed descriptively, including 95% confidence intervals.<br><br>All safety endpoints will be analyzed descriptively.<br><br>Sample size<br><br>A total sample size of approximately 150 subjects will be included in this study; approximately 100 will be randomized to treatment with Sculptra Aesthetic and approximately 50 will be randomized to no treatment. Sample size justifications are given below.<br><br>Previous data<br><br>Since the primary endpoint will be based on a new scale, no existing data is available.<br><br>Assumptions: Based on what is seen in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a responder rate of at least 70% in the Sculptra Aesthetic treatment group at month 12. For the no treatment control group, responder rates up to almost 30% have been observed in data on file. Based on this, it is assumed that the response rate will be maximum 35% in the no-treatment control group at month 12.<br><br>Sample size calculation<br><br>For the responder rate in [redacted], testing the difference using a two-sided test at the 5% significance level will have approximately 90% power to demonstrate difference between a responder rate of 70% in the Sculptra Aesthetic group, and a responder rate of 35% in the no treatment control group when the sample sizes are 84 and 42, respectively. Accounting for 15% drop-outs, approximately 150 subjects need to be randomized in a 2:1 ratio. |

**Study flow chart**



Effective date: 2021-03-24 11:04

Effective

: 5.0

## Abbreviations and Definitions of Terms

| | |
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| AE | Adverse event |
| AESI | Adverse Event of Special Interest |
| Blinded evaluator | An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject. |
| CFR | Code of Federal Regulations |
| CIP | Clinical Investigational Plan |
| CMC | Sodium carboxymethylcellulose |
| CRO | Contract research organization |
| CTA | Clinical trial agreement |
| CTN | Clinical trial number |
| CV | Curriculum vitae |
| Device deficiency | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labelling) |
| DMP | Data management plan |
| eCRF | Electronic case report form |
| FSFV | First Subject First Visit, i.e. first subject who signs the informed consent form |
| FST | Fitzpatrick skin type |
| G | Gauge |
| CCI [redacted] | |
| GCP | Good clinical practice |
| CCI [redacted] | |
| GDPR | General Data Protection Regulation |
| HCl | Hydrochloride |
| ICH | International Conference on Harmonization |
| IFU | Instructions for use |
| Investigational product | Medical device being assessed for safety or performance in a study. “Investigational product” is the same as “study device”, “investigational device”, or ”investigational medical device”. |
| Institution | Any public or private entity or agency or medical or dental facility where a clinical study is conducted. |
| Investigator | The Principal Investigator (PI) or other qualified person, i.e. sub-Investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log |
| Investigator file | Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator. |

Effective date: 2021-03-24 11:04
Effective
: 5.0

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| IRB | Institutional review board |
| ISO | International Organization for Standardization |
| LSFV | Last Subject First Visit |
| LSLV | Last Subject Last Visit |
| MedDRA | Medical dictionary for regulatory activities |
| NLF | Nasolabial fold |
| NSAID | Non-steroidal anti-inflammatory drugs |
| PI | Principal Investigator; qualified person responsible for conducting the study at a study site |
| PP | Per protocol |
| RA | Regulatory authority |
| ROPI | Report of Prior Investigations |
| SAE | Serious adverse event |
| Sponsor file | Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor. |
| Study files | The Investigator file and the Sponsor file |
| Study product | The investigational product |
| Study site | Institution or site where the study is carried out |
| SWFI | Sterile water for injection |
| USP | United States Pharmacopeia |
| WHO | World Health Organization |

Effective date: 2021-03-24 11:04

Effective

. . 5.0

# Table of Contents

**INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE** **2**
**SYNOPSIS** **4**
**STUDY FLOW CHART** **13**
**ABBREVIATIONS AND DEFINITIONS OF TERMS** **14**
**TABLE OF CONTENTS** **16**
**LIST OF TABLES** **20**
**1 ETHICAL CONSIDERATIONS** **21**
1.1 Statement of ethical compliance 21
1.2 Application to institutional review board and regulatory authorities 21
**2 BACKGROUND INFORMATION** **21**
2.1 Indication and population description 21
2.2 Study Product Profile 22
*2.2.1 Investigational product description* *22*
2.3 Study rationale and justification for design 22
2.4 Risks and benefits 23
**3 OBJECTIVE(S) AND ENDPOINT(S)** **24**
3.1 Effectiveness objective and endpoints 24
*3.1.1 Primary effectiveness endpoint* *24*
*3.1.2 Secondary effectiveness endpoints* *24*
CCI [redacted] [redacted]
3.2 Safety objective and endpoints 25
**4 DESIGN OF THE STUDY** **25**
4.1 General outline 25
4.2 Number of subjects 26
4.3 Duration of subject participation 26
4.4 Randomization and blinding 26
*4.4.1 Randomization* *26*
*4.4.2 Blinding* *26*
*4.4.3 Emergency unblinding* *27*
4.5 Medical history 27
4.6 Prior and concomitant therapies 27
*4.6.1 Definition* *27*
*4.6.2 Categories* *27*
*4.6.3 Recording* *27*
*4.6.4 Authorized concomitant therapies* *27*

Effective date: 2021-03-24 11:04

*4.6.5 Prohibited concomitant therapies* 27
4.7 Visits 29
*4.7.1 Visit 1, Screening (Day 30 to Day 1)* ***all subjects*** 31
*4.7.2 Visit 2, Baseline and First Treatment (Day 1)* ***all subjects*** 31
*4.7.3 Visit 2a, Follow up 72 hour telephone call (±24 hours)* ***for treatment group only*** 32
*4.7.4 Visit 3, Treatment 2 (1 month (+5 weeks) after Treatment 1)* ***for treatment group only*** 32
*4.7.5 Visit 3a, Follow up 72 hour telephone call (±24 hours)* ***for treatment group only, subjects who received a second treatment.*** 33
*4.7.6 Visit 4, Treatment 3 (1 month (+5 weeks) after Treatment 2)* ***for treatment group only*** 33
*4.7.7 Visit 4a, Follow up 72 hour telephone call (±24 hours)* ***for treatment group only, subjects who received a third treatment.*** 34
*4.7.8 Visit 5, Treatment 4 (1 month (+5 weeks) after Treatment 3)* ***for treatment group only*** 35
*4.7.9 Visit 5a, Follow up 72 hour telephone call (±24 hours)* ***for treatment group only, subjects who received a fourth treatment.*** 36
*4.7.10 Visits 6, 7 and 8, Follow up month 7 (+ 2weeks), 9 (±2 weeks), 12 (±2 weeks)* ***all subjects*** 36
*4.7.11 Unscheduled Visits* 36
**5 SUBJECTS** **37**
5.1 Subject information and informed consent 37
5.2 Inclusion criteria 37
5.3 Exclusion criteria 38
5.4 Subject number 40
5.5 Withdrawal of subjects 40
**6 STUDY PRODUCTS** **41**
6.1 Investigational product 41
6.2 Reference product 42
6.3 Additional products and materials 42
6.4 Packaging, labelling, and storage 43
*6.4.1 Investigational product* 43
*6.4.2 Reference product* 43
*6.4.3 Product accountability* 43
6.5 Treatment 44
*6.5.1 Treatment procedure* 44
*6.5.2 Treatment regimen (dose and interval)* 45
*6.5.3 Post treatment care* 45
*6.5.4 Post trial provisions* 45
*6.5.5 Treatment compliance* 46
**7 EFFECTIVENESS ASSESSMENTS** **46**
7.1 [redacted] 47
7.2 [redacted] 48

Effective . . 5.0

Effective date: 2021-03-24 11:04


7.3 Global Aesthetic Improvement Scale (GAIS) 49
7.4 Subject Satisfaction Questionnaire 50
7.5 FACE-Q “Satisfaction with Cheeks” 51
7.6 Lifting effect of cheek using 3D imaging 51
7.7 Return to social engagement 51
7.8 Ultrasound 51
7.9 Radiance, skin tightness and jawline contour assessment 52
7.10 Photography 52
7.11 Improvement in cheek wrinkles by Central Independent Reviewer 52
**8 SAFETY ASSESSMENTS 52**
8.1 Assessment of AEs by direct questioning to subject and evaluation of subject 53
8.2 Subject Diary Data 53
8.3 Laboratory assessments 53
8.4 Visual Function assessments 53
*8.4.1 Snellen visual acuity test 54*
*8.4.2 Extraocular muscle function test 54*
*8.4.3 Confrontation visual field 54*
8.5 Other safety assessments 54
*8.5.1 Cheek sensation 54*
*8.5.2 Cheek firmness, symmetry and function 55*
*8.5.3 Mass formation 55*
*8.5.4 Device palpability only for subjects in the treatment group 55*
8.6 Adverse events 55
*8.6.1 Definition of an adverse event 55*
*8.6.2 Definition of a serious adverse event 55*
*8.6.3 Definition of unanticipated adverse effect 56*
*8.6.4 Recording instructions 56*
*8.6.5 Reporting of adverse events 57*
*8.6.6 Reporting of adverse events of special interest (AESIs) 57*
*8.6.7 Reporting of serious adverse events 58*
*8.6.8 Stopping Rule 59*
*8.6.9 Reporting of unanticipated adverse device effects 59*
*8.6.10 Follow up of unresolved events ongoing at termination of the study 59*
*8.6.11 Reporting and follow up of events occurring after subject termination of the study 59*
*8.6.12 Pregnancy 60*
*8.6.13 Anticipated adverse events 60*
8.7 Device deficiencies 60
*8.7.1 Definition of a device deficiency 60*


Effective

. . 5.0

Effective date: 2021-03-24 11:04

*8.7.2 Recording instructions 60*
*8.7.3 Reporting of device deficiencies 60*
**9 DATA HANDLING AND MANAGEMENT 61**
9.1 Data management 61
9.2 Electronic case report forms 61
*9.2.1 Data entry 62*
*9.2.2 The query process 62*
*9.2.3 User identification 62*
*9.2.4 Audit trail 62*
9.3 Source documents 62
9.4 Record keeping and access to source data 63
9.5 Document and data retention 63
**10 STATISTICAL METHODS 63**
10.1 General 63
10.2 Analysis populations 64
10.3 Demographics, baseline assessments, and subject characteristics 64
10.4 Effectiveness analysis 64
*10.4.1 Primary effectiveness analysis 64*
*10.4.2 Secondary effectiveness analysis 65*
10.5 Safety analysis 65
10.6 Handling of missing data 65
10.7 Data monitoring committee 66
10.8 Withdrawals and deviations 66
10.9 Sample size 66
*10.9.1 Previous data 66*
*10.9.2 Assumptions 66*
*10.9.3 Sample size calculations 66*
**11 PROTECTION OF PERSONAL DATA 66**
**12 QUALITY CONTROL AND QUALITY ASSURANCE 67**
12.1 Quality control 67
12.2 Quality assurance 67
12.3 Changes to the clinical investigational plan 67
**13 FINANCING, INDEMNIFICATION, AND INSURANCE 68**
**14 PUBLICATION POLICY 68**
**15 SUSPENSION OR PREMATURE TERMINATION 68**
**16 REFERENCES 69**

Effective

: 5.0

Effective date: 2021-03-24 11:04
Effective
: 5.0

## List of Tables

Table 1 Schedule of events for Treatment Group ..... 29
Table 2 Schedule of events for Control Group/Untreated subjects ..... 30
Table 3 Fitzpatrick Skin Types (FST) ..... 31
Table 4 Grading for subject diary data ..... 53

## List of Appendices

Appendix 1 ..... 70

Effective date: 2021-03-24 11:04

Effective

: 5.0

# 1 Ethical Considerations

## 1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the clinical investigational plan (CIP), good clinical practice (GCP), and applicable regional or national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study) insofar as such revisions are consistent with US treaty obligations and in accordance with US law (1).

