A randomized, multi-center, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Sculptra for correction of Midface Volume Deficit and/or Midface Contour Deficiency

Study product: Sculptra

Clinical Trial Number (CTN): 43CHSA1803

Sponsor: Q-Med AB
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Confidentiality Statement

Summary of Changes in Clinical Study Protocol 43CHSA1803 from Version 1.0 to Version 2.0

Added text is written in **bold** and deleted text is written as strikethrough.

Section in protocol	Rational for changes	Description of changes
Study Administrative Structure	Medical Expert changed.	PPD PPD
Sponsor Signatures	The name of company was added.	PPD **, Q-Med AB**
Sponsor Signatures	Medical Expert changed.	Sponsor's PPD , Q-Med AB PPD
Synopsis: Study Design	Clarify.	Before start of enrolment into Group B, the injection technique will be evaluated by the Sponsor **or designee of Sponsor** and performed after the subjects in Group A for each investigator have received their first treatment, and second treatment.
4.1 General Outline	Clarify.	Before start of enrolment into Group B, the injection technique will be evaluated by the Sponsor **or designee of Sponsor** and performed after the subjects in Group A for each investigator have received their first treatment, and second treatment.
8.3.8 Anticipated Adverse Events	According to the suggestion of the leading site EC, AEs description and precautions were added.	Information regarding anticipated AEs **below** is **also** included in the Sculptra Investigators Brochure. **Subcutaneous papules/, invisible but palpable or visible nodules including periorbital nodules, or areas of induration have been noted in the injection area. Nodules are occasionally associated with inflammation or discolouration. The early occurrence of subcutaneous nodules at the injection site (within 3–6 weeks after treatment) may be minimised by adhering to proper dilution and injection techniques. Delayed occurrences of subcutaneous nodules at the injection site (within 1–14 months post injection) have been reported with sometimes a prolonged duration of up to 2 years. Improper injection techniques such as superficial placement, excessive amount of product or incorrect reconstitution may lead to appearance of papules or nodules at the injection site. Massaging the treatment area to ensure proper distribution of the product may minimise the appearance of such papules or nodules.** **For nodular areas or late granuloma formation, in some cases, they resolved spontaneously or following**

		treatment with multiple intralesional injections of corticosteroids and/or antineoplastic agents (e.g. 5-fluorouracil). Surgical excision of the nodules was sometimes required when they were larger in size, occurring in difficult anatomical regions (e.g. lower eyelid) or persisting after other treatments. **This product must not be injected intramuscularly or intravascularly. Localised superficial necrosis and scarring may occur after injection in or near vessels. It is thought to result from the injury, obstruction, or compromise of blood vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area. Areas with limited collateral blood flow has an increased risk of ischaemia. Aspiration prior to injection is recommended.** **Unintentional introduction of soft tissue fillers into the vasculature in the face may lead to embolisation, occlusion of the vessels, ischaemia, necrosis or infarction at the implant site or in the area supplied by the blood vessels affected. Rare but serious adverse events include temporary or permanent vision impairment, blindness, cerebral ischaemia or cerebral haemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if any of the following symptoms occurs, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist, should an intravascular injection occur.**
Subject information and informed consent form		Updates required: Yes ☒ No ☐
Electronic case report form (eCRF)		Updates required: Yes ☐ No ☒

Study Administrative Structure

Sponsor	Q-Med AB Seminariegatan 21 SE-752 28 Uppsala, Sweden Telephone: +46 18 474 90 00 Facsimile: +46 18 474 90 01

PPD

PPD

Clinical Project Manager

PPD

Study Statistician

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 study protocol (CSP) amendment.

Sponsor Signatures

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

PPD **Q-Med AB** PPD	Electronically signed in the document management system within Q-Med quality management system
Sponsor's PPD **, Q-Med AB** PPD	Electronically signed in the document management system within Q-Med quality management system
Clinical Project Manager, Q-Med AB PPD	Electronically signed in the document management system within Q-Med quality management system
Study Statistician, Q-Med AB	Electronically signed in the document management system within Q-Med quality management system

Signed Agreement of the Clinical Study Protocol

CTN:	43CHSA1803
Title of the CSP:	A randomized, multi-center, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Sculptra for correction of Midface Volume Deficit and/or Midface Contour Deficiency

I, the undersigned, have read and understand the protocol specified above, and agree on the contents. The study protocol, the Clinical Trial Agreement and the additional information given in the Investigator Brochure for Sculptra will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study site

Synopsis

Title of study:	A randomized, multi-center, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Sculptra for correction of Midface Volume Deficit and/or Midface Contour Deficiency
Clinical Trial Number:	43CHSA1803
Countries involved, number of sites/country, number of subjects:	The study will be conducted at approximately 8 sites in China. Group A: Each Treating Investigator will enroll 1 or 2 subjects as group A. These subjects will all receive treatment with Sculptra. Group B: Evaluator treatment-blind group with approximately 189 subjects will be randomized in a 2:1 ratio to treatment group or no-treatment control group, i.e., 126 Subjects assigned to the Treatment Group and 63 subjects assigned to the Control Group.
Objectives:	• To evaluate the effectiveness of Sculptra in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency • To evaluate the safety of Sculptra in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency
Endpoints:	<u>Primary effectiveness endpoint:</u> Percentage of responders, defined by at least 1 point improvement from baseline on the Medicis Midfacial Volume Scale (MMVS) on both sides of the face concurrently, as measured by the blinded evaluator at 12 months in both Treatment Group and Control group. <u>Secondary effectiveness endpoints:</u> • Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the *blinded evaluator* at 6, 9, 18 and 24 months in Treatment Group, and at 6 and 9 months in Control Group. • Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the *treating investigator* at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group. • Volume change from baseline over time of the right and left midface areas combined, as measured by digital 3D photography at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group. • Percentage of responders, defined by having “Improved”, “Much improved” or “Very much improved” according to the Global Aesthetic Improvement Scale (GAIS) on both sides of the face combined, as assessed by the subject and the treating investigator at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group. • Percentage of subjects in each response category of each question in the subject satisfaction questionnaire in Treatment Group at 6, 9, 12, 18 and 24 months.

	* Time of the Follow up visits at 6, 9, 12, 18 and 24 months is calculated from baseline/randomization. Safety endpoints: • Incidence, intensity, duration, and onset of adverse events (AEs) collected throughout the study. • Incidence, intensity, and number of days of anticipated injection related reactions, collected using 4-week subject diaries after each treatment session for the Treatment Group.
Study Design:	For Group A, after screening, eligible subjects will be treated from day 1 and followed up for 24 months. For Group B, the study includes two phases as follows: Main study phase: It is randomized, evaluator-blinded and no-treatment controlled. After screening, all eligible subjects will be randomized either to the Treatment Group or the Control Group in a 2:1 ratio. All the subjects will be followed up for 12 months. Extension study phase: After the main study phase, the Treatment Group will be followed up for additional 12 months. Each Treating Investigator will enroll 1 or 2 subjects as Group A. Before start of enrolment into Group B, the injection technique will be evaluated by the Sponsor or designee of Sponsor and performed after the subjects in Group A for each investigator have received their first treatment, and second treatment. If treatments are found to be correctly performed, no further training is needed, there are no outstanding questions regarding the injection technique and no other corrective actions are identified, the enrolment in Group B can start for that investigator. Summaries of the results for Group A and B will be done separately in the study report. Treatment Each subject assigned to Group A and Treatment Group will receive up to 4 injection sessions with 5(±1) weeks (at least 4 weeks) intervals. Initial treatment will be on Day 1. Study treatments should be stopped if optimal midface augmentation has been obtained or a maximum of 4 injection sessions completed. Subjects assigned to the Control Group will not receive treatment during the study. Evaluation of effectiveness Midface fullness will be assessed using a separate Four-Point MMVS with photo guides for the right and left side by the treating investigator at each visit; and by the blinded evaluator at screening, baseline, 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at screening, baseline, 6, 9 and 12 months in Control Group.

	The measurement of volume change in the midface (right and left combined) from baseline will be calculated by 3D digital image analysis at 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at 6, 9 and 12 months in Control Group. Aesthetic improvement of the Midface fullness will be assessed by the subject and the treating investigator, independent of each other, at each follow-up visit using the 5-graded GAIS. Photographs of baseline condition will be used as reference. Subjects will be asked about their satisfaction with the treatment outcome using a questionnaire at 6, 9, 12, 18 and 24 months in Group A and Treatment Group. <u>Evaluation of safety</u> Information regarding AEs will be collected continuously during the study. 4-week subject diaries will also be used after each treatment session for Group A and Treatment Group to collect information about anticipated injection related reactions (i.e. pain, tenderness, localized redness, bruising, hematoma, edema, and "other"). <u>Interim Analysis</u> An interim analysis will be performed when the month 12 visit completed for all the subjects.
Inclusion criteria:	The subject must meet the following criteria to be eligible for the study: 1. Signed and dated informed consent to participate in the study. 2. Men or women aged 18 years of age or older of Chinese origin. 3. Subjects seeking augmentation therapy for the midface. 4. MMVS score of 2, 3 or 4 on each side of the face as assessed by the blinded evaluator.
Exclusion criteria:	The presence of any of the following exclusion criteria will exclude a subject from enrolment in the study: 1. Known/previous allergy or hypersensitivity to any of the constituents of the product. 2. Known/previous allergy or hypersensitivity to local anaesthetics, e.g. lidocaine or other amide-type anaesthetics. 3. History of severe or multiple allergies, such as anaphylaxis. 4. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, ultrasound, cryotherapy, chemical peeling or dermabrasion in the area to be treated within 6 months before treatment. 5. Previous surgery (including aesthetic facial surgical therapy or liposuction), piercing or tattoo in the area to be treated. 6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent filler, autologous fat, lifting threads or permanent implant in the area to be treated.

	7. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy in the area to be treated within 12 months before treatment. 8. Previous use of any neurotoxin below the level of the lower orbital rim on the face within 9 months before treatment. 9. Presence of any disease or lesions near or at the area to be treated, e.g. - Inflammation, active or chronic infection (e.g., in mouth, head and neck region); - Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes simplex or herpes zoster; - Scars or deformities; - Cancer or pre cancer (e.g. actinic keratosis). 10. History of cancer or radiation in the area to be treated. 11. Subjects with a dental or oral status on visual inspection that in the opinion of the Investigator would make the subject unsuitable for inclusion, or Subjects with dental, oral or sinus surgery within past 6 months prior to treatment or planned surgery, including dental implants, during the study period. 12. History of or active collagen diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis or localized or systemic scleroderma. 13. Tendency to form keloids, hypertrophic scars, or any other healing disorder. 14. History of bleeding disorders or treatment with thrombolytics, anticoagulants or inhibitors of platelet aggregation (e.g. aspirin or other non-steroid anti-inflammatory drugs (NSAIDs), Omega-3, or vitamin E within a relevant period before treatment, per the investigator's judgment. 15. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic corticosteroids within 3 months before treatment (inhaled corticoids are allowed). 16. Treatment with topical (facial below the level of the lower orbital rim) retinoids or corticosteroids within 1 month, or systemic retinoids within 6 months before treatment. 17. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion. 18. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g. subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.

