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## Open label Extension study

*for 43USSA1812 (A randomized, evaluator-blinded, no-treatment controlled, multi-center study to evaluate the effectiveness and safety of Sculptra Aesthetic for correction of cheek wrinkles)*

Study product: *Sculptra<sup>®</sup> Aesthetic*

Clinical trial number (CTN): 43USSA1812ext

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### Study Administrative Structure

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



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### Sponsor Signatures

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

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## Synopsis

<b>Title of study</b>	Open label Extension study for 43USSA1812 (A randomized, evaluator-blinded, multi-center study to evaluate the safety and effectiveness of Sculptra Aesthetic for correction of cheek wrinkles)
<b>Clinical Trial Number</b>	43USSA1812ext
<b>Countries involved</b>	United States
<b>Number of sites</b>	All 13 sites which participated in the pivotal study 43USSA1812 will be invited to participate in the extension study.
<b>Number of subjects</b>	Approximately 150 subjects will be enrolled in study 43USSA1812 and followed for 12 months. Subjects completing the Month 12 visit in the pivotal 43USSA1812 study will be asked to participate in the 12-month extension of the study (i.e. Month 12 to Month 24). Therefore, approximately 150 subjects will be enrolled in the extension study.
<b>Study Design</b>	<p>This is a 12-month extension of the 12-month prospective, randomized, evaluator- blinded, no-treatment controlled study 43USSA1812. Subjects will be asked to provide written informed consent for participation in the extension study.</p> <p>Subjects originally randomized to Control Group (approximately 50 subjects) at baseline in the pivotal 43USSA1812 study will be offered treatment with <i>Sculptra Aesthetic</i> in the extension study. This group will be designated as Group A in this protocol. Subjects originally randomized to Treatment Group (approximately 100 subjects) at baseline in the pivotal 43USSA1812 study will be continued to be followed up during the extension study without further treatment. This group will be designated as Group B in this protocol.</p> <p>Safety and effectiveness data will be collected for up to 12 months in both groups. In all, subjects will be followed for 24 months after baseline in pivotal study 43USSA1812.</p> <p><i>Note: One month is defined as 4 weeks in the study.</i></p>
<b>Effectiveness Objective and Endpoints</b>	<p>To evaluate the effectiveness of <i>Sculptra Aesthetic</i> in the correction of cheek wrinkles</p> <p><u>Effectiveness endpoints include:</u></p> <ul style="list-style-type: none"> <li>Responder rate, using the Galderma Cheek Wrinkle Scale (GCWS) [REDACTED] as assessed live by the Blinded Evaluator, at Months 19, 21 and 24.</li> </ul> <p><i>A responder is defined as a subject with at least 1 grade improvement from pre-treatment on both cheek concurrently.</i></p> <ul style="list-style-type: none"> <li>Responder rate, using the Galderma Cheek Wrinkle Scale (GCWS) [REDACTED], as assessed live by the Blinded Evaluator, at Months 19, 21 and 24.</li> <li>Percentage of subjects having at least “Improved” according to the Global Aesthetic Improvement Scale (GAIS) on both sides of the face combined, as</li> </ul>

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	<p>assessed live by the subject and the Treating Investigator separately at all visits following Month 12 in pivotal study 43USSA1812.</p> <ul style="list-style-type: none"> <li>Percentage of subjects responding in each response category for each question in the subject satisfaction questionnaire at all visits following Month 12 in pivotal study 43USSA1812.</li> <li>Change from pre-treatment in subject satisfaction using the Satisfaction with Cheeks FACE-Q questionnaire with Outcome Rasch transformed total scores as well as proportion of subjects in each response category for each of the individual questions at all visits following Month 12 in pivotal study 43USSA1812.</li> </ul> <p><u>Note:</u></p> <p><i>Pre-treatment = Month 12 (pre-treatment) for Group A subjects (those originally randomized to the Control Group in pivotal study 43USSA1812).</i></p> <p><i>Pre-treatment = Day 1 for Group B subjects (those originally randomized to the Treatment Group in pivotal study 43USSA1812).</i></p> <ul style="list-style-type: none"> <li>Time to return to social engagement after treatment using subject diaries for 28 days after each treatment.</li> </ul>
<b>Safety Objective and Endpoint</b>	<p>To evaluate the safety of <i>Sculptra Aesthetic</i> in the treatment of cheek wrinkles. Safety endpoints include:</p> <ul style="list-style-type: none"> <li>Incidence, intensity, time to onset and duration of adverse events collected throughout the study period.</li> <li>Incidence, intensity and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days following each treatment.</li> <li>Safety assessment by a qualified staff member at all visits according to predefined methods: <ul style="list-style-type: none"> <li>Cheek firmness, symmetry and function</li> <li>Device palpability (pre-treatment assessment excluded for subjects receiving treatment in extension study)</li> <li>Mass formation</li> <li>Cheek sensation</li> <li>Visual function assessments (Group A subjects only)</li> </ul> </li> </ul>
<b>Subject Participation</b>	<p>Subjects who participated in the pivotal study may be involved in the extension of the study for approximately 48 weeks from the 43USSA1812 Month 12 Visit) to the final follow-up visit.</p>
<b>Enrollment</b>	<p>Written informed consent will be obtained before any study related procedure is performed.</p>