The study shall follow the international standard for clinical study of medical devices for human subjects, International Organization for Standardization (ISO) 14155 2011 as applicable for US regulations and the International Conference on Harmonization (ICH) guideline for GCP (E6) as applicable for medical device.

## 1.2 Application to institutional review board and regulatory authorities

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

The study requires application for approval from the US Food and Drug Administration (FDA). 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.

# 2 Background Information

## 2.1 Indication and population description

Sculptra Aesthetic is indicated for use in immune competent people as single regimen for correction of shallow to deep nasolabial fold (NLF) contour deficiencies and other facial wrinkles. (2)

This is a 12-month study to assess the effectiveness and safety of Sculptra Aesthetic for the correction of cheek wrinkles. Approximately 150 subjects, out of which at least 15 will be Fitzpatrick skin type (FST) IV, and 14 will be FST V-VI, will be enrolled. Subjects fulfilling all inclusion criteria but no exclusion criteria as outlined here in the protocol will be randomized in a 2:1 ratio to either treatment with Sculptra Aesthetic (Treatment Group) or no treatment (Control Group).

After successful completion of the study, subjects will be offered to participate in an open extension study. Subjects in the no-treatment control group will then be offered treatment with Sculptra Aesthetic. Subjects in the treatment group will continue to be followed for additional data collection as described in the extension study protocol. The sponsor plans to submit the clinical data obtained in the initial 12-month study in support of the cheek wrinkles indication to the Sculptra Aesthetic label as a Panel-Track supplement.

Effective date: 2021-03-24 11:04

Effective

Version: 5.0

## 2.2 Study Product Profile

### 2.2.1 Investigational product description

Sculptra Aesthetic is a poly-L-lactic acid implant in the form of a suspension, which is reconstituted from a sterile dry powder by the addition of sterile water for injection. Poly-L-lactic acid (PLLA) is the main active ingredient from which the product has achieved its intended purpose. Sodium carboxymethylcellulose (CMC) acts as a suspending agent for maintaining an even distribution of PLLA particles following reconstitution. Mannitol enhances the lyophilisation process and provides the suspension with a consistency that is suitable for injection.

Each vial of dry powder contains 150 mg PLLA, 90 mg CMC and 127.5 mg non-pyrogenic mannitol – in total a vial weight of 367.5 mg and is per approved label to be reconstituted prior to use by the addition of 5 mL of SWFI to form a sterile non-pyrogenic suspension. (2) In this study, commercially available Sculptra Aesthetic labelled for the study will be used and reconstitution will be made with 8 mL of SWFI with addition of 1 mL of 2% lidocaine prior to injection. This is the same changes to the labeled reconstitution as in the ongoing Sculptra Aesthetic IDE study 43USSA1705 for the treatment of nasolabial folds. It has been recommended by experienced physicians to evaluate alternative reconstitution procedures for Sculptra Aesthetic compared to the currently approved instructions for use, primarily to enhance safety of the device by potentially reducing incidence of nodule and papule formation. (3).

Data from this clinical study will be used to support proposed modifications to the current Sculptra Aesthetic label for the correction of cheek wrinkles.

#### *2.2.1.1 Non-clinical documentation*

CCI [redacted]

#### *2.2.1.2 Clinical documentation*

Since the initial approval of Sculptra Aesthetic in 1999, multiple clinical studies have been performed. Please refer to the ROPI for a description of performed clinical studies and results with Sculptra Aesthetic relevant for correction of the cheek wrinkles and to the new reconstitution procedure.

## 2.3 Study rationale and justification for design

The purpose of this study is to investigate the safety and effectiveness of Sculptra Aesthetic for the correction of cheek wrinkles with the objective of an expanded label indication.

It has been recommended by experienced physicians to evaluate a higher reconstitution volume for Sculptra Aesthetic compared to the currently approved instructions for use, primarily to enhance safety of the device by potentially reducing incidence of nodule and papule formation. Moreover multiple treatment sessions at least 4 weeks apart is recommended by leading experts (3).

Evaluations will be performed by the Subject, the Treating Investigator, the Blinded Evaluator and the Central Independent Photographic reviewer. The intention is to improve the aesthetic appearance compared to before treatment. CCI [redacted].

Effective date: 2021-03-24 11:04

Effective

Version: 5.0

CCI

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## 2.4 Risks and benefits

Anticipated benefits for subjects treated with Sculptra Aesthetic for the correction of cheek wrinkles include restoration of a more youthful appearance, relatively long-lasting effects which would reduce the need for frequent touch-up procedures. The benefit of Sculptra Aesthetic for correction of cheek wrinkles is being evaluated in the ongoing, post-approval US clinical study (US10321). (4) Although treatment in the cheek area was secondary to treatment in the nasolabial folds in this study, the interim data results support that treatment for cheek wrinkles is effective and well tolerated.

Since the initial approval of Sculptra Aesthetic in 1999 (EU), the amount of SWFI used to reconstitute Sculptra Aesthetic has gradually increased. Based on medical literature and physician experience, practitioners have reported improved clinical outcomes with increased reconstitution volumes that are up to two times higher than the volume recommended by the manufacturer and usually in combination with anesthetic solutions, like lidocaine 2%. (3, 5) It has also been suggested, that a reduction in frequency of nodules/papules can be achieved with an increased reconstitution volume. (6, 7). Currently, the increased reconstitution volume for treatment of nasolabial folds is evaluated in the ongoing study 43USSA1705.

Risks with Sculptra Aesthetic 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 Aesthetic 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.

Assessments for visual disturbance have been implemented at baseline, all treatment and all follow-up visits with specific instructions to immediately see an ophthalmologist or retina expert should any visual disturbance event occur. Moreover, only study Investigators qualified by education and experience, and who are skilled in the use of soft tissue fillers from their clinical practice and involvement in clinical research, and with a firm knowledge of the vascular anatomy and understanding of the depth and plane of injection as well as knowledge of the signs and symptoms and management of potential complications, will be chosen in order to assure proper device implantation and management of study risk.

For intravascular complications or embolic events, the treating physician should provide prompt medical attention and follow relevant clinical practice guidelines (8) for handling these symptoms. The treating physician should also review the Intravascular Treatment Protocol 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.

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

Stopping rules for the study are included in section 8.6.8.

Effective date: 2021-03-24 11:04

Effective

. . 5.0

Given the anticipated low level of acceptable AEs in connection with the injection, the protocol required safety assessments it was determined the risk-benefit assessment for use of Sculptra Aesthetic with the investigational plan specified reconstitution and injection procedures for correction of cheek wrinkles appears to offer a clinical benefit at reasonable risk.

## 3 Objective(s) and Endpoint(s)

### 3.1 Effectiveness objective and endpoints

Effectiveness objective:

To evaluate the effectiveness of Sculptra Aesthetic versus a no-treatment control in the correction of cheek wrinkles.

#### 3.1.1 Primary effectiveness endpoint

Responder rate based on the [redacted] Scale [redacted], as assessed live by the Blinded Evaluator at month 12.

A responder is defined as a subject with at least 1 grade improvement from baseline on both cheeks concurrently.

#### 3.1.2 Secondary effectiveness endpoints

1. Responder rate based on the [redacted] Scale ([redacted], as assessed live by the Blinded Evaluator at month 7 and 9.

*A responder is defined as a subject with at least 1 grade improvement in both cheeks concurrently from baseline.*

2. Responder rate based on the [redacted] Scale [redacted], as assessed live by the Blinded Evaluator at month 7, 9 and 12.

*A responder is defined as a subject with at least 1 grade improvement in both cheeks concurrently from baseline.*

3. Improvement rate based on the Independent Photographic Reviewer's assessment using random pairings of baseline and month 12 photographs.

*Treatment group: An improved subject is defined as a subject for whom the Independent Photographic Reviewer correctly identified the month 12 photograph in the pair of pre- and post-treatment photographs at rest.*

*Control group: An improved subject is defined as a subject for whom the Independent Photographic Reviewer identified any of the photographs in the pair as post-treatment at rest.*

4. Percentage of subjects having at least "Improved" according to the Global Aesthetic Improvement Scale (GAIS) on both sides of the face combined, as assessed live by the subject and the Treating Investigator separately, at all visits following the Baseline visit for the Treatment Group and at month 7, 9 and 12 for the Control Group.

5. Percentage of subjects responding in each response category for each question in the subject satisfaction questionnaire at all visits following the Baseline visit for the Treatment Group

6. Change from baseline in subject satisfaction using the Satisfaction with Cheeks FACE-Q questionnaire with Outcome Rasch transformed total scores as well as proportion of subjects in each response category for each of the individual questions at all visits following the Baseline visit for the Treatment Group and at month 7, 9 and 12 for the Control Group.

Effective date: 2021-03-24 11:04

7. Time to return to social engagement after treatment using subject diaries for 28 days after each treatment.

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### 3.2 Safety objective and endpoints

Safety objective:
The objective is to evaluate the safety of Sculptra Aesthetic in the correction of cheek wrinkles.

Safety endpoints:

- Incidence, intensity, time to onset and duration of adverse events collected throughout the study period.
- Incidence, intensity and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days from each treatment.
- Safety assessment by a qualified staff member at all visits according to predefined methods at baseline and at all follow-up visits for the Treatment Group and the Control Group:
    - Cheek firmness, symmetry and function (*smiling and chewing*)
    - Device palpability (baseline assessment excluded)
    - Mass formation
    - Cheek sensation
    - Visual Function Assessments

## 4 Design of the Study

### 4.1 General outline

This is a prospective, randomized, evaluator-blinded, no-treatment controlled study to assess the effectiveness and safety of treatment with Sculptra Aesthetic for correction of cheek wrinkles. All subjects in the Treatment Group and in the Control Group will be followed for 12 months after baseline.

Approximately 150 subjects with intent to undergo correction of cheek wrinkles with a CCI [redacted] on each side of the face will be randomized (2:1) to either treatment with Sculptra Aesthetic (Treatment Group) or no treatment (Control Group), 100 subjects to treatment with Sculptra Aesthetic and 50 subjects to no treatment. At least 15 subjects will be Fitzpatrick skin type (FST) IV, and at least 14 will be FST V-VI.

Effective . . 5.0

Effective date: 2021-03-24 11:04

Investigator blinding will be accomplished by using a Treating Investigator to administer the treatments and a Blinded Evaluator, to whom randomization and treatment are concealed, to conduct the blinded assessments. Safety assessments will be performed by non-blinded personnel.