	19. Women who are pregnant or breast feeding, or Woman of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period. 20. Subjects planning to accept any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim during the study (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency etc.). 21. The presence of moderate or severe abnormal rating for midface symmetry, i.e. more than 1 point difference in MMVS score between each side of the face. 22. Intention to change a significant amount of weight (≥2 BMI) during the study period. 23. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company. 24. Participation in any other clinical study within 30 days before treatment.
Investigational product, **dose and mode of administration:**	Sculptra 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. This suspension contains microparticles of poly-L-lactic acid, a crystalline form of polylactic acid. Sculptra dry powder is supplied after aseptic filtration sterilisation in a sterile elongated clear glass vial. Each vial of dry powder contains: 150mg microparticles of poly-L-lactic acid (PLLA), 90mg sodium carboxymethylcellulose, 127.5mg non-pyrogenic mannitol. Sculptra powder should be reconstituted extemporaneously with 8 mL of sterile water for injection. Prior to injection, optionally add another 1 mL of local anaestethic lidocaine (20 mg/mL) to the vial. Scuptra should be injected into the deep dermis, subcutaneous layer or supraperiosteal layer with a 25-26 G needle. Scuptra will be administered inferior to the maxillary prominence, superior to the plane of nasal alae, including the area from the lateral canthus to the medial canthus and lateral to the nose on the subject's right and left sides. When appropriate, the study product could be injected into the lateral and inferior adjacent areas to ensure a smooth transition of midface contour. Each subject will receive up to 4 injection sessions with 5(±1) weeks intervals. Study treatment injections should be stopped if optimal midface augmentation has been obtained or a maximum of 4 injection sessions completed. 1 vial is generally recommended at each treatment session, i.e., initial treatment or each optional treatment respectively. Maximum 2 vials can be used for each treatment session at the discretion of the investigator.
Reference therapy, dose and mode of administration:	Not applicable.

Duration of treatment and follow-up:	Screening period for each subject will be 0~ 21 days. Subjects assigned to Group A and Treatment Group will receive up to 4 treatments with 5(±1) weeks intervals, and be followed up for 24 months after baseline. So the total duration for Group A and Treatment Group is up to 25 months. Subjects assigned to the Control Group will not receive any treatment and be followed up for 12 months after baseline, so the total duration for the Control Group is about 13 months.
Effectiveness Assessment:	**Medicis Midface Volume Scale (MMVS):** MMVS is a Four-Point scale that assesses the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4) as described below. The blinded evaluator and treating investigator will rate the subject's right and left midface for severity of volume deficiency using the MMVS at all applicable study visits.

MMVS	
1	Fairly full midface; cheek prominence projected beyond the infraorbital rim at 45-degree view.
2	Mild loss of fullness in midface area; flatness of midface; cheek prominence at or behind infraorbital rim. May have slight presence of tear trough but not extending past mideye. Can start to see minimum volume loss of anterior cheek.
3	Moderate loss of fullness with slight hollowing below malar prominence; presence of the nasojugal groove extending past mideye.
4	Substantial loss of fullness in the midface area, clearly apparent hollowing below malar prominence; evidenced by significant indentation in the midface area.

3D Digital Imaging analysis:

The measurement of volume change in the midface (right and left combined) from baseline will be calculated by 3D digital images.

Global Aesthetic Improvement Scale (GAIS)

The 5-graded Global Aesthetic Improvement Scale (GAIS) will be used to assess the aesthetic improvement of the midface fullness of both sides of the live subject as compared to photographs taken before treatment. Each midface side will be rated separately. The treating investigator and the subject will, independently of each other, respond to the question: "How would you describe the aesthetic improvement of the midface fullness for each side today compared to the photos taken before treatment?"

Rating	Definition (for treating investigator)
Very much improved	Optimal cosmetic result for the implant in this subject.

	<table><tr><td>Much improved</td><td>Marked improvement in appearance from the original condition, but not completely optimal for this subject.</td></tr><tr><td>Improved</td><td>Obvious improvement in appearance from the original condition.</td></tr><tr><td>No change</td><td>The appearance is essentially the same as original condition.</td></tr><tr><td>Worse</td><td>The appearance is worse than the original condition.</td></tr></table> **Subject satisfaction questionnaire** Subjects in Group A and Treatment Group will be asked about their satisfaction with the treatment outcome using a subject satisfaction questionnaire.
Safety Assessment:	AE will begin to be collected after ICF signed. Each subject will be questioned about AEs at each clinical visit following the screening visit. The question asked will be "*Since your last clinical visit have you had any health problems* Information on AEs can also be obtained from laboratory test report, signs and symptoms detected during each examination, observations by the study personnel, subject diaries or spontaneous reports from the subjects. Anticipated injection related reactions will be collected using 4-week subject diaries after each treatment session for Group A and Treatment Group. The subject will record the presence and maximum intensity of anticipated injection related reactions, i.e. pain, tenderness, localized redness, bruising, hematoma, edema, and "other"). The Investigator will assess the presence of any papules (< 5mm in diameter) or nodules (≥ 5mm in diameter). If present, the papules/nodules will be recorded as AE and should be further assessed as visible/non-visible and inflammatory/non-inflammatory.
Statistical Methods:	All summaries will be done separately for Group A and B. For statistical inference, only Group B will be used. **Primary analysis** The percentage of responders (a responder will be defined as a subject with at least 1 point improvement from baseline MMVS on both sides of the face concurrently) will be calculated at 12 months based on the blinded evaluator's assessment. The percentage of responders in the Sculptra treated subjects will then be compared with the percentage of responders in the no-treatment control group using a Fisher's exact test at a significance level of 5%. In addition, for each group the two-sided 95% confidence intervals around the estimates of the percentage of responders will also be calculated. The treatment will be deemed a success if the p-value for the treatment difference on the primary endpoint is less than 0.05. **Secondary analysis** The percentage of responders based on the MMVS on both sides of the face concurrently will also be derived at all applicable follow-up visits for both the

	blinded evaluator's assessment and the treating investigator's assessment respectively. The response rates and their 95% confidence interval will be presented by visit and group. Fisher's exact test will be used to compare the response rates at Month 6 and 9 based on the blinded evaluator's assessment. For response rates based on the treating investigator's assessment, response rates will be compared at Month 6, 9 and 12 using Fisher's exact test. The volume change in the midface area as compared with baseline (right and left sides combined) obtained by 3D imaging will be presented by treatment for all applicable follow-up visits. GAIS (by treating investigator and subject) and satisfaction with the treatment outcome will be analyzed descriptively. **Safety** Anticipated injection related reactions, as collected in Treatment Group, as collected in 4-week diaries after each treatment session, will be summarized using frequency tables. Adverse event incidences will be summarized by MedDRA system organ class (SOC) and preferred term (PT). **Sample size** There are no available clinical data for Sculptra studied under conditions similar to the current study. However, based on what is seen in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a response rate of at least 60% in the Sculptra Treatment Group at Month 12. For the no treatment Control Group, response rate of 25.8% has been observed in an ongoing clinical trial in China. Based on this, it was assumed that the response rate will be maximum 30% in the no-treatment Control Group at Month 12. With a sample size of 100 subjects treated with Sculptra and 50 subjects in the no-treatment control group, Fisher's Exact test will have approximately 90% power to detect difference between the anticipated percentage of responders at a 5% significance level (two-sided). To account for 20% drop-outs, approximately 126 will be randomized to the Sculptra group and approximately 63 to the control group.

Abbreviations and definitions of terms

AE	Adverse Event
Blinded Evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject.
Co-ordinating Investigator	An Investigator assigned the responsibility for the coordination of Investigators at different centers participating in a multicenter study
CSP	Clinical Study Protocol
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
FAS	Full Analysis Set
G	Gauge
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic acid
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
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 clinical studies are conducted.
Investigator	The Principal Investigator or other qualified person, i.e. sub-Investigator, designated and supervised by the Principal Investigator at a study site to perform critical study-related procedures and/or make important study-related decisions as specified on the delegation log.
Investigator File	Essential documents relating to a clinical study as defined in GCP guidance document and maintained by the Investigator.
MedDRA	Medical Dictionary for Regulatory Activities
MMVS	Medicis Midface Volume Scale
NMPA	National Medical Products Administration
NSAIDs	non-steroid anti-inflammatory drugs
PI	Principal Investigator

PP	Per protocol
QA	Quality assurance
RA	Regulatory authority
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
SOC	System organ class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
U-HCG	Urinary human chorionic gonadotropin
WHO	World Health Organization

Table of Contents

List of Tables

List of Figures

List of Appendices

1 Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the Clinical Trial Agreement (CTA), the Clinical Study Protocol (CSP), applicable Good Clinical Practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2011 shall be followed. The International Conference on Harmonisation (ICH) guideline for GCP (E6) shall be followed as applicable for medical device. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix 1).

1.2 Application to independent ethics committee and/or regulatory authorities

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

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

In Europe, Sculptra is indicated as a medical device for increasing the volume of depressed areas, particularly to correct skin depressions, such as in skin creases, wrinkles, folds, scars, and for skin aging. Sculptra is also suitable for large volume corrections of the signs of facial fat loss (lipoatrophy).

In this study, Chinese subjects of at least 18 years old will be studied to evaluate the effectiveness and safety of Sculptra in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency. Subjects with grade 2, 3 or 4 of MMVS on each side of the face as assessed by the blinded evaluator will be included.

2.2 Investigational product description

Sculptra 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. This suspension contains microparticles of poly-L-lactic acid, a crystalline form of polylactic acid. Poly-L-lactic acid is a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family.

Sculptra dry powder is supplied after aseptic filtration sterilisation in a sterile elongated clear glass vial with an aluminium ring at one end, which is hermetically sealed by a rubber bung,

covered by a flip-off cap. Each vial of dry powder contains: 150mg microparticles of poly-L-lactic acid (PLLA), 90mg sodium carboxymethylcellulose, 127.5mg non-pyrogenic mannitol.