<b>Inclusion criteria</b>	<p>The subjects must meet the following criteria to be eligible for the extension of the study:</p> <ol style="list-style-type: none"> <li>1. Subject completed Month 12 of study 43USSA1812</li> <li>2. Subjects willing to comply with the requirements of the extension of the study and providing a signed written informed consent.</li> </ol> <p>For subjects eligible for treatment in the extension study:</p> <ol style="list-style-type: none"> <li>3. Female subjects who are exempt from birth control requirements must be postmenopausal for at least 1 year; if the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test at the extension study entry visit and prior to all injection visits. Acceptable forms of effective birth control methods include: <ul style="list-style-type: none"> <li>• Combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 28 days prior to enrollment</li> <li>• Hormonal or copper intrauterine device (IUD) inserted at least 28 days prior to Enrollment</li> <li>• Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository</li> <li>• Bilateral tubal ligation prior to Enrollment</li> <li>• Vasectomized partner (in monogamous relationships) for at least 3 months prior to Enrollment</li> <li>• Strict abstinence (at least one month prior to enrollment and agrees to continue for the duration of the study or use acceptable form of birth control).</li> </ul> </li> </ol>
<b>Exclusion criteria</b>	<p>For subjects eligible for treatment in the extension study, the exclusion criteria for study 43USSA1812 applies. The presence of any of the exclusion criteria noted in <a href="#">Section 5.3</a> will exclude a subject from treatment in the extension study.</p>
<b>Investigational product</b>	<p><i>Sculptra Aesthetic</i> is a sterile, freeze-dried, injectable poly-L-lactic acid (PLLA) with excipients. Each vial of dry powder contains:</p> <p>150 mg PLLA 90 mg sodium carboxymethylcellulose 127.5 mg of non-pyrogenic mannitol</p> <p>The contents in one vial will be reconstituted prior to use by the addition of 8 mL of sterile water for injection (SWFI) at the investigational site. Immediately prior to injection, 1 mL of 2% lidocaine will be added to make a total volume of 9 mL.</p>
<b>Reference therapy</b>	Not applicable
<b>Treatment</b>	<p>Each subject eligible for treatment in the extension study will receive a single regimen of <i>Sculptra Aesthetic</i>. A single regimen consists of up to four (4) injection sessions with 1-month (+2 week) intervals. <i>Sculptra Aesthetic</i> will be administered using a 25G (gauge) needle using the bolus, fanning, cross-</p>