Eligible subjects will perform a screening visit and baseline visit, these visits may be combined if appropriate. All subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1, the procedure is outlined in section 6. Sufficient amount of product, as determined by the Treating Investigator, should be injected to achieve optimal correction, which is defined as at least a one grade improvement on the [redacted] Scale [redacted] At Rest and best correction that could be achieved as agreed upon by the Treating Investigator and the subject. Three additional treatment sessions may be performed if needed to achieve optimal correction, as determined by the Treating Investigator and subject. Treatment will stop when optimal correction has been achieved and subsequent visits will be follow-up visits. All subjects in both the treatment and the control group will return to the clinic at month 7, 9 and 12. The Schedule of Events is outlined in Tables 1 & 2.

### 4.2 Number of subjects

Approximately 150 subjects will be enrolled. The duration of the enrollment period is expected to be three months.

### 4.3 Duration of subject participation

The total duration of the study is expected to be 17 months. A subject will be involved in the study for up to 13.5 months.

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

End of study is when enrollment has reached the target number of subjects and all subjects have completed the last study visit.

### 4.4 Randomization and blinding

#### 4.4.1 Randomization

Approximately 150 subjects will be randomized (2:1) to either treatment with Sculptra Aesthetic (Treatment Group) or no treatment (Control Group). At least 15 subjects will be Fitzpatrick skin type (FST) IV, and a least 14 subjects will be FST V-VI. Before starting the study, a randomization list will be prepared under the supervision of a designated statistician from the Sponsor. The randomization will be stratified by FST group (FST I-III, FST IV, and FST V-VI). Subjects in the FST I-III stratum will be further stratified by center; subjects in the FST IV and FST V-VI strata will not be further stratified by center due to the small sample size in these groups, randomization numbers will be allocated in ascending sequential order to each subject. Randomization will be performed using an Interactive Response System by assigning each subject to treatment group or control group according to the randomization list.

#### 4.4.2 Blinding

Blinding will be accomplished by using a Treating Investigator to administer the treatments and a Blinded Evaluator, to whom randomization and treatment are concealed, to conduct the blinded assessments. The Treating Investigator will not be blinded. The Blinded Evaluator is not allowed to discuss treatments with the Treating Investigator or subjects. No study related documents that contain information regarding the treatment of subjects should be available to the Blinded Evaluator. Safety assessments will be performed by non-blinded personnel who are qualified by training and experience.

Effective

: 5.0

Effective date: 2021-03-24 11:04

Effective

. . 5.0

#### 4.4.3 Emergency unblinding

Not applicable as the treating Investigator is not blinded to treatment.

### 4.5 Medical history

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

### 4.6 Prior and concomitant therapies

#### 4.6.1 Definition

Prior therapies are defined as therapies that have been used within 30 days of the Screening visit or within the timelines specified in the Inclusion/Exclusion criteria.

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

#### 4.6.2 Categories

The following three categories are to be considered for prior and concomitant therapies:

- Drugs/therapies including but not limited to prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to dental work, such as root canals or sinus surgery
- Aesthetic procedures including, Resurfacing (laser, photomodulation, light, radiofrequency, ultrasound, chemical peel, dermabrasion, or other ablative/non- ablative procedures, needling or mesotherapy, cryotherapy, neurotoxin injections, lipolytic injections (e.g. dexycholic acid or other lipolytic substances), previous tissue augmenting therapy, contouring or revitalization treatment in the face.

#### 4.6.3 Recording

Prior and concomitant therapies are to be recorded in source documents and 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, or dose modification for a chronic condition.

#### 4.6.4 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (Section 4.6.5), all therapies are authorized.

#### 4.6.5 Prohibited concomitant therapies

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

Effective date: 2021-03-24 11:04

Effective

: 5.0

- Anticoagulants or inhibitors of platelet aggregation that have the ability to prolong bleeding times (e.g. aspirin, non-steroidal anti-inflammatory drugs [NSAIDs]), 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.
- Chemotherapy, immunosuppressive agents (inhaled corticosteroids allowed) or immunomodulatory therapy (e.g. monoclonal antibodies or antiviral treatment for HIV or Hepatitis C).
- Prescribed corticosteroids or prescription retinoids for topical use in the treatment area or systemic use.
- Planned aesthetic facial plastic surgery (e.g. surgery to either the upper or lower lip, facelift, rhinoplasty, facial liposuction etc.) or cosmetic procedures (e.g. lifting threads, tissue grafting, tissue augmentation with permanent implants, silicone, or fat)
- Treatment/procedure in the face that would interfere with the study injections and/or study assessments or exposes the study subject to undue risk by study participation, e.g.:

  a. Resurfacing (laser, photomodulation, intense pulsed light (IPL), radiofrequency, ultrasound, chemical peel, dermabrasion, needling, or other ablative/non- ablative procedures)

  b. Needling or mesotherapy

  c. Cryotherapy

  d. Neurotoxin injections (glabella or forehead lines treatment allowed)

  e. Lipolytic injections (e.g. dexycholic acid or other lipolytic substances)

  f. Planned oral surgery or dental work, such as root canals or sinus surgery, tattoo or piercing in the area to be treated
- Tissue augmenting therapy, contouring or revitalization treatment in the face, except the lips;

  a. with Collagen or Hyaluronic Acid

  b. with Calcium Hydroxyapatite (CaHa), Poly L- Lactic Acid (PLLA) or permanent (non-biodegradable
- Participation in any interventional clinical study.
- 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 anti-arrhythmics, as the systemic toxic effects can be additive.

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.

## 4.7 Visits

### Table 1 Schedule of events for Treatment Group

| | Visit 1 | Visit 2 | Visit 2a | Visit 3 | Visit 3a | Visit 4 | Visit 4a | Visit 5 | Visit 5a | Visit 6 & 7 | Visit 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening[1] | Baseline/ Treatment 1[1] | Telephone Contact | Treatment 2[4] (Optional) | Telephone Contact | Treatment 3[4] (Optional) | Telephone Contact | Treatment 4[4] (Optional) | Telephone Contact | Follow-up | Final visit/Early termination |
| | *(≤ 30 days of Baseline)* | *Day 1 Baseline* | *72 hours (±24 hrs) after Treatment 1* | *1 month (+5 weeks) after Treatment 1* | *72 hours(±24 hrs) after Treatment 2* | *1 month (+5 weeks) after Treatment 2* | *72 hours (±24 hrs) after Treatment 3* | *1 month (+5 weeks) after Treatment 3* | *72 hours (±24 hrs) after Treatment 4* | *Month 7 ( +2 weeks) Month 9 (+2 weeks ) after Baseline* | *Month 12 ( +2 weeks) after Baseline* |
| Informed consent | X | | | | | | | | | | |
| Inclusion/Exclusion criteria | X | X[3] | | X[3] | | X[3] | | X[3] | | | |
| Demographics incl height and weight | X | X[9] | | | | | | | | X[9] | X[9] |
| Medical history | X | X[3] | | | | | | | | | |
| Previous therapies | X | | | | | | | | | | |
| Concomitant therapies | X | X | X | X | X | X | X | X | X | X | X |
| Urine pregnancy test[2] | X | X[3] | | X[3] | | X[3] | | X[3] | | | |
| Randomization | | X[3] | | | | | | | | | |
| Photography (2D and 3D) | | X[3] | | X | | X | | X | | X | X |
| Sculptra Aesthetic administration | | X | | X[4] | | X[4] | | X[4] | | | |
| Adverse events assessment | | X | X | X | X | X | X | X | X | X | X |
| Safety assessments[8] | X | X | | X | | X | | X | | X | X |
| Visual Function assessments[10] | X | X[3,7] | | X[3,6,7] | | X[3,6,7] | | X[3,6,7] | | X | X |
| Device deficiencies | | X | | X[6] | | X[6] | | X[6] | | | |
| Dispense subject diary | | X | | X[6] | | X[6] | | X[6] | | | |
| Collect subject diary | | | | X[3] | | X[3,5] | | X[3,5] | | X[5] | |
| Ultrasound (at selected sites) | | X[3] | | | | | | | | X | X |
| **Treating Investigator Assessments** | | | | | | | | | | | |
| GAIS | | | | X[3] | | X[3] | | X[3] | | X | X |
| Radiance, skin tightness and jawline contour | | | | | | | | | | X | X |
| [redacted] | X[3] | X[3] | | X[3] | | X[3] | | X[3] | | | |
| **Blinded Evaluator Assessments** | | | | | | | | | | | |
| [redacted] | X[3] | X[3] | | | | | | | | X | X |
| **Subject Assessments** | | | | | | | | | | | |
| GAIS | | | | X[3] | | X[3] | | X[3] | | X | X |
| Subject satisfaction questionnaire | | | | X[3] | | X[3] | | X[3] | | X | X |
| FACE-Q | | X[3] | | X[3] | | X[3] | | X[3] | | X | X |

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. *If applicable (i.e. if treatment was performed at the previous visit)*
6. *If applicable (i.e. if treatment is performed at this visit)*
7. *30 minutes post-treatment*
8. *Safety assessments include; Cheek firmness, symmetry and function, Device palpability (baseline assessment excluded), Mass formation, Cheek sensation*
9. *Weight only*
10. *Visual Function assessments include: Snellen visual acuity test, Extraocular muscle function test, Confrontation visual field*

***Abbreviations: GAIS (Global Aesthetic Improvement Scale), C[redacted], ET (Early Termination)***

***Note: One month is defined as four weeks in the study.***

**Table 2 Schedule of events for Control Group/Untreated subjects**

| | Visit 1 | Visit 2 | Visit 3 & 4 | Visit 5 |
|---|---|---|---|---|
| | **Screening**[1] | **Baseline** | **Follow-up** | **Final visit/Early termination** |
| | *(≤ 30 days of Baseline)* | *Day 1 Baseline* | *Month 7( +2 weeks) Month 9 (±2 weeks) after Baseline* | *Month 12 ( ±2 weeks) after Baseline* |
| Informed consent | X | | | |
| Inclusion/Exclusion criteria | X | X | | |
| Demographics, incl height and weight | X | X[4] | X[4] | X[4] |
| Medical history | X | X | | |
| Previous therapies | X | | | |
| Concomitant therapies | X | X | X | X |
| Urine pregnancy test[2] | X | X | | |
| Randomization | | X | | |
| Photography (2D and 3D) | | X | X | X |
| Adverse events assessment | | X | X | X |
| Safety assessments[3] | X | X | X | X |
| Visual Function Assessments[5] | X | X | X | X |
| Ultrasound (at selected sites) | | X | X | X |
| **Treating Investigator Assessments** | | | | |
| GAIS | | | X | X |
| [redacted] | X | X | | |
| Radiance, skin tightness and jawline contour | | | X | X |
| **Blinded Evaluator Assessments** | | | | |
| [redacted] | X | X | X | X |
| **Subject Assessments** | | | | |
| GAIS | | | X | X |
| FACE Q | | X | X | X |

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. *Safety assessments include; Cheek firmness, symmetry and function,), Mass formation, Cheek sensation*
4. *Weight only.*
5. *Visual Function assessments include: Snellen visual acuity test, Extraocular muscle function test, Confrontation visual field*

***Abbreviations: GAIS (Global Aesthetic Improvement Scale), [redacted] ET (Early Termination)***

***Note: One month is defined as four weeks in the study.***

Effective date: 2021-03-24 11:04

Effective

- - 5.0

#### 4.7.1 Visit 1, Screening (Day -30 to Day 1) - ***all subjects***

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.
- Record the subject's medical history (including any prior dermatological procedures or implants).
- Record the subject's prior and concomitant therapies.
- Obtain demographic and baseline 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. (9, 10). For determination of the FST, see Table 3 below.
    - Height may be self-reported, weight is to be measured at clinic.
- Assess [redacted]): Treating Investigator and Blinded Evaluator
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation
- Perform Visual Function Assessments (Snellen visual acuity, Extraocular muscle function and Confrontation visual field tests) for all subjects (prior to treatment for subjects in the treatment group).
- For all females of childbearing potential, perform Urine Pregnancy Test (UPT) 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.