Sculptra dry powder is reconstituted with 8 mL of sterile water for injection to form a sterile nonpyrogenic suspension. As an optional means to provide pain relief during the injection procedure, an additional 1 mL of sterile 2% (20 mg/mL) lidocaine solution may be added to the vial of reconstituted product prior to injection for a final volume of 9 mL (Section"Treatment procedure").

Sculptra consists of a suspension of solid poly-L-lactic particles with a defined narrow particle size distribution and slow degradation kinetics due to high molecular weight and high degree of crystallinity. The particle size and narrow particle size distribution enables the injection of the poly-L-lactic particles into the deep dermis or subcutaneous layer, where they provide soft tissue augmentation that will improve over the course of a few weeks, as the microparticles are gradually surrounded by host connective tissue.

For further description of Sculptra, refer to the Investigator Brochure.

2.3 Reference product description

Not applicable as no filler intended for midface volume deficit and/or midface contour deficiency is available in China at the time of this protocol.

2.4 Previous experience

2.4.1 Non-Clinical Documentation

A biological evaluation of Sculptra has been performed according to ISO 10993-1 (Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.) and data from the biological testing of Sculptra have shown that the product is safe and does not cause irritation, toxicity or any unwanted local effects after implantation. On a microscopic level, the product has been judged to be a moderate irritant. Furthermore, a pyrogenicity study was performed and the product is non-pyrogenic.

The biological evaluation for Sculptra concludes that the nonclinical testing is relevant when assessing the biocompatibility profile. It is concluded that the biocompatibility testing performed on Sculptra is sufficient and supports the intended clinical use.

2.4.2 Clinical Documentation

2.4.2.1 Manufacturer-sponsored or acquired clinical studies

The safety and effectiveness of Sculptra as a treatment to correct the signs of facial fat loss in patients with HIV-associated lipoatrophy has been demonstrated in 6 clinical studies with extended follow-up periods (up to 5 years) and more than 650 subjects [1-5]. All 6 studies were open label and non-comparative with regards to the product. Sculptra was proved to be a long term, well-tolerated and effective treatment for facial lipoatrophy in subjects seropositive for HIV. The clinical efficacy of Sculptra was maintained during the follow-up periods; all measures of efficacy in the studies showed improvement with Sculptra.

The use of Sculptra in the correction of facial wrinkles and folds was evaluated in four clinical studies, including a randomized evaluator blinded study comparing PLLA against a collagen implant for treatment of nasolabial folds[6-8], the study results demonstrated wrinkle severity

improvement and global aesthetic improvement compared to the pre-treatment condition, as well as subject satisfaction with the results.

Sculptra demonstrated an acceptable safety profile in the HIV-positive patients and treatment related AEs were generally limited to transient events associated with the immediate injection procedure. Long-term AEs, even with a follow-up period of up to 5 years, were limited to small, asymptomatic subcutaneous nodules and papules in the treatment area. The results were similar in the immune competent subjects.

Post market surveillance data for Sculptra also support that the AE profile is acceptable.

2.4.2.2 Clinical data in the published literature

Sculptra has been also documented in scientific publications. Articles reporting results from sponsored studies associated with the manufacturer were omitted from the analysis because the data is covered in Section 2.4.2.1 above.

The results from treatment of HIV and non-HIV-associated facial lipoatrophy demonstrated, the aesthetic improvement remained at least 18 months after last treatment with some variation between subjects and studies[9-22]. Results from correction of wrinkles, folds, volume loss, skin depressions, in immune-competent subjects have also demonstrated aesthetic improvement remained for up to 36 months and 24 months (facial volume and nasolabial folds) with some variation between subjects and studies[23-28]. All the treatments have been well tolerated.

Among all the studies, there are 4 studies [23-26] focused on midface/cheek in immune-competent subjects, and all of them showed long-lasting volume increase and good safety profiles.

2.5 Study rationale and Justification for design

Based on pre-clinical testing/previous clinical experience as described in Section 2.4, it is considered justified to conduct a study to investigate superiority of Sculptra relative to no-treatment in the treatment of Midface volume Deficit and/or Midface Contour Deficiency by measuring the percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face, at 12 months. The study will be used as clinical documentation for registration of the product in China. No treatment control is chosen as no filler intended for midface volume deficit and/or midface contour deficiency is available in China at the time of this protocol.

Evaluation with standardised evaluation tools will be used in the study. The MMVS is a validated scale[29] and was used in the Restylane Lyft registration clinical trial [30] for midface augmentation in US and accepted by FDA.

2.6 Risk and benefits

As all other injectable medical devices, Sculptra has the potential to cause complications. After the injection of Sculptra, some common injection-related reactions might occur. These reactions include pain, tenderness, localized redness, bruising, hematoma and edema, which generally resolve within 2–6 days.
Subcutaneous papules, invisible but palpable or visible nodules including periorbital nodules,

or areas of induration have been noted in the injection area. Nodules are occasionally associated with inflammation or discolouration. The early occurrence of subcutaneous nodules at the injection site (within 3–6 weeks after treatment) may be minimised by adhering to proper dilution and injection techniques. Delayed occurrences of subcutaneous nodules at the injection site (within 1–14 months post injection) have been reported with sometimes a prolonged duration of up to 2 years.

For nodular areas or late granuloma formation, in some cases, they resolved spontaneously or following treatment with multiple intralesional injections of corticosteroids and/or antineoplastic agents (e.g. 5-fluorouracil). Surgical excision of the nodules was sometimes required when they were larger in size, occurring in difficult anatomical regions (e.g. lower eyelid) or persisting after other treatments.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discolouration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolisation. Rare but serious cases of ischemic events associated with temporary or permanent vision impairment, blindness, cerebral ischaemia or stroke have been reported following facial aesthetic treatments.

By April 2018, Sculptra had marketing approval in 18 countries/regions worldwide, including US, EU, Canada, Australia, Hong Kong, Taiwan, South Korea, etc. Sculptra has been proven safe and well tolerated with sustained aesthetic improvement for facial lipoatrophy or volume loss. The primary potential benefit of the study is a perceived improvement in the treated areas. However, there is a risk that the subject will not gain the full aesthetic correction of Midface volume Deficit and/or Midface Contour Deficiency. There is also a risk of device dislocation.

Given the anticipated low level of acceptable adverse events (AE) in connection with the injection, the risk-benefit assessment of the use of Sculptra for treatment of Midface volume Deficit and/or Midface Contour Deficiency appears to offer a clinical benefit at reasonable risk.

In addition, only study investigators qualified by education and experience, and who are skilled in the use of soft tissue fillers from their clinical practice and participation in clinical research, will be chosen in order to assure proper device implantation and management of study risk.

3 Objectives and Endpoints

3.1 Objectives of the study

- To evaluate the effectiveness of Sculptra in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.
- To evaluate the safety of Sculptra in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.

3.2 Endpoints of the study

3.2.1 Primary effectiveness endpoint:

- Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the blinded evaluator at 12 months in both Treatment Group and Control group .

3.2.2 Secondary effectiveness endpoints:

- Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the blinded evaluator at 6, 9, 18 and 24 months in Treatment Group, and at 6 and 9 months in Control Group.
- Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the treating investigator at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group.
- Volume change from baseline over time of the right and left midface areas combined, as measured by digital 3D photography at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group.
- Percentage of responders, defined by having “Improved”, “Much improved” or “Very much improved” according to the Global Aesthetic Improvement Scale (GAIS) on both sides of the face combined, as assessed by the subject and the treating investigator at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group.
- Percentage of subjects in each response category of each question in the subject satisfaction questionnaire in Treatment Group at 6, 9, 12, 18 and 24 months.

*Time of the Follow up visits at 6, 9, 12, 18 and 24 months is calculated from baseline/randomization.

3.2.3 Safety endpoints:

- Incidence, intensity, duration, and onset of adverse events (AEs) collected throughout the study.
- Incidence, intensity, and number of days of expected post-treatment events collected using 4-week subject diaries after each treatment session for the Treatment Group.

4 Design of the Study

4.1 General Outline

For Group A, after screening, eligible subjects will be treated from day 1 and followed up for 24 months.

For Group B, the study includes two phases as follows:

Main study phase: It is randomized, evaluator-blinded and no-treatment controlled. After screening, all eligible subjects will be randomized either to the Treatment Group or the Control Group in a 2:1 ratio. All the subjects will be followed up for 12 months.

Extension study phase: After the main study phase, the Treatment Group will be followed up for additional 12 months.

Each Treating Investigator will enroll 1 or 2 subjects as Group A. Before start of enrolment into Group B, the injection technique will be evaluated by the Sponsor or designee of Sponsor and performed after the subjects in Group A for each investigator have received their first treatment, and second treatment. If treatments are found to be correctly performed, no further training is needed, there are no outstanding questions regarding the injection technique and no other corrective actions are identified, the enrolment in Group B can start for that investigator.

Summaries of the results for Group A and B will be done separately in the study report.

Treatment

Each subject assigned to Group A and Treatment Group will receive up to 4 injection sessions with 5(±1) weeks (at least 4 weeks) intervals. Initial treatment will be on Day 1. Study treatments should be stopped if optimal midface augmentation has been obtained or a maximum of 4 injection sessions completed. Optimal midface augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the treating investigator and subject.

Subjects assigned to the Control Group will not receive treatment during the study.

Evaluation of effectiveness

Midface fullness will be assessed using a separate Four-Point MMVS with photo guides for the right and left side by the treating investigator at each visit; and by the blinded evaluator at screening, baseline, 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at screening, baseline, 6, 9 and 12 months in Control Group.

The measurement of volume change in the midface (right and left combined) from baseline will be calculated by 3D digital image analysis at 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at 6, 9 and 12 months in Control Group.

Aesthetic improvement of the Midface fullness will be assessed by the subject and the treating investigator, independent of each other, at each follow-up visit using the 5-graded GAIS. Photographs of baseline condition will be used as reference.