	<p>hatching, linear threading injection technique or other techniques at the discretion of the Treating Investigator. Injections will be made sub-dermally, i.e. in the subcutaneous and supraperiosteal region. A maximum of 18 mL (2 vials) of <i>Sculptra Aesthetic</i> will be administered per treatment session with a maximum of 9 mL (1 vial) per cheek, evenly distributed within the treatment area.</p> <p>The treatment area is within the following borders:</p> <ul style="list-style-type: none"> <li>• Superior border - from top of tragus to top of alar crease</li> <li>• Medial border - from top of the alar crease, along the nasolabial fold (NLF) to the inferior border of the mandibular ramus</li> <li>• Inferior border - from medial border at mandibular ramus to angle of mandibular ramus</li> <li>• Lateral border - from angle of mandibular ramus to top of tragus</li> </ul>
<b>Study Procedures</b>	<p><u>Effectiveness Assessments:</u></p> <ul style="list-style-type: none"> <li>• Cheek wrinkles by Blinded Evaluator and Treating Investigator using GCWS CCI</li> <li>• Global aesthetic improvement by Treating Investigator and Subject using GAIS.</li> <li>• Subject's satisfaction after treatment using a Subject Satisfaction Questionnaire.</li> <li>• Subject's satisfaction using FACE-Q "Satisfaction with Cheeks".</li> <li>• .</li> <li>• Return to social engagement after treatment using subject diaries.</li> <li>• by Treating Investigator.</li> </ul> <p><u>Evaluation of Safety:</u></p> <ul style="list-style-type: none"> <li>• Incidence, intensity, time to onset and duration of adverse events collected throughout the study period.</li> <li>• Incidence, intensity and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days following each treatment.</li> <li>• Safety assessment by a qualified staff member at all visits according to pre- defined methods: <ul style="list-style-type: none"> <li>○ Cheek firmness, symmetry and function (smiling and chewing)</li> <li>○ Device palpability (pre-treatment assessment excluded for subjects receiving treatment in extension study)</li> <li>○ Mass formation</li> <li>○ Cheek sensation</li> <li>○ Visual function assessments (Group A subjects only).</li> </ul> </li> </ul> <p><u>Study Report</u></p> <p>A study report will be compiled at the conclusion of the study.</p>



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<p><b>Statistical Methods</b></p>	<p>All effectiveness analyses will be conducted descriptively. Responder rates in CCI [REDACTED] and GAIS (Investigator's and subject's assessments separately), will be presented using n, percentage and 95% confidence intervals. Results for the right and left side of the face separately as well as combined will be presented. FACE-Q and subject satisfaction will be presented descriptively.</p> <p>All safety endpoints will be analyzed descriptively. All AEs will be coded according to MedDRA. AEs related to study product or injection procedure will be summarized by system organ class (SOC) and preferred term (PT) as well as by SOC, PT and maximal severity. Time to onset and duration of related AEs will also be summarized. Serious AEs will be listed.</p> <p><u>Sample Size:</u> This is an extension of study 43USSA1812. Subjects completing the 12-month visit in study 43USSA1812 will be considered for inclusion in the extension study.</p>
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## Abbreviations and Definitions of Terms

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



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



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## 1 Ethical Considerations

### 1.1 Statement of ethical compliance

The study shall be conducted in compliance with the Clinical Trial Agreement (CTA), the Clinical Investigational Plan (CIP), Good Clinical Practice (GCP), and applicable regional or national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study) insofar as such revisions are consistent with US treaty obligations and in accordance with US law (1).

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

### 1.2 Application to Institutional Review Board and/or Regulatory Authorities

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

The study requires application for approval from the US Food and Drug Administration (FDA). The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed.

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

## 2 Background Information

### 2.1 Indication and population description

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

Study 43USSA1812ext is an extension to pivotal study 43USSA1812 to assess the long-term effectiveness and safety of *Sculptra Aesthetic* for the treatment of cheek wrinkles. Safety and effectiveness data for both study groups (A and B) will be collected for up to 12 months. In all, subjects will be followed for 24 months after baseline in pivotal study 43USSA1812.

### 2.2 Study product Profile

#### 2.2.1 Investigational product description

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

Each vial of dry powder contains 150 mg PLLA, 90 mg CMC and 127.5 mg non-pyrogenic mannitol – in total a vial weight of 367.5 mg and is per approved label to be reconstituted prior to use by the addition of 5 mL of SWFI to form a sterile non-pyrogenic suspension. (2) In this study, commercially available *Sculptra Aesthetic* labeled for the study will be used and reconstitution will be made with 8 mL of SWFI with addition of 1 mL of 2% lidocaine prior to injection. It has been recommended by experienced physicians to evaluate alternative reconstitution procedures for *Sculptra Aesthetic* compared to the





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currently approved instructions for use, primarily to enhance safety of the device by potentially reducing incidence of nodule and papule formation. (3).

#### 2.2.1.1 *Non-clinical documentation*

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#### 2.2.1.2 *Clinical documentation*

Please refer to the *Sculptra Aesthetic* Instructions for Use (IFU) document. The study specific IFU summarizes the adverse effects experienced with *Sculptra Aesthetic* injections along with precautions that can minimize these potential complications. For intravascular complications and recommended treatments, refer to the Intravascular Treatment Protocol.