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#### 4.7.2 Visit 2, Baseline and First Treatment (Day 1) - ***all subjects***

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
- Obtain weight measured at clinic.

Effective date: 2021-03-24 11:04

Effective

. . 5.0

- Assess [redacted]) Treating Investigator and Blinder Evaluator
- 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:

- Randomize the subject.
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation
- Perform Visual Function Assessments (Snellen visual acuity, Extraocular muscle function and Confrontation visual field tests) for all subjects (prior to treatment for subjects in the treatment group).
- Obtain pre-treatment Photography (2D and 3D).
- Instruct the subject to complete Face-Q assessment (pre-treatment)
- Perform pre-treatment ultrasound (at selected sites).
- Instruct the subject to complete the FACE-Q questionnaire.
- Sculptra Aesthetic administration (treatment group only).
- Evaluate for device deficiencies (treatment group only).
- Dispense diary and instruct subject on daily Diary completion. Remind subject to bring the Diary to the next on-site visit (treatment group only).
- 30 minutes following injection, perform Visual Function Assessments (treatment group only).
- Evaluate the subject for post-treatment AEs- Treating Investigator.
- Schedule the next follow up visit (1 month *(+5 weeks)* for treatment group) / (Month 7 *(+2 weeks)* for control group)

#### 4.7.3 Visit 2a, Follow up 72 hour telephone call (±24 hours) - ***for treatment group only***

- 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 site 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.

#### 4.7.4 Visit 3, Treatment 2 (1 month (+5 weeks) after Treatment 1) - ***for treatment group only***

- Review the subject's concomitant therapies.
- Collect and review subject diary.
- Interview for AEs.
- Assess for AEs- Treating Investigator
- Assess [redacted]) Treating Investigator (pre-treatment)

Effective date: 2021-03-24 11:04

Effective

. . 5.0

- Obtain Photography 2D and 3D (if receiving a treatment at this visit, perform prior to treatment)
- Perform Visual Function Assessments for all subjects (if receiving a treatment at this visit, perform prior to treatment).
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability.
- GAIS: Perform GAIS assessment (if receiving a treatment at this visit, perform prior to treatment) - Investigator and Subject.
- Instruct the subject to complete the Subject satisfaction questionnaire (pre-treatment).
- Instruct the subject to complete Face-Q assessment.
- 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
    - 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:

- Prior to any treatment being provided, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive treatment.
- Administer Sculptra Aesthetic.
- Evaluate for device deficiencies.
- 30 minutes following injection, perform Visual Function Assessments.
- Dispense new subject diary and instruct subject on daily diary completion. Remind subject to bring the diary to the next on-site visit.
- Evaluate the subject for post-treatment AEs- Treating Investigator.
- Schedule the next follow up visit (1 month +5 weeks) after treatment 2 visit

#### 4.7.5 Visit 3a, Follow up 72 hour telephone call (±24 hours) - ***for treatment group only, subjects who received a second treatment.***

- 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 site 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.

#### 4.7.6 Visit 4, Treatment 3 (1 month (+5 weeks) after Treatment 2) - ***for treatment group only***

- Review the subject's concomitant therapies.

Effective date: 2021-03-24 11:04

Effective

. . 5.0

- Collect and review subject diary (only applicable for subjects who received a treatment at Treatment 2 visit).
- Interview for AEs.
- Assess for AEs- Treating Investigator
- Assess [redacted] Treating Investigator (if receiving a treatment at this visit, perform prior to treatment)
- Obtain Photography 2D and 3D (if receiving a treatment at this visit, perform prior to treatment)
- Perform Visual Function Assessments for all subjects (if receiving a treatment at this visit, perform prior to treatment).
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability.
- GAIS: Perform GAIS assessment (if receiving a treatment at this visit, perform prior to treatment) - Investigator and Subject.
- Instruct the subject to complete the Subject satisfaction questionnaire (pre-treatment).
- Instruct the subject to complete Face-Q assessment.
- 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
    - 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:

- Prior to any treatment being provided, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive treatment.
- Administer Sculptra Aesthetic.
- Evaluate for device deficiencies.
- 30 minutes following injection, perform Visual function Assessments.
- Dispense new subject diary and instruct subject on daily diary completion. Remind subject to bring the diary to the next on-site visit.
- Evaluate the subject for post-treatment AEs- Treating Investigator.
- Schedule the next follow up visit (1 month +5 weeks) after treatment 3 visit

#### 4.7.7 Visit 4a, Follow up 72 hour telephone call (±24 hours) - ***for treatment group only, subjects who received a third treatment.***

- 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 site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.

Effective date: 2021-03-24 11:04

- 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.

#### 4.7.8 Visit 5, Treatment 4 (1 month (+5 weeks) after Treatment 3) - ***for treatment group only***

- Review the subject's concomitant therapies.
- Collect and review subject diary (only applicable for subjects who received a treatment at Treatment 3 visit).
- Interview for AEs.
- Assess for AEs- Treating Investigator
- Assess [redacted] Treating Investigator (if receiving a treatment at this visit, perform prior to treatment)
- Obtain Photography 2D and 3D (if receiving a treatment at this visit, perform prior to treatment)
- Perform Visual Function Assessments for all subjects (if receiving a treatment at this visit, perform prior to treatment).
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability (if receiving a treatment at this visit, perform prior to treatment).
- GAIS: Perform GAIS assessment (if receiving a treatment at this visit, perform prior to treatment) - Investigator and Subject.
- Instruct the subject to complete the Subject satisfaction questionnaire (pre-treatment).
- Instruct the subject to complete Face-Q assessment.
- Assess whether optimal treatment result has been obtained (as agreed by the Treating Investigator and Subject).
    - If a fourth treatment is to be performed, confirm eligibility criteria
    - 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 fourth treatment:

- Prior to any treatment being provided, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive treatment.
- Administer Sculptra Aesthetic.
- Evaluate for device deficiencies.
- 30 minutes following injection, perform Visual function Assessments.
- Dispense new subject diary and instruct subject on daily diary completion. Remind subject to bring the diary to the next on-site visit.
- Evaluate the subject for post-treatment AEs- Treating Investigator.
- Schedule the next follow up visit month 7 (+ 2 weeks) after baseline

Effective

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Effective date: 2021-03-24 11:04

Effective

: 5.0

4.7.9 Visit 5a, Follow up 72 hour telephone call (±24 hours) - ***for treatment group only, subjects who received a fourth treatment.***

- 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 site 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.

4.7.10 Visits 6, 7 and 8, Follow-up month 7 (+ 2weeks), 9 (±2 weeks), 12 (±2 weeks) ***all subjects***

- Obtain weight measured at clinic.
- Review the subject's concomitant therapies.
- Collect and review subject diary (only applicable for subjects in the treatment group who received a treatment at Treatment 4 visit).
- Obtain 2D and 3D Photographs.
- Perform ultrasound (at selected sites).
- Interview for AEs
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability (treatment group only for device palpability).
- Perform Visual function assessments: Snellen visual acuity test, Extraocular muscle function test and Confrontation visual field
- Assess for AEs- Treating Investigator
- Assess GAIS - Investigator and subject.
- [redacted] assessment – Blinded Evaluator.
- Radiance, skin tightness and jawline contour: Perform radiance, skin tightness and jawline contour assessment – Treating Investigator.
- Instruct the subject to complete the Subject satisfaction questionnaire (treatment group only).
- Instruct the subject to complete Face-Q assessment.

4.7.11 Unscheduled Visits

- When necessary, unscheduled visits could take place (in particular because of an AE needing a specific treatment)
- Unscheduled visits related to the study should be documented and all adverse events captured.

Effective date: 2021-03-24 11:04

Effective

: 5.0

# 5 Subjects

## 5.1 Subject information and informed consent

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

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 IRB. 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 informed consent form and to consider participation in the study. Before any study-related activities are performed, the informed consent form 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. The subjects will be recognizable on the photographs, but their names will not be disclosed.

All original signed informed consent forms shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated informed consent form and any other written information.

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

## 5.2 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. Women or men over 21 years of age.
3. Intent to undergo correction of cheek wrinkles on both sides of the face and a [redacted] of Moderate or Severe on EACH side of the face, as assessed on Day 1 by the Blinded Evaluator as well as the Treating Investigator, but agreement on score is not required. The [redacted] score for each side of the face does not need to be equal; however, the difference between the two sides should be limited to 1 grade.
4. Female subjects must be postmenopausal for at least 1 year; if the subject is a female of childbearing potential, she 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

Effective date: 2021-03-24 11:04

Effective

. . 5.0

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 baseline and agrees to continue for the duration of the study or use acceptable form of birth control).

### 5.3 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 Aesthetic constituents.

2. Known/previous allergy or hypersensitivity to lidocaine and other local anesthetics, e.g. amide-type anesthetics or topical anesthetics 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 tissue augmenting therapy, contouring or revitalization treatment in the face, except the lips, with any of the following filler prior to Baseline visit:

    a. Collagen, Hyaluronic Acid – 12 months

    b. Calcium Hydroxyapatite (CaHa), Poly L- Lactic Acid (PLLA) or permanent (non-biodegradable)- Prohibited

5. Previous treatment/procedure in the face in the previous 6 months that, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the study subject to undue risk by study participation, e.g.:

    a. Resurfacing (laser, photomodulation, light, radiofrequency, ultrasound, chemical peel, dermabrasion, or other ablative/non- ablative procedures)

    b. Needling or mesotherapy

    c. Cryotherapy

    d. Neurotoxin injections

    e. Lipolytic injections (e.g. dexycholic acid or other lipolytic substances)

    f. Dental work, such as root canals or sinus surgery

    or is planning to undergo any of these procedures affecting the treatment area, at any time during the study.

6. 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

Effective date: 2021-03-24 11:04

Effective

. . 5.0

b. Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes zoster/ herpes simplex and acanthosis

c. Scars or deformities

d. Cancer or precancerous condition (e.g. actinic keratosis or actinic cheilitis)

7. History of severe elastosis and/or excessive sun exposure that in the opinion of the Treating Investigator, could affect the safety and effectiveness outcome of the study.

8. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation (e.g. aspirin or other NSAIDs), Omega-3, or vitamin E within 14 days before treatment. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.

9. Treatment with chemotherapy, immunosuppressive agents (inhaled corticosteroids allowed), immunomodulatory therapy (e.g. monoclonal antibodies or antiviral treatment for HIV or Hepatitis C) within 6 months before treatment.

10. Use of topical corticosteroids or topical prescription retinoids (in the treatment area) within 1 month of the Baseline visit or systemic retinoid treatment within 6 months of the Baseline visit.

11. Previous surgery including plastic surgery, lifting threads, tissue grafting or tissue augmentation with permanent implants, silicone or fat, or tattoo, affecting the treatment area.

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. Presence of piercing, beard or facial hair that could interfere with study evaluation.

17. Abnormal result on functionality, sensation, symmetry, mass formation or palpation assessments in the treatment area.

18. Abnormal result on extraocular muscle function test or confrontational visual field assessment.

19. Presence of a dental, oral, or facial condition which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment, e.g. has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities.

20. 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.

21. 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 that may interfere with the outcome of the study).

22. Other condition preventing the subject from entering the study in the Treating Investigator's opinion, e.g. subjects failing baseline safety assessments, subjects not likely to avoid other

Effective date: 2021-03-24 11:04

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.

23. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), or employees and close relatives of employees at the Sponsor company.

24. Participation in any interventional clinical study within 30 days of screening.

### 5.4 Subject number

Prior to any study procedures being conducted, the subject must sign the informed consent form. Each subject who has signed the informed consent form will be assigned a screening number. Upon randomization, each subject will be assigned a subject numbers that will be allocated in ascending order within each center. A screen failure is a subject who signed the informed consent but never enrolled (i.e. was randomized and/or 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.

### 5.5 Withdrawal of subjects

Each subject should be advised in the 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 adverse events 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 document sand eCRFs. 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

Effective

: 5.0

Effective date: 2021-03-24 11:04

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 8.6.11.

## 6 Study Products

The term "study product" refers to Sculptra Aesthetic. The study product will be provided by sponsor.

### 6.1 Investigational product

Sculptra Aesthetic is a poly-L-lactic acid implant in the form of a sterile non-pyrogenic suspension, which is reconstituted from a sterile dry powder by the addition of sterile water for injection. The suspension contains microparticles of poly-L-lactic acid. Poly-L-lactic acid is a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family.

Sculptra Aesthetic is available in a glass vial and is to be reconstituted prior to use by the addition of 8 mL SWFI to form a sterile non-pyrogenic suspension. 1 mL of 2% Lidocaine Hydrochloride (HCl) is to be added immediately prior to injection.

Each vial of Sculptra Aesthetic contains:

- Poly-L-lactic acid 150 mg
- Sodium carboxymethylcellulose 90 mg
- Non-pyrogenic mannitol 127.5 mg

| **Investigational Study Product** | |
|---|---|
| **Trade Name or Equivalent** | Sculptra Aesthetic |
| **Treatment Substance** | Poly-L-lactic acid (PLLA) |
| **Concentration** | 367.5 mg |
| **Packaging** | Single use vial |
| **Storage Conditions** | Store at room temperature, up to 30°C (86°F). DO NOT FREEZE. Refrigeration is not required.<br>Upon reconstitution, Sculptra Aesthetic can be stored for up to 72 hours at temperatures between 5- 30°C. |
| **Reconstitution Volume** | 8 mL SWFI |
| **Additional Anesthetic** | 1 mL of Lidocaine Hydrochloride 2% added to vial immediately prior to injection |

Effective

: 5.0

Effective date: 2021-03-24 11:04

Effective

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| **Recommended Maximum Volume per treatment session** | ○ Maximum of 18 mL (2 vials) of Sculptra Aesthetic will be administered per treatment session<br>○ Maximum of 9 mL (1 vial) per cheek, evenly distributed within the treatment area. |
| **Frequency** intervals | Four (4) injection sessions with 1-month (+5 weeks). |
| **Reconstitution needle size** | 18G |
| **Injection needle size** | 25G |
| **Mixing Instructions** | Immediate use after mix |
| **Injection Technique** | Bolus, fanning, cross-hatching, linear threading injection technique or other techniques at the discretion of the Treating Investigator |
| **Injection Depth** | Subdermal regions |
| **Treatment Area** | Within the following borders:<br>□ Superior border - from top of tragus to top of alar crease<br>□ Medial border - from top of the alar crease, along the nasolabial fold (NLF) to the inferior border of the mandibular ramus<br>□ Inferior border - from medial border at mandibular ramus to angle of mandibular ramus<br>□ Lateral border - from angle of mandibular ramus to top of tragus |

### 6.2 Reference product

Not applicable.

### 6.3 Additional products and materials

The following will be supplied by the study sites:

- 18 G sterile needles (for reconstitution)
- 25 G sterile needles (for injection)
- 2% Lidocaine HCl. (Only the 3 Lidocaine products listed below should be used and only for the treatment group).
    - 2% Lidocaine HCl- Hospira with 0.1% Methyl paraben
    - 2% Lidocaine HCl- West Ward with 0.1% Methyl paraben
    - 2% Lidocaine HCl- West Ward without preservatives
- Sterile Water for Injection (SWFI), United States Pharmacopeia (USP)

Effective date: 2021-03-24 11:04

- Single use 5 mL sterile syringes
- Single use 1 mL or 3 mL sterile syringes
- Antiseptic (such as alcohol)

Topical or local anesthesia may be used at the discretion of the Treating Investigator before the treatment. If used, the anesthesia shall be supplied by the study site. Type of anesthesia, administration route, product name, and quantity used must be recorded in the eCRF.

## 6.4 Packaging, labelling, and storage

### 6.4.1 Investigational product

Sculptra Aesthetic 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 Aesthetic contains one vial of poly-L-lactic acid, sodium carboxymethylcellulose, non-pyrogenic mannitol.

Each vial of Sculptra Aesthetic is packaged for single-use only.

Labelling will be performed according to United States Code of Federal Regulations (CFR) 21 CFR 812.5: Labelling of investigational devices. The carton will be labelled with lot number, expiration date, CTN number, and the following:

"CAUTION – Investigational Device. Limited by Federal Law to Investigational Use."

Sculptra Aesthetic can be stored at room temperature, up to 30ºC (86ºF). Upon reconstitution, Sculptra Aesthetic can be stored for up to 72 hours at temperatures between 5-30°C. DO NOT FREEZE. Refrigeration is not required.

Detailed product information is provided in the study IFU.

### 6.4.2 Reference product

No treatment control, i.e. reference product is not applicable.

### 6.4.3 Product accountability

The study product will be released to the Investigator or his/her authorized designee after study approvals have been received from the FDA and IRB and the CTA has been signed by all parties.

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

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

When the study is completed, all unused or expired investigational product at each study site shall be returned to the Sponsor representative for destruction, or be destroyed locally at the site if documented as agreed with Sponsor.

Any malfunctioning investigational products shall be reported as described in Section 8.7.3.

Products deliberately or accidentally destroyed during shipment or at a study site shall be accounted for and documented. Used vials, syringes, needles, and any 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 site. Disposal of hazardous material, i.e. syringes and needles must conform to applicable laws and

Effective

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Effective date: 2021-03-24 11:04

Effective

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regulations.

The study products must not be used outside of the study.

All study products sent to the Investigator will be accounted for and no unauthorized use is permitted.

## 6.5 Treatment

### 6.5.1 Treatment procedure

The investigational product is reserved for use by Treating Investigators who are experienced in treating cheek wrinkles.

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 investigational product is reserved for use by doctors trained in the appropriate injection technique. 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. All traces of make-up in the treatment area should be removed prior to any injection. The treatment site should be cleaned with a suitable antiseptic solution.

An ice pack can be applied on the site for a short period. Topical or local injection anesthesia may be used 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 on the eCRFs.

Sculptra Aesthetic (sterile, freeze-dried, injectable poly-L-lactic acid) is available in 367.5 mg dose vials and will be reconstituted prior to use by the addition of 8 ml of SWFI at the investigational site following the reconstitution instructions in the study IFU.

Immediately prior to injection, 1 mL of 2% lidocaine shall be added to make a total volume of 9 mL and the vial should be shaken

For intravascular complications or embolic events, the treating physician should provide prompt medical attention and follow relevant clinical practice guidelines (8) for handling these symptoms. The treating physician should also review the Intravascular Treatment Protocol provided separately as a supportive tool.

Sculptra Aesthetic will be administered using a 25G needle. Injections will be made subdermally, i.e. in the subcutaneous and supraperiosteal region. A maximum of 18 mL (2 vials) of Sculptra Aesthetic will be administered per treatment session with a maximum of 9 mL (1 vial) per cheek, evenly distributed within the treatment area.

In this study, the study products will be administered in the Treatment area defined within the following anatomical borders:

- Superior border - from top of tragus to top of alar crease
- Medial border - from top of the alar crease, along the NLF to the inferior border of the mandibular ramus
- Inferior border - from medial border at mandibular ramus to angle of mandibular ramus
- Lateral border - from angle of mandibular ramus to top of tragus

Effective date: 2021-03-24 11:04

Effective

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Injection technique

The injection technique is important for the aesthetic effect of the treatment. It is recommended to use a standard injection technique for all subjects per site to limit variability due to technique. Before product is injected, aspiration should be done to avoid intravascular injection.

The injection technique is at the discretion of the investigator, proposed techniques are:

- Antegrade linear threading: also called push-ahead technique as some product is pushed ahead of the needle. Once the needle is in place, the product is injected ahead while inserting the needle in the tissue.
- Retrograde linear threading: the needle is threaded into the tissue at the appropriate depth, and the product in injected as a straight line on withdrawal of the needle
    - Bolus: multiple aliquot injections of the product is injected along a line or regions of the tissues
- Fanning: a number of linear threads to spread the product over a wider area
- Cross-hatching: combines multiple injections of linear threading that crisscross at right angle to provide volume in a square shape

### 6.5.2 Treatment regimen (dose and interval)

Eligible subjects randomized to the treatment group will receive a single regimen of Sculptra Aesthetic. A single regimen consists of up to 4 injection sessions with 1-month (+5 weeks) intervals. The first treatment will be administered on Day 1/ Baseline visit. Sufficient amount of study product, as determined by the Treating Investigator, should be injected to achieve optimal correction:

- Optimal correction is defined as at least a one-step improvement on the [redacted]t and the best correction that can be achieved as agreed by Treating Investigator and subject.
- Three additional treatment sessions may be performed if needed to achieve optimal correction, as determined by the Treating Investigator and subject.

Treatment will stop when optimal correction has been achieved and subsequent visits will be follow-up visits. 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.

### 6.5.3 Post-treatment care

The subject should avoid excessive sun, UV lamp exposure and extreme temperature until any initial swelling and redness has resolved.

The subject should be asked to avoid touching or shaving the treated area and not to apply any creams or cosmetics in the treated area before the skin has healed completely in order to prevent infections or elicit an inflammatory reaction. The subject should also be reminded to abstain from prohibited medications, treatments, and procedures.