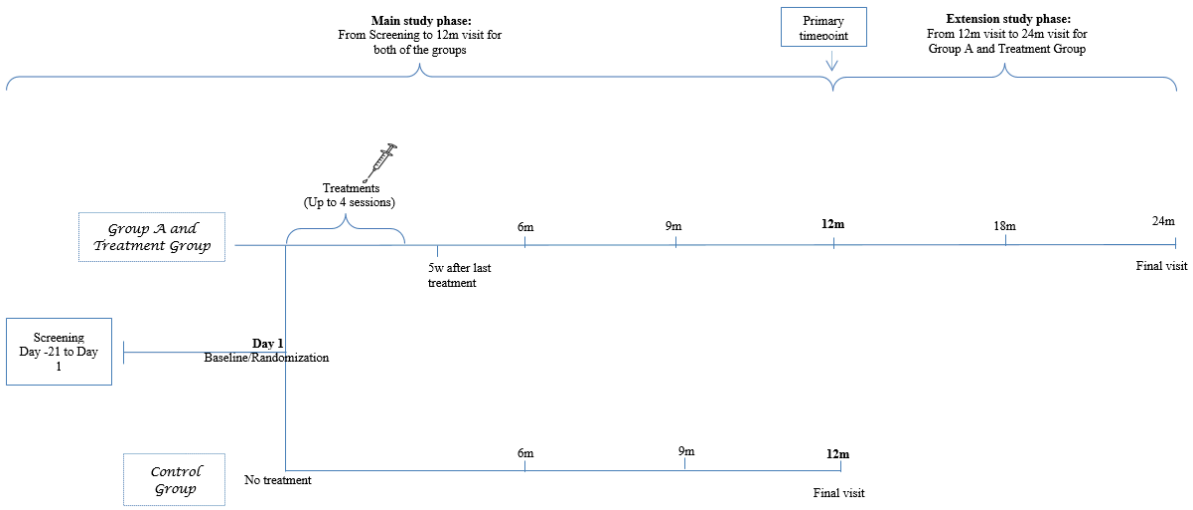
Subjects will be asked about their satisfaction with the treatment outcome using a questionnaire at 6, 9, 12, 18 and 24 months in Group A and Treatment Group.

Evaluation of safety

Information regarding AEs will be collected continuously during the study.

4-week subject diaries after each treatment session will also be used for Group A and Treatment Group to collect information about anticipated injection related reactions (i.e. pain, tenderness, localized redness, bruising, hematoma, edema, and “other”) at the treated area.

Figure 1. Flow chart



* Time of the Follow up visits at 6, 9, 12, 18 and 24 months is calculated from baseline/randomization.

4.2 Number of Subjects

The study will be performed at approximately 8 sites in China and approximately 32 subjects in Group A and 189 subjects in group B will be enrolled.

4.3 Duration of Subject Participation

Screening period for each subject will be 0~ 21 days.

Subjects assigned to Group A and Treatment Group will receive up to 4 treatments with 5 (±1) weeks intervals, and then be followed up for 24 months after baseline. So the total duration for Group A and the Treatment Group is up to 25 months.

Subjects assigned to the Control Group will not receive any treatment and be followed up for 12 months after baseline, so the total duration for the Control Group is about 13 months.

4.4 Randomization and blinding

4.4.1 Randomization

Approximately 189 subjects in group B will be randomized in a 2:1 ratio to treatment with Sculptra or to no treatment. Before starting the study, a computer generated randomization list will be prepared under the supervision of a designated statistician. The randomization list will be stratified by site.

Each eligible subject will be assigned a subject number as they arrive for the baseline visit. For group B, randomization will be performed via the eCRF system. The treatment information will be kept by the Treating Investigator during the study not to be disclosed to the Blinded Evaluator.

4.4.2 Blinding

Only the evaluator will be blinded, both treating investigator and subjects will be open-labelled.

The Blinded Evaluator shall not be allowed to retrieve study supplies or to be present during opening of the study supplies or injections. The Treating Investigator is not allowed to discuss treatments with the blinded evaluator or the subjects. All documents with information on study products shall be kept in a separate binder not available to the blinded evaluator.

4.4.3 Emergency unblinding

Not applicable as the Treating Investigator is unblinded.

4.5 Medical history

History of surgical events and medical conditions that are judged as relevant by the Investigator shall be documented in the eCRF using medical terminology.

Any concomitant medications and any relevant medical history (including prior facial dermatological procedures performed, and fillers or implants used) or concurrent diseases will be asked for.

4.6 Concomitant Medication, Treatment, and Procedure

Except as noted below, concomitant medications or other treatments or procedures may be utilized when the PI or his/her authorized designee considers it medically necessary.

Information regarding any use of concomitant medications, including over-the-counter medications administered during the study is to be recorded in the eCRF. The generic name or the trade name of all concomitant medication or a description of the procedure and the reason for its use shall be documented in the eCRF.

The following medications, treatments, and procedures are restricted or prohibited during the study:

- Thrombolytics, anticoagulants or inhibitors of platelet aggregation (*e.g.* aspirin or other non-steroidal anti-inflammatory drugs [NSAIDs]), Omega-3, or Vitamin E should not be used within two weeks before treatment to avoid increased bruising or bleeding at injection sites.
- At the treatment days, lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics e.g., certain antiarrhythmics, since the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (*e.g.,* monoclonal antibodies) is prohibited.
- Long term concomitant treatment with systemic or topical (facial) corticosteroids is prohibited (inhaled corticoids are allowed). Corticosteroids should be used with caution and should be adjudged as necessary by the Investigator.
- Use of systemic or topical (facial) retinoic acid is prohibited.
- Facial tissue augmenting therapy, contouring or revitalization treatment with fillers, lifting threads, permanent implant, mesotherapy, radiofrequency, ultrasound,

cryotherapy, fat-injection, neurotoxin, laser or light treatment, chemical peeling or dermabrasion below the level of the lower orbital rim are prohibited.

- Planned surgery including aesthetic facial surgical therapy or facial liposuction, sinus surgery or dental root surgery, or tattoo in the area to be treated is prohibited.
- Participation in any other clinical study is prohibited

If a subject has used any of the above prohibited medications or performed any of the above prohibited procedures, a protocol deviation will be documented. The subject should continue in the study for the scheduled follow-up visits.

4.7 Schedule of events

Table 1. Schedule of Events for Group A and Treatment Group

	Screening	Baseline / Treatment 1	Treatment 2 (Optional) [b]	Treatment 3 (Optional) [b]	Treatment 4 (Optional) [b]	Follow-up	Follow-up	Final visit / Early termination
	D-21 to D1	D1	5W(±1w) after treatment 1	5W(±1w) after treatment 2	5W(±1w) after treatment 3	5W(±1w) after Last treatment	6M (±2w) , 9M (±2w) , 12M (±2w) , and 18M (±3w) after Baseline	24M (±4w) after Baseline
Informed consent	X							
Demography	X							
Height		X						
Weight		X					X	X
Medical history & concurrent diseases	X	X[a]						
Concomitant medication/procedures	X	X[a]	X	X	X	X	X	X
Vital signs		X[c]						
Laboratory tests	X						X[d]	X[e]
Pregnancy test for childbearing potential women	X	X[a,c]	X[c]	X[c]	X[c]			X
Inclusion and Exclusion criteria	X	X[a]						
Randomization		X						

Treatment		X	X	X	X			
MMVS (Blinded Evaluator)	X	X[a,c]					X	X
MMVS (treating investigator)	X	X[a,c]	X[c]	X[c]	X[c]	X	X	X
Photography		X[c]	X[c]	X[c]	X[c]	X	X	X
GAIS (Treating investigator and Subject)			X[c]	X[c]	X[c]	X	X	X
Subject satisfaction questionnaire							X	X
Dispense subject diary		X	X	X	X			
Review and collect subject diary			X	X	X	X		
Device deficiencies		X	X	X	X			
Assessment of AE	X	X[a]	X	X	X	X	X	X
Study termination								X

a) Omitted if screening and baseline visit occur on the same day.
b) The visit is omitted if optional treatment was not performed.
c) Performed prior to treatment.
d) Only performed at 12M.
e) Only performed at early termination if termination occurs before 12M visit.

Table 2. Schedule of Events for Control Group

	Screening	Baseline	Follow-up	Final visit / Early termination
	D-21 to D1	D1	6M(±2w) and 9M (±2w) after Baseline	12M (±2w) after Baseline
Informed consent	X			
Demography	X			
Height		X		
Weight		X	X	X
Medical history & concurrent diseases	X	X[a]		
Concomitant medication/procedures	X	X[a]	X	X
Vital signs		X		
Laboratory tests	X			
Pregnancy test for childbearing potential women	X			
Inclusion and Exclusion criteria	X	X[a]		
Randomization		X		
MMVS (Blinded Evaluator)	X	X[a]	X	X
MMVS (treating investigator)	X	X[a]	X	X
Photography		X	X	X
GAIS (Treating investigator and Subject)			X	X
Assessment of AE	X	X[a]	X	X
Study termination				X

a) Omitted if screening visit and baseline visit occur on the same day.

4.8 Visits

4.8.1 Visits for Group A and Treatment Group

4.8.1.1 Screening (D-21 to D1)

- Informed consent
- Demography (Initials, Date of birth, Gender and Ethnic origin)
- Screening laboratory tests (haematology and serum chemistry)
- Inclusion and exclusion criteria
- Pregnancy test for childbearing potential women
- MMVS (by Blinded Evaluator and treating investigator)
- Medical history/concurrent diseases including prior facial dermatological procedures performed, and fillers or implants used
- Concomitant medications/procedures
- AE during the visit

4.8.1.2 Baseline (D1)

- Height and Weight
- Medical history/concurrent diseases
- Vital signs (before treatment, pulse rate, blood pressure, respiratory rate, body temperature)
- Inclusion and exclusion criteria
- Randomization
- Pregnancy test for childbearing potential women (before treatment)
- Photography (before treatment)
- MMVS (before treatment, by Blinded Evaluator and treating investigator)
- Treatment
- Dispense subject diary
- Concomitant medications /procedures
- Device deficiencies
- AE since last visit

If screening and baseline visit occur on the same day, the following procedures for baseline will not be repeated.

- Medical history/concurrent diseases
- Inclusion and exclusion criteria
- MMVS (before treatment, by Blinded Evaluator and treating investigator)
- Concomitant medications /procedures
- Pregnancy test for childbearing potential women(before treatment)
- AE since last visit

4.8.1.3 Optional treatment 2, 3, and 4 (only for subjects who receive the treatment)

- Photography (before treatment)

- MMVS (before treatment, by treating investigator)
- GAIS (before treatment, by treating investigator and subject)
- Pregnancy test for childbearing potential women (before treatment)
- Treatment
- Collect and review subject diary
- Dispense subject diary
- Concomitant medications/procedures
- Device deficiencies
- AE since last visit

4.8.1.4 5W(±1w) after last treatment

- Photography
- MMVS (by treating investigator)
- GAIS (by treating investigator and subject)
- Collect and review subject diary
- Concomitant medications /procedures
- AE since last visit

4.8.1.5 6M (±2w), 9M (±2w), 12M (±2w), and 18M (±3w) Follow-up

- Weight
- Photography
- MMVS (by Blinded Evaluator and treating investigator)
- GAIS (by treating investigator and subject)
- Subject satisfaction questionnaire
- Concomitant medications /procedures
- AE since last visit
- Laboratory tests (Only performed at 12M)

4.8.1.6 24M (±4w) Final visit or Early termination

- Weight
- Photography
- MMVS (by Blinded Evaluator and treating investigator)
- GAIS (by treating investigator and subject)
- Subject satisfaction questionnaire
- Pregnancy test for childbearing potential women
- Concomitant medications/procedures
- AE since last visit
- Laboratory tests (Only performed at early termination if termination occurs before 12 months visit)
- Study termination

4.8.2 Visits for Control Group

4.8.2.1 Screening (D-21 to D1)

- Informed consent
- Demography (Initials, Date of birth, Gender and Ethnic origin)
- Screening laboratory tests (haematology and serum chemistry)
- Inclusion and exclusion criteria
- Pregnancy test for childbearing potential women
- MMVS (by Blinded Evaluator and treating investigator)
- Medical history/concurrent diseases including prior facial dermatological procedures performed, and fillers or implants used
- Concomitant medications/procedures
- AE during the visit

4.8.2.2 Baseline (D1)

- Height and Weight
- Medical history/concurrent diseases
- Vital signs (pulse rate, blood pressure, respiratory rate, body temperature)
- Inclusion and exclusion criteria
- Randomization
- Photography
- MMVS (by Blinded Evaluator and treating investigator)
- Concomitant medications /procedures
- AE since last visit

If screening and baseline visit occur on the same day, the following procedures for baseline will not be repeated.