Please refer to the study Report of Prior Investigations (ROPI) for a description of performed non-clinical and clinical studies and results with *Sculptra Aesthetic*.

### 2.3 Study rationale and justification for design

This study is an extension of study 43USSA1812, which evaluated the effectiveness and safety of *Sculptra Aesthetic* for treatment of cheek wrinkles, with the objective of an expanded label indication. The purpose of this extension of the study is to evaluate long-term safety and effectiveness data of *Sculptra Aesthetic* beyond the Month 12 duration of the pivotal study 43USSA1812, to help characterize the long-term safety and effectiveness profile of the more dilute suspension.

### 2.4 Risks and benefits

Anticipated benefits for subjects treated with *Sculptra Aesthetic* for the correction of cheek wrinkles include restoration of a more youthful appearance, relatively long-lasting effects that would reduce the need for frequent touch-up procedures. Another benefit is better knowledge about the safety profile for *Sculptra Aesthetic* in the new reconstitution volume, including assessment of the risks for late onset papules, nodules, and granuloma as well as other potential adverse event cases associated with *Sculptra Aesthetic*.

The benefit of *Sculptra Aesthetic* for correction of cheek wrinkles is also being evaluated in the ongoing, post-approval US clinical study (US10321). (4) Although treatment in the cheek area was secondary to treatment in the nasolabial folds in this study, the interim data results support that treatment for cheek wrinkles is effective and well tolerated.

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

Most recently, the increased reconstitution volume for treatment of nasolabial folds was evaluated in study 43USSA1705.

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

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



ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures.

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

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

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

Additional information about reported AEs and anticipated risks are included in the study Instructions for use (IFU) and ROPI. Stopping rules for the study are included in Section 8.6.8. Given the anticipated low level of acceptable AEs in connection with the injection and the protocol required safety assessments, it was determined the risk-benefit assessment for use of *Sculptra Aesthetic* using investigational reconstitution and injection procedures for correction of cheek wrinkles appears to offer a clinical benefit at reasonable risk.

### 3 Objectives and Endpoints

#### 3.1 Effectiveness objective and endpoints

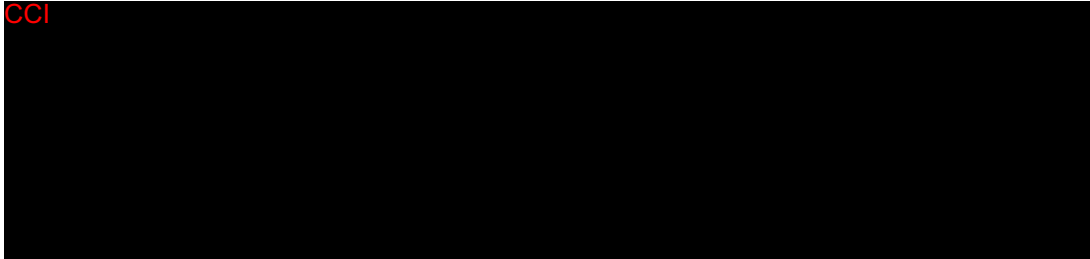
The objective is to evaluate the long-term effectiveness of *Sculptra Aesthetic* in the correction of cheek wrinkles.

Effectiveness endpoints include:

- Responder rate, using the [REDACTED] (GCWS) [REDACTED] as assessed live by the Blinded Evaluator at Months 19, 21 and 24.  
*A responder is defined as a subject with at least 1 grade improvement from pre-treatment on both cheeks concurrently.*
- Responder rate, using the [REDACTED] (GCWS) [REDACTED] c, as assessed live by the Blinded Evaluator, at Months 19, 21 and 24.
- Percentage of subjects having at least “Improved” according to the Global Aesthetic Improvement Scale (GAIS) on both sides of the face combined, as assessed live by the subject and the Treating Investigator separately at all visits following Month 12 in pivotal study 43USSA1812.
- Percentage of subjects responding in each response category for each question in the subject satisfaction questionnaire at all visits following Month 12 in pivotal study 43USSA1812.
- Change from pre-treatment in subject satisfaction using the Satisfaction with Cheeks FACE-Q questionnaire with Outcome Rasch transformed total scores as well as proportion of subjects in each response category for each of the individual questions at all visits following Month 12 in pivotal study 43USSA1812.