A subject diary will be handed out after each treatment session, and the subject should be reminded to record all expected symptoms in the treated area.

Detailed information regarding the post-treatment care and patient instruction is provided in the study IFU.

### 6.5.4 Post-trial provisions

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

Effective date: 2021-03-24 11:04

Effective

: 5.0

#### 6.5.5 Treatment compliance

The treatment will be administered by the Treating Investigator at the investigational site and be recorded in the eCRF.

## 7 Effectiveness 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:

- [redacted]
- Photography 2D and 3D
- GAIS
- Subject Satisfaction Questionnaire,
- FACE-Q “Satisfaction with Cheeks”
- Return to social engagement after treatment recording
- Ultrasound
- Radiance, skin tightness and jawline contour assessment.

In addition, a Central Independent Photographic Reviewer will assess photographs.

Effective date: 2021-03-24 11:04

Effective

Version: 5.0

### 7.1 [redacted]

The severity of cheek wrinkles will be assessed live by the Blinded Evaluator and the Treating Investigator using the validated 5-graded [redacted]S At Rest during the study. The [redacted] scale is a validated (11) photograph-based outcome instrument. A photo guide of the scale is provided below. The subject is to have a relaxed face during the assessment.

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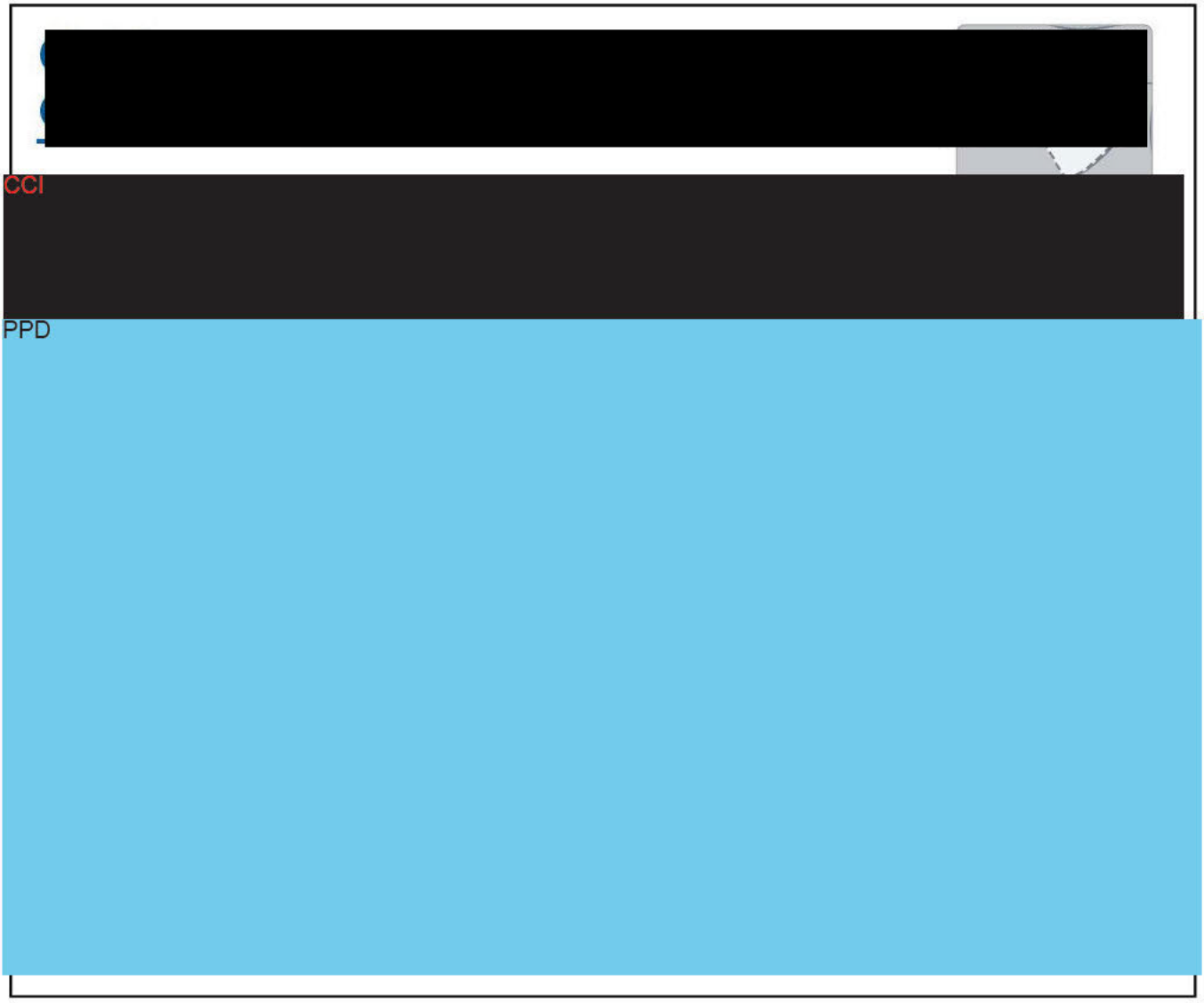

Effective date: 2021-03-24 11:04

Effective

Version: 5.0

### 7.2 [redacted]

The severity of cheek wrinkles will be assessed live by the Blinded Evaluator using the validated 5-graded [redacted] during the study. The [redacted] is a validated (11) photograph-based outcome instrument. A photo guide of the scale is provided below. The subject is to have a closed maximum smile during the assessment.

Effective date: 2021-03-24 11:04

Effective

: 5.0

### 7.3 Global Aesthetic Improvement Scale (GAIS)

The 7-graded GAIS will be used to live assess the aesthetic improvement of cheek wrinkles by the Treating Investigator and the subject, by comparing to a photograph taken at the baseline visit before the first treatment. 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.

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Effective date: 2021-03-24 11:04

Effective

: 5.0

### 7.4 Subject Satisfaction Questionnaire

Subject satisfaction with treatment result will be assessed using a subject satisfaction questionnaire.

[redacted]

Effective date: 2021-03-24 11:04

Effective

Version: 5.0

### 7.5 FACE-Q "Satisfaction with Cheeks"

Subject satisfaction will be assessed using the "Satisfaction with Cheeks" FACE-Q questionnaire.

**SATISFACTION WITH CHEEKS**

**These questions ask about how you look right now. For each question, circle only one answer. With your cheeks in mind (the side of your face below your cheekbones), in the past week, how satisfied or dissatisfied have you been with:**

CCI [redacted]

### 7.6 Lifting effect of cheek using 3D imaging

Lifting effect of cheek will be assessed using [redacted] 3D camera and software. Camera equipment will be provided by the Sponsor or their designee. Further details regarding 3D-photography procedure will be specified in a separate user guide. Site should follow the maintenance instructions from the equipment manufacturer and keep records of maintenance in the investigator file.

### 7.7 Return to social engagement

Subjects will record the date and earliest time he/she felt comfortable to return to social engagement following treatment in a subject diary. Return to social engagement is defined as making public/social appearances, including but not limited to returning to work at a business office or other public work place; having dinner in a public restaurant; attending a social event/gathering such as dinner party, etc. Subjects will record the time they feel comfortable (with or without covering make-up) resuming social interactions, not necessarily the time for their first social interaction.

Subjects will be asked to complete the following questions in the subject diary:

Did you feel comfortable to return to social engagement today?

- Yes or No

If yes, what was the earliest time you felt comfortable to return to social engagement?

- Record Date and Time (using 24-hour clock)

### 7.8 Ultrasound

Dermal thickness will be assessed using ultrasound, a select number of sites will conduct the assessment. Ultrasound equipment will be supplied by the sponsor to sites. Further instructions regarding the equipment and procedure will be specified in a separate user guide.

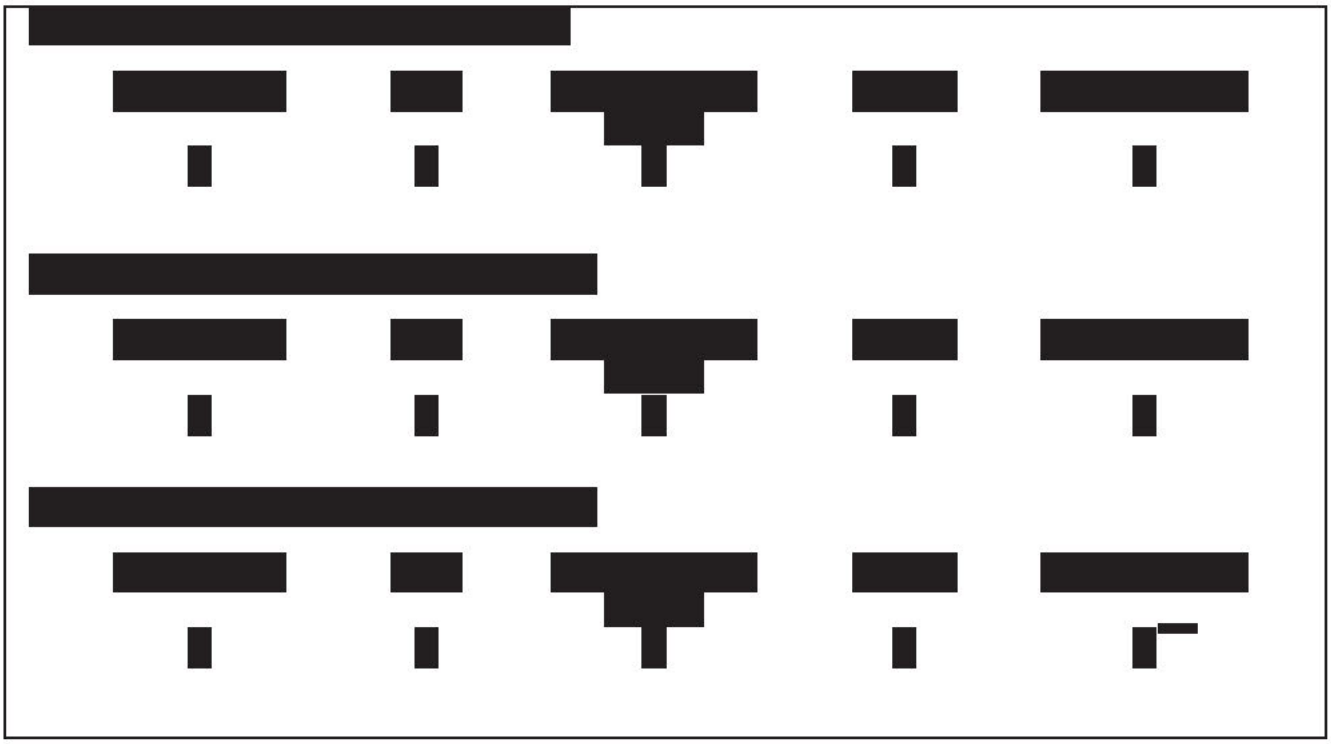
Effective date: 2021-03-24 11:04

Effective

: 5.0

### 7.9 Radiance, skin tightness and jawline contour assessment

The Treating Investigator will assess skin radiance, skin tightness and jawline contour after treatment based on review of baseline photographs and live assessment by responding to the following questions:



### 7.10 Photography

Photographs shall be taken at the time points indicated in the Schedule of Events. For those randomized to treatment, this should occur prior to the first injection of the study product and before each additional treatment. Camera equipment will be provided by the Sponsor or their designee and standardized photographs should be taken. Instructions for photography are provided in a separate photography manual. Baseline photographs may be used as a reference in the assessment of GAIS by the Treating Investigator and subject. Photographs may also be taken to document AEs at the Treating Investigator's discretion. Personnel will be trained in the photographic equipment and technique before the study start.