- Medical history/concurrent diseases
- Inclusion and exclusion criteria
- MMVS (by Blinded Evaluator and treating investigator)
- Concomitant medications /procedures
- AE since last visit

4.8.2.3 6M (±2w), 9M (±2w) Follow-up

- Weight
- Photography
- MMVS (by Blinded Evaluator and treating investigator)
- GAIS (by treating investigator and subject)
- Concomitant medications /procedures
- AE since last visit

4.8.2.4 12M (±2w) Follow-up / Final visit or early termination

- Weight
- Photography

- MMVS (by Blinded Evaluator and treating investigator)
- GAIS (by treating investigator and subject)
- Concomitant medications /procedures
- AE since last visit
- Study termination

5 Subjects

5.1 Subject information and informed consent

The PI or his/her authorised designee must always use the IEC-approved subject information and Informed Consent Form and it must not be changed without prior discussion with the Sponsor and approval from the applicable IEC.

It is the responsibility of the PI or his/her authorised 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 IEC. 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 effect on 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 authorised designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and transferred to countries outside China. The data will not contain any information that can be used to identify any subject.

All 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 subject must meet the following criteria to be eligible for the study:

1. Signed and dated informed consent to participate in the study.
2. Men or women aged 18 years of age or older of Chinese origin.
3. Subjects seeking augmentation therapy for the midface.
4. MMVS score of 2, 3 or 4 on each side of the face as assessed by the blinded evaluator.

5.3 Exclusion Criteria

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

1. Known/previous allergy or hypersensitivity to any of the constituents of the product.
2. Known/previous allergy or hypersensitivity to local anaesthetics, e.g. lidocaine or other amide-type anaesthetics.
3. History of severe or multiple allergies, such as anaphylaxis.
4. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, ultrasound, cryotherapy, chemical peeling or dermabrasion in the area to be treated within 6 months before treatment.
5. Previous surgery (including aesthetic facial surgical therapy or liposuction), piercing or tattoo in the area to be treated.
6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent filler, autologous fat, lifting threads or permanent implant in the area to be treated.
7. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy in the area to be treated within 12 months before treatment.
8. Previous use of any neurotoxin below the level of the lower orbital rim on the face within 9 months before treatment.
9. Presence of any disease or lesions near or at the area to be treated, e.g.

   - Inflammation, active or chronic infection (e.g., in mouth, head and neck region);

   - Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes simplex or herpes zoster;

   - Scars or deformities;

   - Cancer or pre cancer (e.g. actinic keratosis).
10. History of cancer or radiation in the area to be treated.
11. Subjects with a dental or oral status on visual inspection that in the opinion of the Investigator would make the subject unsuitable for inclusion, or Subjects with dental, oral or sinus surgery within past 6 months prior to the treatment visit or planned surgery, including dental implants, during the study period.
12. History of or active collagen diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis or localized or systemic scleroderma.
13. Tendency to form keloids, hypertrophic scars, or any other healing disorder.
14. History of bleeding disorders or treatment with thrombolytics, anticoagulants or inhibitors of platelet aggregation (e.g. aspirin or other non-steroid anti-inflammatory drugs (NSAIDs), Omega-3, or vitamin E within a relevant period before treatment, per the investigator's judgment.

15. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic corticosteroids within 3 months before treatment (inhaled corticoids are allowed).
16. Treatment with topical (facial below the level of the lower orbital rim) retinoids or corticosteroids within 1 month, or systemic retinoids within 6 months before treatment.
17. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion.
18. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g. subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.
19. Women who are pregnant or breast feeding, or Woman of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period.
20. Subjects planning to accept any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim during the study (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency etc.).
21. The presence of moderate or severe abnormal rating for midface symmetry, i.e. more than 1 point difference in MMVS score between each side of the face.
22. Intention to change a significant amount of weight (≥2 BMI) during the study period.
23. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.
24. Participation in any other clinical study within 30 days before treatment.

5.4 Screening and Subject Numbers

Each screened subject will be assigned a screening number consisting of "S" and the site number followed by a consecutive number starting with 01 at each site, e.g. S101, S102.The screening number shall be listed on a subject screening and inclusion log.

A "screening failure" is defined as a subject who does not fulfil the eligibility criteria. For screening failures, the eCRF screening visit shall be completed to an extent that makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria. The reason for excluding a subject from entering the study shall also be specified in the subject screening and inclusion log.

When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each enrolled subject will be assigned a subject number by the eCRF. For group A, consisting of a capital letter A, the site number, then followed by a consecutive number starting with 001 at each site, e.g. A1001, A1002; for group B, consisting of the site number followed by a consecutive number starting with 001 at each site, e.g. 1001, 1002.

The subject number, subject name, and other information sufficient to link the eCRF to the medical records (e.g. national identification number, chart number, etc.) shall be recorded on a subject identification list. The subject identification list shall only be available at the site, both throughout and after the study.

5.5 Withdrawal of Subjects

Each subject shall be advised in the Informed Consent Form 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's discretion at any time.
The withdrawal criteria are:

- **Medical reasons**: If the subject suffers from a medical condition that in the judgement of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons shall document the specific condition for withdrawing the subject.
- **Withdrawal of informed consent:** 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 authorised 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, e.g. call three times at different hours and leave messages if applicable before declaring the subject lost to follow-up.
- **Other:** Examples of other reasons for withdrawal may be failure to comply with protocol requirements or to complete the protocol-specified evaluations.

The reason and date for withdrawal shall be documented in the eCRF. When possible, an explanatory comment shall be added in the study termination module/pages to further explain the reason for 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 together with the study termination eCRF module.

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. In these cases the eCRF for the early termination visit should be completed. The subject will need to follow the same requirements for the final visit.

If a subject is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses.

A withdrawn or discontinued subject must not be replaced or re-entered into the study.

If an AE which, according to the Investigator's assessment, is related to the use of the study product and is still ongoing at the time of the withdrawal, such events shall be followed-up after the last study visit until resolved, assessed as chronic or stable, or for at least three months.

6 Study Products

6.1 Investigational Product

Sculptra 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. This suspension contains microparticles of poly-L-lactic acid, a crystalline form of polylactic acid. Sculptra dry powder is supplied after aseptic filtration sterilisation in a sterile elongated clear glass vial. Each vial of dry powder contains: 150mg microparticles of poly-L-lactic acid (PLLA), 90mg sodium carboxymethylcellulose, 127.5mg non-pyrogenic mannitol.

6.2 Reference Product

Not applicable.

6.3 Additional Products and Materials

- Sterile water for injection
- 18G needles for reconstitution
- 5ml Plastic syringes for reconstitution
- 25G or 26G needles for injection
- 1ml or 2ml Plastic syringes for injection
- 2% Lidocaine HCl

6.4 Reconstitution instructions

Sculptra is reconstituted extemporaneously in the following way:

1). Remove the flip-off cap from the vial and clean the penetrable stopper of the vial with an antiseptic.

Please note that the following steps 2–5 should be performed to ascertain air pressure relief in the vial and to allow for sufficient head-space when shaking the vial to dissolve the content.

2). Attach an 18G sterile needle to a sterile single-use 5 mL syringe.

3). Draw 5 mL of sterile water for injection into the 5 mL syringe.

4). Introduce the 18G sterile needle into the stopper of the vial, find the open slit in the stopper and slowly add all sterile water for injection into the vial letting the water flow on to the inner wall of the vial. Remove the syringe and needle.

5). Shake the vial vigorously for about 1 minute to dissolve the excipients. Inspect the vial for any lumps, and if needed shake more. A translucent suspension with some foam on the top will be obtained.

6). Add 3 mL of additional sterile water for injection using the syringe and a new 18G needle. Remove the syringe and needle. Shake again in order to get a homogenous suspension.

Following reconstitution, Sculptra can be used immediately or may be stored for up to 72 hours prior to injection.

7). Product should be gently agitated immediately prior to use. Agitate the vial until a homogenous translucent suspension is obtained. A single vial swirling agitator may be used.

As it is a single use vial, discard any material remaining after use or after 72 hours following reconstitution.

8). Clean the penetrable stopper of the vial with an antiseptic, and use a new 18G sterile needle to withdraw an appropriate amount of the suspension into a single-use 1-2 mL sterile syringe. Tilt the vial horizontally and withdraw suspension from the lower lateral of the vial to avoid withdrawing foam. Do not store the reconstituted product in the syringe.

9). Replace the 18G needle with a 25G or 26G sterile needle before injecting the product into the deep dermis, subcutaneous layer or supraperiosteal layer. Do not inject Sculptra using needles of an internal diameter smaller than 26G.

10). To withdraw remaining contents of the vial, repeat steps 8 through 9. Do not inject the foam.

If desired for the purpose of providing pain relief during the injection procedure, after completion of step 6 of the Reconstitution instructions described above, add another 1 mL of 2% (20 mg/mL) lidocaine solution to the vial immediately prior to injection. Clean the penetrable stopper of the vial with an antiseptic, add the lidocaine solution and an 18G sterile needle and shake the suspension. Go to step 7 of the Reconstitution instructions described above and complete the procedure. It should be noted that the addition of lidocaine according to these instructions will lead to a final vial volume of 9 mL with a lidocaine concentration of 2.2 mg/mL.

6.5 Packaging, Labelling and Storage

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

The vials are labelled with name of the product, name of the manufacturer (Q-Med AB) and are packed in cartons. Each carton of Sculptra contains only one vial. The carton will be labelled in local language, specifying the protocol number, lot number, expiry date and that the product is to be used for clinical studies exclusively.

Sculptra powder should be stored at room temperature away from heat (maximum 30°C). Upon reconstitution, Sculptra can be stored up to 72 hours at refrigeration (2–8°C) or room temperature up to 30°C.

Do not freeze.

After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local requirements.

6.6 Product accountability

The study product will be released to the PI or his/her authorised designee after study approvals have been received from the IEC and the CTA has been signed by all parties.

The PI must ensure that the study product is kept in a secure location, with access limited to those authorised by the PI.

The study product must be traceable from the manufacturer to its use in subjects until return or disposal. It is therefore important that the PI maintains accurate product accountability records, i.e. documentation of the physical location of all study product, deliveries, and return of study product between the Sponsor or a third-party vendor and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all study products received from the Sponsor; including the product name, date received, batch number, expiration date, and amount received. In addition, dispensing logs shall be maintained including the product name, dispense date, the number of syringes used, the number of syringes left in stock, and the subject receiving study product. A log for accountability procedure is provided by the Sponsor.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor or a third-party vendor for destruction. Any malfunctioning study products shall be reported as described in Section 8.5.3.

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

6.7 Treatment

6.7.1 Treatment Procedure

Before treatment with Sculptra, the patient should be informed completely of the indications, contraindications, warnings, and precautions for use, possible side effects and mode of administration of Sculptra.

Make sure to work under aseptic and hygienic conditions. Clean the injection site with an antiseptic. Local anesthetics (topical, infiltrative, or regional blocks) before the treatment will be used at the discretion of the treating Investigator.

The subject should not wear make-up on the day of treatment, if make-up was already applied this must be completely removed prior to any injection.

Sculptra dry powder will be reconstituted with 8 mL of sterile water for injection to form a sterile nonpyrogenic suspension. As an optional means to provide pain relief during the injection procedure, an additional 1 mL of sterile 2% (20 mg/mL) lidocaine solution may be added to the vial of reconstituted product prior to injection for a final volume of 9 mL.

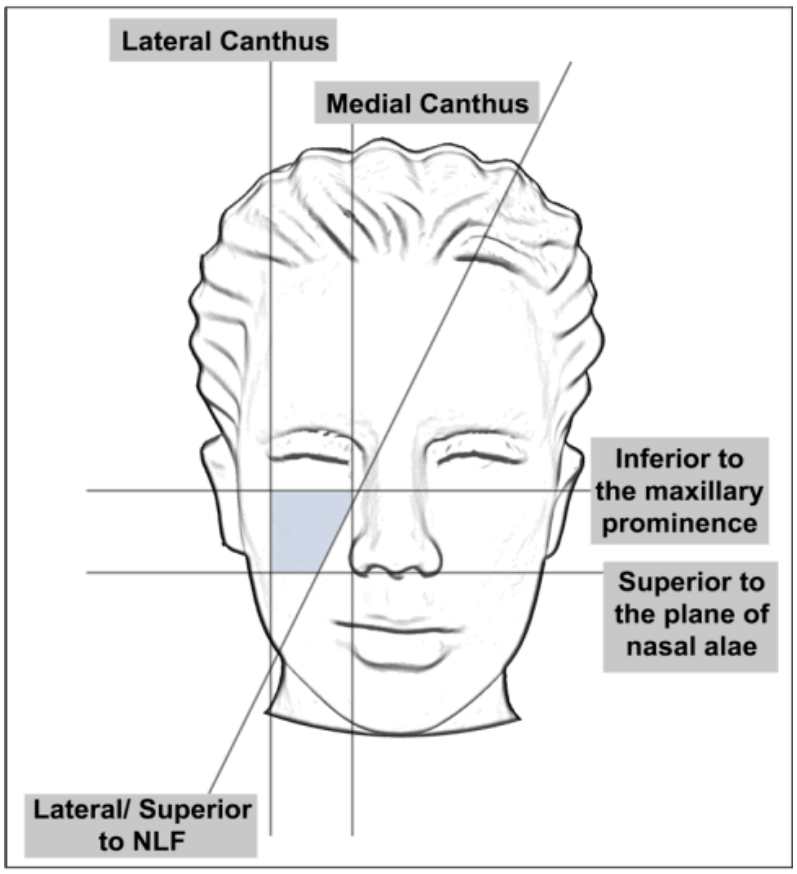
Scuptra should be injected into the deep dermis, subcutaneous layer or supraperiosteal layer with a 25G or 26 G needle. To avoid breakage of the needle, do not attempt to bend it before or during treatment. If the needle gets bent, discard it and complete the procedure with a replacement needle.

Sculptra will be administered inferior to the maxillary prominence, superior to the plane of nasal alae, including the area from the lateral canthus to the medial canthus and lateral to the nose on the subject's right and left sides (Figure 2). When appropriate, the study product

is injected into the lateral and inferior adjacent area to ensure a smooth transition of midface contour.

To maintain a homogeneous suspension throughout the procedure, intermittently, agitate the product in the syringe. Before initial injection, expel a few drops of the product through the attached needle to eliminate air and to check for needle blockage. If the needle becomes occluded or dull during an injection session, replacement may be necessary. If clogging occurs, remove the needle, expel a small amount of product, attach a new sterile needle, then expel a few drops of Sculptra to eliminate the air and re-check for needle blockage.

Figure 2. Treatment Area



6.7.2 Treatment regimen (dose)

Each subject will receive up to 4 injection sessions with 5(±1) weeks intervals. Study treatment injections should be stopped if optimal midface augmentation has been obtained or a maximum of 4 injection sessions completed. Optimal midface augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the treating investigator and subject.

1 vial is generally recommended at each treatment session, i.e., initial treatment or each optional treatment respectively. Maximum 2 vials can be used for each treatment session at the discretion of the investigator.

6.7.3 Post-treatment Care

After the injection session, ice (in a suitable cloth, avoiding any direct contact with the skin) should be applied to the treatment area in order to reduce swelling and/or bruising.

It is important to thoroughly massage the treated area(s) to evenly distribute the product (use of an appropriate cream may help to reduce the friction on the skin surface during massaging).

The patient must avoid exposing the treated area to heat (sun bathing, sauna, steam baths, etc.), ultraviolet or extreme cold least until any initial swelling and erythema has resolved.

6.7.4 Post-trial provisions

After the study is finalised Q-Med AB will not supply any more treatments to the subjects, even if the result does not persist.

6.7.5 Electronic case report form recordings

The following details of each injection are to be recorded in the eCRF:

- Date for administration
- Lot number
- Whether 2% Lidocaine added.
- Local anaesthetic used (product name, volume injected/amount applied, and concentration)
- Administered volume per side
- Injection technique per side
- Depth of injection per side
- Post-treatment care (massage, ice pack, etc)

In addition, any technical problems (device deficiencies) or clinical complications (AEs) associated with the injection will be recorded in the eCRF.

6.7.6 Treatment compliance

The treatment is an implant administered by the Treating Investigator and the details of the administration are recorded in the eCRF. No other measurements of treatment compliance will be made.

7 Effectiveness Assessments

7.1 General information

The methods for collecting effectiveness data include assessment of MMVS [9](Section 7.3), 3D digital imaging analysis (section 7.4), GAIS (Section 7.5), and Subject satisfaction questionnaire (Section 7.6).
Assessments will be performed by the subjects, the treating Investigator, and the blinded evaluator, as described in the respective section. To avoid inter-observer variability, every

effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations.

7.2 Photography

Digital photographs will be taken of each subject pre-treatment at visits when treatment is performed and at each follow-up visit. Standardized 3D photographs will be achieved for effectiveness assessment. 2D photographs will be used to document condition at baseline, for GAIS evaluation and to document AEs in the treated area. If necessary, the photo should be taken when AEs occur.

Photographs will be taken in a standardized way according to the instructions for image procedures. The subject shall have a neutral facial expression and no covering make-up should be used on the photographs.

Each Investigator and other study site personnel designated to take photographs, if applicable, shall be thoroughly trained in the equipment and techniques, and how to upload photographs to the secured web portal, if applicable, before study start. The same photographic equipment and standardized setting must be used at each visit (e.g., distance, light, facial position and expression). For further details, please see the instruction of image procedures in the photo user guide.

7.3 Medicis Midface Volume Scale (MMVS)

MMVS is a Four-Point scale assesses the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4) as described below. A validation study concluded that the accuracy of this assessment tool was acceptable for use in assessing correction of midface volume loss and/or contour deficiency[29]. The blinded evaluator will rate the subject's right and left midface for severity of volume deficiency using the MMVS at screening, baseline, 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at screening, baseline 6, 9 and 12 months in Control Group. The treating investigator will do the MMVS evaluation at all visits in each group. The blinded evaluator and treating investigator will conduct their MMVS assessments using a photographic scale (Appendix 2).

Table 3. Medicis Midface Volume Scale

MMVS	
1	Fairly full midface; cheek prominence projected beyond the infraorbital rim at 45-degree view.
2	Mild loss of fullness in midface area; flatness of midface; cheek prominence at or behind infraorbital rim. May have slight presence of tear trough but not extending past mideye. Can start to see minimum volume loss of anterior cheek.
3	Moderate loss of fullness with slight hollowing below malar prominence; presence of the nasojugal groove extending past mideye.
4	Substantial loss of fullness in the midface area, clearly apparent hollowing below malar prominence; evidenced by significant indentation in the midface area.

7.4 3D Digital Imaging analysis

The measurement of volume change in the midface (right and left combined) from baseline will be calculated by 3D digital image analysis at 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at 6, 9 and 12 months in Control Group.

7.5 Global Aesthetic Improvement Scale (GAIS)

The 5-graded Global Aesthetic Improvement Scale (GAIS) will be used to assess the aesthetic improvement of the midface fullness of both sides of the live subject as compared to photographs taken before treatment. Each midface side will be rated separately. The treating investigator and the subject will, independently of each other, respond to the question: "How would you describe the aesthetic improvement of the midface fullness for each side today compared to the photos taken before treatment?" GAIS will be assessed by treating investigator and subjects at each follow up visit.

Table 4. Global Aesthetic Improvement Scale

Rating	Definition (for treating investigator)
Very much improved	Optimal cosmetic result for the implant in this subject.
Much improved	Marked improvement in appearance from the original condition, but not completely optimal for this subject.
Improved	Obvious improvement in appearance from the original condition.
No change	The appearance is essentially the same as original condition.
Worse	The appearance is worse than the original condition.