### 7.11 Improvement in cheek wrinkles by Central Independent Reviewer

Improvement in cheek wrinkles will be assessed by a Central Independent Photographic Reviewer by comparing random blinded pairs of photographs of the baseline visit and the follow-up visits at month 12. The photos from the follow up visits will include subjects from both the treatment and no treatment group in a blinded fashion. The reviewer will answer the question "Which photo represents post treatment" by responding right, left or neither photo.

## 8 Safety Assessments

Safety assessments for this study include an evaluation and an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an AE, a subject diary, laboratory tests, Cheek firmness, function and symmetry, Device palpability (baseline assessment excluded), Mass formation, Cheek sensation as well as visual function assessments.

Effective date: 2021-03-24 11:04

Information on AEs can also be obtained from signs and symptoms detected during each examination by the Investigator or designee, which should include visual inspection of the treatment area.
AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product. Events that occur after Screening but prior to randomization should be recorded in the subject's medical history.
If in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and the eCRF.

It is the responsibility of the Treating Investigator to determine severity of the AE and relatedness of the event to the study product and/or injection procedures. Adverse Events must be reported as outlined below in section 8.6.

### 8.1 Assessment of AEs by direct questioning to subject and evaluation of subject

Each subject should be questioned about AEs at each visit following randomization and/or treatment. Definition and Reporting requirements are found in section 8.6.

### 8.2 Subject Diary Data

A subject diary will be dispensed to all subjects for daily completion for 28 days beginning on injection day for each treatment with direct questioning for pain, tenderness, redness, bruising, swelling, itching, lumps/bumps and "other".

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The subject will also be specifically instructed to record presence of any of the following symptoms in the "other" section; Changes in vision (i.e. loss of vision, blurriness, double vision, pain in or around your eye, blindness, blind spots, problems moving your eyes), Skin changing color around the eyelids, Crusty or scabby skin around the eyelids, Pain, Headache, Fever, Dizziness, Confusion, Weakness or numbness in the arms or legs, Changes to consciousness or alertness, Difficulty speaking/ speech impairment or Face droop. The diary will include specific instructions to seek immediate medical attention if any of these symptoms or signs are observed.

Diary data will be counted and displayed separately from other AE data.

### 8.3 Laboratory assessments

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

### 8.4 Visual Function assessments

Visual function assessments will be performed for all subjects. For subjects in the treatment group, the assessments will be performed both prior to and post injection of the study product at baseline and all scheduled treatment visits. The post-treatment assessments should be performed 30 min after the injections are completed. In the event of blindness or any significant ophthalmic sign or symptom,

Effective

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Effective date: 2021-03-24 11:04

Effective

. . 5.0

subjects are to undergo immediate evaluation by an ophthalmologist or a retina specialist. All incidences of visual disturbances, regardless of relationship to study product or seriousness, are considered Adverse Events of Special Interest (AESIs) and include but are not limited to the following: any loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving eyes. AESI's should be reported (using the Adverse Event Clarification Form) within 24 hours of awareness. Please refer to recording instructions in section 8.6.6.

#### 8.4.1 Snellen visual acuity test

A Snellen Eye Chart will be used to assess visual acuity for distance vision. Visual Acuity will be conducted using the subject's best distance correction (e.g. with contacts or spectacles) at a distance of 6 feet from the chart. Each eye will be measured separately by either using an occluder or having the subject cover one eye at a time. The subject will be asked to start reading the letters at the top of the chart working their way to the bottom. The smallest row of letters that the subject can read will indicate their visual acuity listed on the chart. Snellen Visual Acuity will be recorded in their source documentation and eCRF. If there are two or more visual acuity line changes during the course of study, these should be reviewed and assessed by the Investigator for a potential adverse event.

#### 8.4.2 Extraocular muscle function test

Extraocular muscle function testing examines the function of the eye muscles. This test observes the movement of the eyes in six specific directions to evaluate weakness or other problems in the extraocular muscles. The subject will be asked to sit or stand with their head up and looking straight ahead. The assessor will hold a pen or other object approximately 16 inches in front of the subject's face. The assessor will then move the object in several directions and ask the subject to follow it with their eyes, without moving their head. Normal or Abnormal will be recorded in the source documentation and eCRF. Changes in movement of the eyes during the course of the study should be reviewed and assessed by the Investigator for a potential adverse event.

#### 8.4.3 Confrontation visual field

The Confrontation Visual Field test will be used to assess the subject's peripheral vision. The examiner will sit facing the subject, about 3 to 4 feet away from the subject and ask the subject to fix their gaze on the examiner's eye. The examiner will hold their arms straight out to the side and bring their hands into the subject's visual field from the sides in each quadrant. The subject will signal as soon as the hand is seen. Results will be recorded as normal or abnormal in the source documentation and eCRF. Changes in the visual field of the eyes during the course of the study should be reviewed and assessed by the Investigator for a potential adverse event.

### 8.5 Other safety assessments

At all physical visits, a study staff member who is qualified by training and experience to perform safety assessments, will assess each subject's cheek sensation; firmness and symmetry; and mass formation. After treatment with the study product, product palpability will be performed at each physical visit.

#### 8.5.1 Cheek sensation

Cheek sensation will be tested at all physical study visits using two methods:

1) Monofilament test - assessing the subject's ability to feel the sensation of a 0.4G monofilament on 3 points on right and left cheek *and*

2) Cotton Wisp test - assessing the subject's ability to feel the sensation of a cotton wisp on 3 points on the right and left cheek. The 3 different points on each side will be tested randomly.

Effective date: 2021-03-24 11:04

Effective

. . 5.0

Subjects will be blindfolded and asked to acknowledge sensation or lack of sensation at each point. Any lack of sensation should be further assessed by the Investigator for confirmation of any potential adverse event.

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#### 8.5.2 Cheek firmness, symmetry and function

At all physical visits, a study staff member who is qualified by training and experience to perform safety assessments will assess each subject's cheek firmness, symmetry (with face at rest and with eyes tightly closed), and function (puff cheeks, broad smile, and chewing motion). These parameters will be rated as "Normal" or "Abnormal." Any abnormal result should be further assessed by the Investigator for confirmation of any potential adverse event.

#### 8.5.3 Mass formation

Mass formation in the cheeks will be assessed by a study staff member that is qualified by training and experience to perform safety assessments at screening/baseline and at all physical visits. Mass formation will be defined as lumps or aggregation of coherent material. An assessment of mass formation is to be recorded as an adverse event.

#### 8.5.4 Device palpability- only for subjects in the treatment group

Device palpability will be assessed at each scheduled post-treatment visit and will assess whether or not the palpability is the normal expected feel. An unexpected feel is to be recorded as an adverse event.

### 8.6 Adverse events

#### 8.6.1 Definition of an adverse event

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[1], whether or not related to the study product.

This definition includes:

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

b) events related to the procedures involved

#### 8.6.2 Definition of a serious adverse event

A serious adverse event (SAE) is an 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[2] illness or injury, or
2. a permanent impairment of a body structure or body function, or

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

[2] 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).

Effective date: 2021-03-24 11:04

Effective

. . 5.0

3. in-patient or prolonged hospitalization[3], or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death, or a congenital abnormality 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 8.6.5).

#### 8.6.3 Definition of unanticipated adverse effect

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the investigational product, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with a device that relates to the right, safety or welfare of the subject (see US requirement CFR 812.3 (s).

#### 8.6.4 Recording instructions

Each subject with an AE occurring after enrollment through study exit should be fully recorded in the source document(s) for further transcription into the eCRF. Each subject should be questioned about AEs at each study visit following randomization and treatment. . 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 site personnel, subject diaries, or spontaneous reports from the subjects or their relatives.

When an AE is related to a device deficiency (refer to Section 8.7), 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 separately in the investigator file, and the eCRF.

Investigators, or other study site 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 8.6.4.1)
f) Seriousness (serious or not serious, according to definition in Section 8.6.4.2)
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 pre-defined, expected post-treatment events shall be assessed separately. These events shall be collected daily by subjects in a diary for up to 28 days after each treatment.

[3] 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).

Effective date: 2021-03-24 11:04

Effective

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*8.6.4.1 Intensity*

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.

*8.6.4.2 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.

### 8.6.5 Reporting of adverse events

Adverse event reporting on each subject shall start upon enrollment (i.e. randomized and/or treated) in the study. Any 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.

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

### 8.6.6 Reporting of adverse events of special interest (AESIs)

All incidences of visual disturbances, regardless of relationship to study product or seriousness, are considered Adverse Events of Special Interest (AESIs) and include but are not limited to the following: any loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving eyes.

AESIs should be reported (using the AE Clarification Form) within 24 hours of awareness to the Contract Research Organization (CRO) at the email address CCI [redacted] In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted with follow up information provided within 24 hours of awareness of the new information.

The following information should be provided when reporting an AESI:

- Subject identification (subject number and initials)
- Event description including observed symptoms
- Medical history related to event

Effective date: 2021-03-24 11:04

- Event onset date and time
- Depth of injection
- Interventions implemented to treat event
- Event outcome (with resolution date and time if applicable)
- Relatedness to study product or procedure
- Seriousness of event
- Study treatment information (number of injections, date of injections, name of product injected, batch number/lot number, volume injected, injection depth etc.)

If the Investigator assesses an AESI to be serious, an SAE report should be submitted as specified in Section 8.6.7.

Upon receipt of the AESI report, the Medical Monitor and Sponsor will review the information provided, assess the event, and report to the RA, as applicable. The investigator is responsible for reporting events to the IRB per the IRB reporting guidelines.

#### 8.6.7 Reporting of serious adverse events

The Investigator shall report any **SAE** to the 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 43USSA1812
- 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 (investigational product or no-treatment)\
- 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.)

**E-mail** for SAE reporting: CCI [redacted]

Effective

. . 5.0

Effective date: 2021-03-24 11:04

Effective

. . 5.0

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 site. The blinded evaluator should perform live effectiveness assessments only and not discuss the treatment or any potential adverse events with the patient.

In addition, the PI shall report SAEs to the responsible IRB without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her IRB 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, if applicable and according to national regulations.

#### 8.6.8 Stopping Rule

Enrollment and injections at an investigational site 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 investigational product or device injection procedure, and presents an unreasonable risk to study subjects, enrollment and/or injections will be immediately suspended for all study sites until the event can be properly characterized and an appropriate treatment strategy is established to prevent recurrence of the unanticipated event. All Investigators will be notified of the suspension. The IRB and RA will also be notified.
- If the SAE does not meet the above criteria, then enrollment and injections in the study will continue.

#### 8.6.9 Reporting of unanticipated adverse device effects

The Investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during the study as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (see US requirement 21 CFR 812:150 (a.), for contact details, see section 8.6.7.

#### 8.6.10 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.

#### 8.6.11 Reporting and follow-up of events occurring after subject termination of the study

All adverse events 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 8.6.4. The report can be sent via e-mail according to contact details specified in Section 8.6.7.

Effective date: 2021-03-24 11:04

Effective

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#### 8.6.12 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 be submitted to the Sponsor according to contact details specified in section 8.6.7. 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.

#### 8.6.13 Anticipated adverse events

Information regarding anticipated AEs for Sculptra Aesthetic is included in the study specific IFU.(1)

### 8.7 Device deficiencies

#### 8.7.1 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[4], or performance.

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

#### 8.7.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator and the source data recorded in the eCRF. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to section 8). If no SAE was experienced as a result of the device deficiency, the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,
- Circumstances had been less fortunate

In Part B of the clinical study complaint form, the Sponsor will make the same assessment.

#### 8.7.3 Reporting of device deficiencies

The Investigator shall send the completed clinical study complaint form to the CRO.

**E-mail** for device deficiencies reporting: [redacted]

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

Effective date: 2021-03-24 11:04

Effective

. . 5.0

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 24 hours after the Investigator's awareness (for contact information, see section 8.6.7). 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 IRB.

The deficient study product shall be kept by the study site 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 site.

# 9 Data Handling and Management

## 9.1 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 CIP 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 *e*CRFs 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.

## 9.2 Electronic case report forms

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 site before inclusion of the first subject.

Authorized study site personnel designated by the PI shall complete data collection. Appropriate training and security measures shall be completed with all authorized investigation site 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 site as part of the Investigator file.

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

Effective date: 2021-03-24 11:04

Effective

. . 5.0

#### 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 site 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 site personnel shall answer the queries in the eCRF within a reasonable timeframe Answered queries will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged. Answered queries will then be closed by the appropriate study personnel (i.e. data manager, site monitor, etc.)

#### 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.

### 9.3 Source documents

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 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.

Effective date: 2021-03-24 11:04

Effective

: 5.0

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.

### 9.4 Record keeping and access to source data

The PI/Institution shall permit study-related monitoring, audits, IRB 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 informed consent forms 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.

### 9.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, informed consent forms, study product accountability records, source documents, and other study documentation must be retained for retained for as long as is specified in the CTA after study completion or longer if required by national legislation. Sponsor will inform the site(s) 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, a security sealed CD with electronic study data shall be provided by the eCRF vendor 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 Statistical Methods

### 10.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be developed.

All study data will be listed in subject data listings.

All statistical analyses, including summary tables and data listings, will be performed using SAS. Confidence intervals will be two-sided and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided.

All endpoints will be summarized descriptively. Continuous endpoints will be summarized using mean, median, standard deviation, minimum and maximum values, for the observed value as well as the change from baseline. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

Effective date: 2021-03-24 11:04

Effective

5.0

### 10.2 Analysis populations

The following populations will be defined:

- Safety — Includes all subjects who were treated with Sculptra Aesthetic or randomized to no treatment control group. Subjects are analyzed based on the as treated principle (i.e. according to the treatment actually received).
- Intention-to-treat (ITT) — Includes all subjects who were randomized based on the as randomized principle (i.e. according to the treatment they were randomized to).
- Per protocol (PP) — Includes all subjects in ITT who complete the 12 month after baseline visit without any deviations considered to have substantial impact on the primary effectiveness outcome.

ITT is the primary population for all effectiveness analyses. The primary effectiveness analysis will be repeated using the PP analysis set if there is at least a 10% difference in the number of subjects between the PP and ITT sets. Safety analysis is performed based on the safety population set.

The disposition of subjects will be presented in tables and/or figures as appropriate.

### 10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented by treatment group, based on the ITT analysis set using descriptive statistics, as appropriate.

### 10.4 Effectiveness analysis

No adjustment to the level of significance will be done; p-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of the results.

For responder rates based on the [redacted] and GAIS, and percentage of improved subjects according to IPR, results for the right and left side of the face combined as well as separately, will be calculated.

Number and percent of subjects in each response category for [redacted] GAIS and IPR, will also be presented.

#### 10.4.1 Primary effectiveness analysis

CCI [redacted]

The null hypothesis will be that there is no relationship between responder rate and treatment. The alternative hypothesis will be that there is a relationship between responder rate and treatment.

The estimates of the responder rate in each treatment group will be presented along with the difference in responder rates. Corresponding confidence intervals for responder rates as well as difference in responder rates and p-value for difference in responder rates will also be presented.

In order to investigate the poolability of the results of the primary analysis across different subgroups, subgroups defined by study center, age (≥55 vs <55), and FST (I-III vs IV-VI) will be used. Logistic regression models will be fitted which will include the subgroup factor as well as the corresponding interaction term (subgroup x treatment) in order to obtain estimates and confidence intervals at each level of the subgroup factor. These will be displayed in graphs.

Effective date: 2021-03-24 11:04

10.4.2 Secondary effectiveness analysis

*Responder rate based on* [redacted] *by Blinded Evaluator at month 7 and 9*

CCI [redacted]

*Time to return to social engagement after treatment based on subject diaries*

Return to social engagement will be analyzed using Kaplan-Meier methods. The median time to return to social engagement will be estimated and Kaplan-Meier plots will be created.

*Other effectiveness endpoints*

All other secondary and all CCI [redacted] ffectiveness endpoints will only be analyzed by the means of standard descriptive statistics, including 95% confidence intervals.

## 10.5 Safety analysis

Number and percentage of subjects reporting each pre-defined, expected, post-treatment symptoms, as collected in the 28-day diary, will be presented in total and by maximum intensity. Number of days with the event will be presented by treatment group and category: 1, 2-7, 8-14, and 15-28 days.

All AEs will be coded according to MedDRA and summarized by system organ class (SOC), preferred term (PT) and treatment.

AEs related to study product or injection procedure and unrelated AEs will be presented by maximum intensity, SOC and PT. 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 by SOC and PT. Serious AEs will be listed.

In addition, a summary of all AEs will be provided, which will include (but is not limited to):

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

To evaluate consistency of AEs across different subgroups, AEs will also be summarized by subgroups, such as study center, age group, FST, and baseline [redacted]. In addition, the analysis of AEs will also be stratified based on different injection techniques.

Functionality, sensation, firmness, symmetry, mass formation and palpation assessments will be analyzed descriptively as appropriate.

## 10.6 Handling of missing data

Number of missing values will be summarized and reported as appropriate.

For ITT analysis of the Blinded Evaluator [redacted] At Rest responder rate at month 12 (primary endpoint), missing values will be assumed to be missing due to lack of effect. Therefore the primary method of imputation will use the baseline observation carried forward (BOCF) method. Impact of

Effective

: 5.0

Effective date: 2021-03-24 11:04

Effective

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missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the observed cases in the ITT set.

All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases.

### 10.7 Data monitoring committee

Not applicable to this study.

### 10.8 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 CIP 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 CSR. If the need of changing the statistical plan arises before DBL but after the finalization of the SAP, the SAP will be amended.

### 10.9 Sample size

A total sample size of approximately 150 subjects will be included in this study; approximately 100 will be randomized to treatment with Sculptra Aesthetic and approximately 50 will be randomized to no treatment. Sample size justifications are given below.

#### 10.9.1 Previous data

Since the primary endpoint will be based on a new scale, no existing data is available.

#### 10.9.2 Assumptions

Based on what is seen in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a responder rate of at least 70% in the Sculptra Aesthetic treatment group at month 12. For the no treatment control group, responder rates up to almost 30% have been observed in data on file. Based on this, it is assumed that the response rate will be maximum 35% in the no-treatment control group at month 12.

#### 10.9.3 Sample size calculations

For the responder rate in [redacted], testing the difference using a two-sided test at the 5% significance level will have approximately 90% power to demonstrate difference between a responder rate of 70% in the Sculptra Aesthetic group, and a responder rate of 35% in the no treatment control group when the sample sizes are 84 and 42, respectively. Accounting for 15% drop-outs, approximately 150 subjects need to be randomized in a 2:1 ratio.

## 11 Protection of personal data

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 Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the study subject should be made aware of this exception in

Effective date: 2021-03-24 11:04

Effective

: 5.0

the informed consent. The Institution and Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the investigation but the data collected until the consent was withdrawn may be used in the statistical analyses.

Authorized representatives from the Sponsor or a RA may visit the investigational site to perform audits/inspections, including source data verification, i.e., comparing data in the subjects' medical records and the eCRF. Data and information will be handled with strict confidentiality.

The study shall include collection and processing of personal data as specified in the Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR) on the protection of individuals with regard to the processing of personal data. For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

## 12 Quality Control and Quality Assurance

### 12.1 Quality control

On-site 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 CIP, subsequent amendment(s), GCP and the applicable regulatory requirements.

Any CIP 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 CIP 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 IRB if required by national regulations. Deviations will be reviewed to determine the need to amend the CIP or to terminate the study.

### 12.2 Quality assurance

The study site 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 site 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 site 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.

### 12.3 Changes to the clinical investigational plan

The PI and other site personnel involved in the study must not implement any changes to the CIP without agreement with the Sponsor and prior review and documented approval from the IRB and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CIP must be documented in a dated and version-controlled written protocol amendment. However, administrative changes may be documented in the Sponsor file without

Effective date: 2021-03-24 11:04

Effective

: 5.0

requiring a protocol amendment. The Sponsor will assess if the changes require prior FDA approval, and inform the Investigator when such approval has been received.

## 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 CIP 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 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[5]. 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 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.

## 15 Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IRB 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.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrolment or non-compliance with the CIP, GCP, or applicable regulatory requirements.

In the event of premature termination, Q-Med AB will provide information on the handling of currently enrolled subjects who have not completed the study.

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

Effective date: 2021-03-24 11:04

Effective

: 5.0

## 16 References


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4. GLI.04.SPR.US10321 Sculptra PAS 2-yr Clinical Study Report; data on file MA-39427.

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Effective date: 2021-03-24 11:04

Effective

: 5.0

**Appendix 1**

**Investigator Signature Page**

## Signed Agreement of the Clinical Investigational Plan

CTN: 43USSA1812

Title of the CIP: **A randomized, evaluator-blinded, no-treatment controlled, multicenter study to evaluate the effectiveness and safety of Sculptra Aesthetic for correction of cheek wrinkles**

We, the undersigned, have read and understand the Clinical Investigational Plan (CIP) specified above, and agree on the contents. The CIP, the clinical trial agreement (CTA) and the additional information given in the instructions for use (IFUs) and the Report of Prior Investigations (ROPI) will serve as a basis for co-operation in this study.

**Principal Investigator**

| Printed name | Signature | Date |
|---|---|---|

Study site

Effective date: 2021-03-24 11:04

Effective

: 5.0

# SIGNATURES PAGE

| Date | Signed by |
|---|---|
| 2021-03-24 10:16 | PPD |
| **Justification** | [redacted] |

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| **Justification** | [redacted] |