7.6 Subject satisfaction questionnaire

Subjects will be asked about their satisfaction with the treatment outcome using a questionnaire at 6, 9, 12, 18 and 24 months in Group A and Treatment Group.

1). Do you think your Cheek Volume Deficit and/or Contour Deficiency has been improved with the treatment?

☐ Yes

☐ No

2). Do you think that the overall result of the treatment looks natural?

☐ Yes

☐ No

3). Would you say that the study treatment?

☐ Surpass your expectations

☐ Meet your expectations

☐ Do not meet your expectations

☐ You did not have any specific expectations before the injections

4). Do you think that the treatment brings you more?

(tick all boxes that apply)

☐ Youth

☐ Beauty

☐ Harmony

☐ Symmetrical appearance

☐ Pep/Liveliness/Freshened look

☐ Self esteem /confidence

5). Would you say that you feel more attractive?

☐ Yes

☐ No

6). How do you feel about yourself since the treatment was performed?

☐ Very much better

☐ Much better

☐ Somewhat better

☐ The Same

☐ Worse; if worse, please explain why:

7). Overall, how satisfied are you with the treatment result?

☐ Very satisfied

☐ Satisfied

☐ Somewhat satisfied

☐ Not satisfied

8). Did you get any feedback about your look from your family, friends, colleagues?

☐ Positive feedback

☐ Negative feedback

☐ No feedback

9). Would you recommend this treatment to friends?

☐ Yes

☐ No

10). Would you do like to receive the same treatment again?

☐ Yes, exactly the same

☐ No ; if no, please explain why_____.

8 Safety Assessments

8.1 Anticipated injection related reactions

The subjects of for Group A and Treatment Group will evaluate anticipated injection related reactions, i.e. pain, tenderness, localized redness, bruising, hematoma and edema, which generally resolve within 2-6 days. The subject will be instructed by the Investigator to record pain, tenderness, localized redness, bruising, hematoma, edema and other daily for evaluation of these events in 4-week diaries after each treatment session. The presence and maximum intensity of the symptoms will be recorded for the treated area (table 5). The treating Investigator will review the diary at the next visit after each treatment and if necessary, appropriate intervention (treatment or procedure) will be carried out at the discretion of the Investigator. If required, the Investigator can also decide that the subject's participation in the study should be terminated.

Table 5. Grading for pain, tenderness, localized redness, bruising, hematoma, edema and other, in the subject diary

None	
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)

8.2 Laboratory assessment

Laboratory samples for Haematology and Serum chemistry assessment will be taken at the screening visit (day -21 to day 1) for all subjects. In Group A and Treatment Group, it will also be taken at 12 months visit or at early termination if termination occurs before 12 months visit.

The following laboratory assessments will be performed:

- Haematology: haemoglobin, red blood cells, white blood cells, differential count and platelet count.
- Serum chemistry: renal function tests (creatinine and BUN); and liver function tests (aspartate amino transferase (ASAT), alanine amino transferase (ALAT) total bilirubin, direct bilirubin and indirect bilirubin).

Pregnancy test (Urine HCG) will be performed at screening, all injection visits (prior to treatment and the study completion/early termination for Group A and Treatment Group, and at screening for Control group, in all women of childbearing potential, including those currently using contraception. The test result must be negative for the subject to receive any treatment with study product.

Other laboratory test might be performed at the discretion of the investigator. All laboratory assays will be performed at a local laboratory. Reference ranges will be supplied by the

laboratory and used by the Investigator to assess the laboratory data for clinical significance and out of range pathological changes.

The results of the hematology and serum chemistry will only be used for safety assessment by investigator and will not be collected in the eCRF. The pregnancy test for women of childbearing potential will be recorded in the eCRF.

8.3 Adverse Events

8.3.1 Definition of Adverse Events

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*, whether or not related to the study product.

This definition includes:

- events related to the investigational product or the reference product
- events related to the procedures involved

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

8.3.2 Definition of 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** illness or injury, or
2. a permanent impairment of a body structure or body function, or
3. in-patient or prolonged hospitalisation***, 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 foetal distress, foetal 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 8.4.4).

**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).

*** Planned hospitalisation 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).

8.3.3 Recording Instructions

AE will begin to be collected after ICF signed. Each subject will be questioned about AEs at each clinical visit following the screening visit. The question asked will 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 by the study personnel, subject diaries or spontaneous reports from the subjects.

The Investigator will assess the presence of any papules (<5mm in diameter) or nodules (≥5mm in diameter). If present, the papules/nodules will be recorded as AE and should be further assessed as visible/non-visible and inflammatory/non-inflammatory.

When an AE is related to a device deficiency (refer to section 8.4), including technical device malfunction, the AE shall be recorded on the AE module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form.

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

- Event term (recorded in standard medical terminology and avoiding abbreviations),
- Description of event and affected area (if applicable),
- Start date (First day with symptoms)
- Stop date (Last day with symptoms)
- Intensity (mild, moderate or severe according to definition in section 8.3.3.1)
- Seriousness (serious or not serious, according to definition in section 8.3.2)
- Causal relationship to study product and study product injection procedure (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment or other procedures/ tests, subject withdrawn)
- Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at study end)

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

8.3.3.1 Intensity

For each reported AE, the intensity will be recorded. The following definitions of intensity are to be used:

Mild:	A mild AE means awareness of symptoms or signs, but easily tolerated (acceptable).
Moderate:	A moderate AE means enough discomfort to interfere with usual activity (disturbing).
Severe:	A severe AE means incapacity to work or to do usual activity (unacceptable).

If the intensity changes over time the maximum intensity of the AE should be recorded.

8.3.3.2 Causal Relationship and Seriousness

Each AE, serious as well as non-serious, will 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) will be used for 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.

8.3.4 Reporting of Adverse Events

AE reporting on each subject will start after the ICF has been signed. The reporting will 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.

8.3.5 Reporting of Serious Adverse Events

After becoming aware of any SAE, the Investigator shall report it to his/her administrative department of medical device clinical trials under the clinical trial institution, which in turn shall notify the Sponsor Representative in writing. This initial report can be made via fax or 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
- Subject identification (age, gender, subject number)
- AE description
- date when AE occurred
- date when AE became serious
- Name of PI and original reporter (if other than Investigator)
- Name of study product
- Treatment specification

The Investigator will assure completeness of the SAE information and the supporting documentation.

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the Sponsor via Sponsor's representative 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 Medication Form/list
- Concomitant Procedure/Treatment Form/list
- AE Form/list
- Medical History Form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

Fax number for SAE reporting:	+46 18 474 91 01
E-mail for SAE reporting:	safety.q-med@galderma.com
Surface mail for providing complementary information:	Q-Med AB Attn. Corporate Medical Affairs & Vigilance Seminariegatan 21 SE-752 28 UPPSALA, Sweden
E-mail for Device deficiency, Clinical Study Complaint Form:_	Complaints.q-med@galderma.com

E-mail address will be pre-programmed in the eCRF system.

For non-urgent complementary information not possible to send by e-mail or fax, please use surface mail.

The SAE form (NMPA template in Chinese) 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 or faxed to the Sponsor (contact details refer to 24-hour contact person list in ISF). A copy of the fully completed SAE form shall be kept at the site.

In addition, according to national regulations, the investigator will report a SAE Form (NMPA SAE template) to the administrative department of medical device clinical trials in his/her hospital, and they should, within 24 hours, deliver a written report to the corresponding Ethics Committee and the local food and drug administrative department of province, autonomous region and municipality at the place where the clinical trial institution locates. In case of a death incident, the clinical trial institutions and investigators should furnish the Ethics Committee and the Sponsor Representative with all required materials.

The Sponsor Representative is responsible for, within five (5) business days upon being informed, reporting any SAE or device defect with the likelihood of SAE to Shanghai Municipal FDA and Shanghai Municipal Health Commission by fax or mail. The relevant correspondence will be documented in TMF; meanwhile, the Sponsor Representative should notify other clinical trial institutions and investigators participating in the study, and promptly report it to

the Ethics Committee of the involved clinical trial institutions via the administrative department of medical device clinical trials according to national regulations.

8.3.6 Follow-up of Unresolved Events after study termination and new Events after study termination.

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 for at least three months. Final outcome after study end should be reported on a paper AE form.

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure with onset after subject participation in the study has ended shall be collected and reported to Sponsor on a paper AE form or in the post marketing AE form or SAE paper form if applicable. The events shall thereafter be followed up until resolved or considered chronic or stable, or for at least three months. Final outcome shall be reported on the AE follow up form or in the post marketing AE form. The Investigator shall report any such AE or SAE including all previous Adverse events reported during the study and medical history of the patient to the Sponsor immediately but not later than 24 hours of awareness of the event. This report can be made via fax or e-mail according to contact details specified in section 8.3.5.

8.3.7 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period the subject must continue to be followed within the study and the outcome of pregnancy must be reported even if the expected date of 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 8.3.5. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to foetal distress, foetal 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 hospitalisation, shall be reported and handled as SAEs. Elective abortions without complications will not be reported as AEs.

8.3.8 Anticipated Adverse Events

Information regarding anticipated AEs below is also included in the Sculptra Investigators Brochure.
Subcutaneous papules/, invisible but palpable or visible nodules including periorbital nodules, or areas of induration have been noted in the injection area. Nodules are occasionally

associated with inflammation or discolouration. The early occurrence of subcutaneous nodules at the injection site (within 3–6 weeks after treatment) may be minimised by adhering to proper dilution and injection techniques. Delayed occurrences of subcutaneous nodules at the injection site (within 1–14 months post injection) have been reported with sometimes a prolonged duration of up to 2 years. Improper injection techniques such as superficial placement, excessive amount of product or incorrect reconstitution may lead to appearance of papules or nodules at the injection site. Massaging the treatment area to ensure proper distribution of the product may minimise the appearance of such papules or nodules.

For nodular areas or late granuloma formation, in some cases, they resolved spontaneously or following treatment with multiple intralesional injections of corticosteroids and/or antineoplastic agents (e.g. 5-fluorouracil). Surgical excision of the nodules was sometimes required when they were larger in size, occurring in difficult anatomical regions (e.g. lower eyelid) or persisting after other treatments.

This product must not be injected intramuscularly or intravascularly. Localised superficial necrosis and scarring may occur after injection in or near vessels. It is thought to result from the injury, obstruction, or compromise of blood vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area. Areas with limited collateral blood flow has an increased risk of ischaemia. Aspiration prior to injection is recommended.

Unintentional introduction of soft tissue fillers into the vasculature in the face may lead to embolisation, occlusion of the vessels, ischaemia, necrosis or infarction at the implant site or in the area supplied by the blood vessels affected. Rare but serious adverse events include temporary or permanent vision impairment, blindness, cerebral ischaemia or cerebral haemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if any of the following symptoms occurs, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist, should an intravascular injection occur.

8.4 Device Deficiencies

8.4.1 Definition of Device Deficiency

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

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

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

8.4.2 Recording Instructions

When a device deficiency is discovered the Clinical Study Complaint Form in the eCRF will be completed by the Investigator. 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 module or a SAE Form should be completed following instructions in section 8.3. 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

The Sponsor will also make the same assessment in the Clinical Study Complaint Form.

8.4.3 Reporting Device Deficiency

The Investigator will complete the Clinical Study Complaint Form to the Sponsor using the contact details specified in section 8.3.5. A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported within 24 hours after the Investigator's awareness in accordance to section 8.3.5.

In order to fulfil regulatory reporting requirements, all deficiencies with the study product must be assessed by both the Investigator and the Sponsor to determine if it could have led to a SAE.

If an SAE has resulted from a device deficiency or if either the Investigator or the Sponsor assesses that the device deficiency could have led to an SAE the event will be reported in accordance with Regulatory requirements, as applicable.

The deficient study product shall be kept, if applicable, by the study site until the QA complaints group 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 handling eCRFs, database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the CSP. Data validation will be performed by computerised 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) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked.

Study data will be transferred to SAS datasets which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

9.2 Electronic case report forms

An eCRF is required and shall be completed electronically for each screened subject (screening visit) and included 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 will be transcribed directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorised study site personnel designated by the PI shall complete data collection. Appropriate training and security measures shall be completed with all authorised study 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 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 in a signature and delegation log.

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 within 5 working days 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 by 100%. 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 authorised 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 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 authorised designee. The appropriate study site

personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged.

9.2.3 User identification

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. 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 User ID 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

The eCRF is essentially considered a data entry form and does not constitute the original (or source) medical records unless otherwise specified. 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 photographs, memoranda, material dispensing records, subject files, etc.

The PI is responsible for maintaining source documents. These shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as photographs, should be clearly identified with the 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 and IEC review 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 should 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 should 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 shall 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.

The source data location log specifies what data that should be available in the medical record. The source data location log should also specify the data for which the eCRF serves as the source. Such data only need to be recorded in the eCRF and are typically associated with study-specific procedures and not with normal clinical care practice. For this type of study data the Investigator would not be expected to duplicate the information into the medical record.

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 after study completion according to national legislation and the CTA. Sponsor will inform the sites as to when these documents no longer needs to be retained. Measures should be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorised access, preferably by storage in a fire-proof cabinet). Refer to the CTA.

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 Q-Med AB 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 written and finalized prior to database lock (DBL). All summaries for Group A and B will be done separately. For Group A, only descriptive statistics will be used. All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9.4 or later).

Continuous variables will be summarised using standard statistical measures, such as mean, median, standard deviation, minimum and maximum values. Categorical variables will be presented in frequency tables with number and percent of observations for each level.

All confidence intervals will be two-sided and use the 95% confidence level. All statistical testing will be two-sided and performed at a significance level of 5%.

10.2 Analysis Populations

The following populations will be defined:

- Safety — Includes all subjects in Group B who were treated with Sculptra or randomized to no-treatment group. Subjects are analyzed based on the as treated principle.
- Full Analysis Set (FAS) — Includes all subjects in Group B who were treated with Sculptra or randomized to no-treatment group. Subjects are analyzed according to the randomisation assignment.

- Per Protocol (PP) — Includes all subjects in FAS that comply to the protocol procedures with no deviations that can affect the evaluation of the primary variable.

The FAS population is the primary population for all effectiveness analyses. All safety analyses will be based on the Safety population.

For Group A, all analyses will be performed based on all subjects.

10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints and subject characteristics will be presented by study product using descriptive statistics.

10.4 Effectiveness Analysis

Primary analysis

The percentage of responders (a responder will be defined as a subject with at least 1 point improvement from baseline MMVS on both sides of the face concurrently) will be calculated at 12 months both in Treatment Group (denoted as $\pi_{12M\ Sculptra}$) and Control Group (denoted as $\pi_{12M\ Control}$) based on the blinded evaluator's assessment. The null hypothesis H_0: $\pi_{12M\ Sculptra} = \pi_{12M\ Control}$ will be tested against the alternative hypothesis H_1: $\pi_{12M\ Sculptra} \neq \pi_{12M\ Control}$ by using a Fisher's exact test at a significance level of 5%. In addition, for each group the two-sided 95% confidence intervals around the estimates of the percentage of responders will also be calculated. The treatment will be deemed a success if the p-value for the treatment difference on the primary endpoint is less than 0.05 (i.e. the proportion of responders is statistically significantly larger in the Treatment Group compared to the Control Group).

Secondary analysis

The percentage of responders based on the MMVS on both sides of the face concurrently will also be derived at all applicable follow-up visits for both the blinded evaluator's assessment and the treating investigator's assessment respectively. The response rates and their 95% confidence interval will be presented by visit and group.

Fisher's exact test will be used to compare the response rates in the Treatment group versus the Control group based on the blinded evaluator's assessment and the treating investigator's assessment respectively. In other words, the null hypothesis H_0: $\pi_{t,Sculptra} = \pi_{t,\ Control}$ will be tested against the alternative hypothesis H_1: $\pi_{t,Sculptra} \neq \pi_{t,\ Control}$ for each of the timepoints t = Month 6 and Month 9 for the blinded evaluator's assessment, and t = Month 6, Month 9 and Month 12 for the treating investigator's assessment.

The volume change in the midface area as compared with baseline (right and left sides combined) obtained by 3D imaging will be presented descriptively by treatment for all applicable follow-up visits.

GAIS (by treating investigator and subject) and satisfaction with the treatment outcome will be analyzed descriptively.

10.5 Safety Analysis

Number and percentage of subjects reporting anticipated injection related reactions, as collected in diaries will be presented in total and by maximum intensity. A graph will be generated to illustrate the incidence over time. Number of days with the event will be summarized using mean, SD, min, max and median.

All AEs will be coded according to MedDRA.

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

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

Related AEs as well as number of subjects with related AEs will be summarised by SOC, PT and intensity and by treatment. In addition, for related AEs the number of days to onset and the duration of event will be summarised by SOC and PT and treatment using mean, SD, min, max and median. Action taken for related AEs will also be summarized.

Serious AEs will be listed.

Non- related AEs will be summarised by SOC, PT, and intensity and by treatment.

10.6 Handling of Missing Data

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

Different assumptions regarding the missing data will be used. For the primary effectiveness analysis, missing values in the FAS will be assumed to be missing due to lack of effect. Therefore missing data up to the Month 12 visit will be imputed using the baseline observation carried forward (BOCF) method. As an alternative approach, missing data will be assumed to be unrelated to treatment effect. To impute data under this assumption, missing data up to the Month 12 visit will be imputed using the hot deck method. More details will be given in the SAP. Both of these alternatives will estimate the effectiveness of the treatment policy (irrespective of use of unallowed treatments, procedures, or medications) rather than the true, clinical treatment effect.

To obtain an estimate of the true, clinical treatment effect, the primary effectiveness analysis will be performed using the PP population.

All other endpoints will be analysed on available data, i.e. no imputations will be done.

10.7 Interim Analysis

An interim analysis will be performed when the month 12 visit completed for all the subjects.

10.8 Data monitoring committee

Not applicable for this study.

10.9 Withdrawals and deviations

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

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

Deviations from the statistical plan will be documented in protocol Deviation log.

10.10 Sample Size

There are no available clinical data for Sculptra studied under conditions similar to the current study. However, based on what is seen in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a response rate of at least 60% in the Sculptra Treatment Group at Month 12. For the no treatment Control Group, response rate of 25.8% has been observed in an ongoing clinical trial in China. Based on this, it was assumed that the response rate will be maximum 30% in the no-treatment Control Group at Month 12.

With a sample size of 100 subjects treated with Sculptra and 50 subjects in the no-treatment control group, Fisher's Exact test will have approximately 90% power to detect difference between the anticipated percentage of responders at a 5% significance level (two-sided). To account for 20% drop-outs, approximately 126 will be randomized to the Sculptra group and approximately 63 to the control group.

11 Protection 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.

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the PI are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and the PI are located. The Sponsor will ensure that all requirements are complied with for data processing, which is carried out in Sweden by the Sponsor.

The Informed Consent Form shall contain information about what personal data to be collected in the study and that this will be kept confidential. The provided information shall be sufficient to enable all subjects to give their consent not only to the participation in the study, but also to the processing of personal data. Such information includes information regarding the purposes of the collecting, processing, data transfer to countries outside China, and the length of time during which personal data will be stored. The subject shall have the right of access to stored personal data, and the right to correction of incorrect information. If a subject decides to terminate the study prematurely, data collected before withdraw of consent will be used in the evaluation of the study, however no new data may be collected. Authorised representatives from the Sponsor or a RA may visit the study site to perform

audits/inspections, including source data verification, i.e. comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

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 CSP, subsequent amendment(s), GCP and the applicable regulatory requirements.

Any CSP deviation shall be reported in the eCRF, which shall be verified, discussed, and collected, by the monitor and appropriate corrective and preventive actions shall be taken. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor as well as the IEC if required by national regulations. Deviations shall be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations shall be performed as described in the monitoring manual.

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. The CV shall give name, date and place of birth, address and place of work, and shall show the training, appointments and, for the PI, any other information that confirms the suitability of the PI to be responsible for 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 study protocol

The PI and other site personnel involved in the study must not implement any deviation from or changes to the CSP without agreement with the Sponsor and prior review and documented approval from the IEC, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a written protocol amendment. However, administrative changes are to be documented in the Sponsor file without requiring a protocol amendment.

13 Financing, Indemnification, and Insurance

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

14 Publication Policy

The PI's, institutions, 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 multicentre 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*. 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 should 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.

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

15 Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IEC or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons.
The Sponsor may also decide to close a single study site due to unsatisfactory subject enrolment or non-compliance with the CSP, 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

16 References

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17 Appendices

Appendix 1 Declaration of Helsinki

Appendix 2 Photo guide for MMVS

Appendix 1
Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician

or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In

addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

Appendix 1
Declaration of Helsinki

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

Appendix 1
Declaration of Helsinki

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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Appendix 2
Photo guide for MMVS

SIGNATURES PAGE

Date	Signed by
2019-06-19 10:26	[redacted]
Justification	Approved by Technical Expert

2019-06-19 10:58	[redacted]
Justification	Approved by Technical Expert

2019-06-19 11:50	[redacted]
Justification	Approved by Owner

2019-06-20 00:56	[redacted]
Justification	Approved by Project Manager