*Note: Pre-treatment = Month 12 (pre-treatment) for Group A subjects (those originally randomized to the Control Group in pivotal study 43USSA1812). Pre-treatment = Day 1 for Group B subjects (those originally randomized to the Treatment Group in pivotal study 43USSA1812).*

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



### 3.2 Safety objective and endpoints

To evaluate the safety of *Sculptra Aesthetic* in the treatment of cheek wrinkles.

Safety endpoints include:

- Incidence, intensity, time to onset and duration of adverse events collected throughout the study period.
- Incidence, intensity and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days following each treatment.
- Safety assessment by a qualified staff member at all visits according to predefined methods:
  - Cheek firmness, symmetry and function
  - Device palpability (pre-treatment assessment excluded for those receiving treatment in the extension study)
  - Mass formation
  - Cheek sensation
  - Visual function assessments (Group A subjects only)

## 4 Design of the Study

### 4.1 General outline

This is a 12-month extension of the prospective, randomized, evaluator- blinded, no-treatment controlled study 43USSA1812.

Subjects originally randomized to Control Group (approximately 50 subjects) in the pivotal study will be offered treatment with *Sculptra Aesthetic* in the extension study. This group of subjects is designated as **Group A** within this protocol.

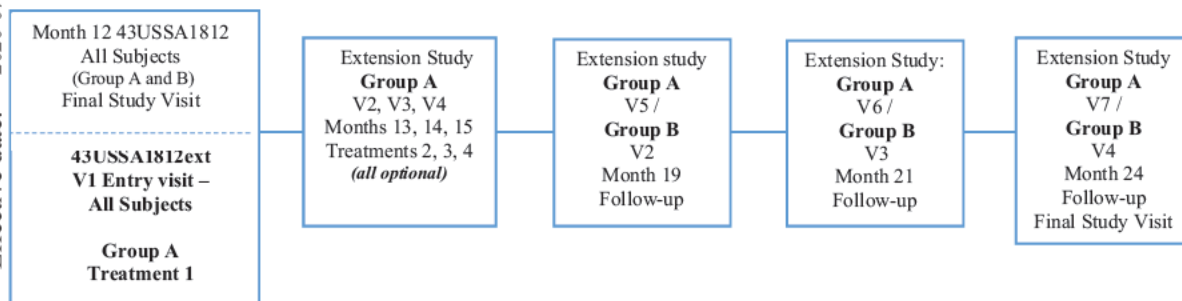
Subjects originally randomized to Treatment Group (approximately 100 subjects) in the pivotal study will be continued to be followed up during the extension study without further treatment. This group of subjects is designated as **Group B** within this protocol.

Safety and effectiveness data will be collected for up to 24 months in subjects randomized to the Treatment Group (who are not treated in the extension study) and for up to 12 months in subjects randomized to the Control Group (who are treated in the extension study). In all, subjects will be followed for 24 months after the baseline visit in the pivotal study.

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



**Figure 1. Study Flow Chart**



## 4.2 Number of Subjects

Approximately 150 subjects will be enrolled at up to 13 US study sites. Subjects must have participated in the 43USSA1812 study in order to be enrolled in this extension study

## 4.3 Duration of subject participation

A subject may be involved in the study for approximately 52 weeks (including visit windows) from Month 12 to the final follow-up visit.

End of study is when all enrolled subjects have completed all visits or were prematurely discontinued from the study.

## 4.4 Randomization and blinding

### 4.4.1 Randomization

Randomization took place in the pivotal study. No further randomization is performed in this extension study.

### 4.4.2 Blinding

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

### 4.4.3 Emergency unblinding

Not applicable as the treating Investigator is not blinded to treatment. All subjects have received treatment during the course of the pivotal study or in the extension study.

## 4.5 Medical history

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

## 4.6 Prior and concomitant therapies

### 4.6.1 Definition

Therapies are defined as medications, treatments and procedures.

Concomitant therapies are defined as follows:

- Any therapy ongoing at the time the subject exited study 43USSA1812, Month 12.
- Any changes to existing therapies (such as changes in dose or formulation) during the course of the study, or
- Any new therapies started after exiting study 43USSA1812 Month 12.

#### 4.6.2 Categories

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

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

#### 4.6.3 Recording

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

#### 4.6.4 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies ([Section 4.6.5](#)) all therapies are authorized.

#### 4.6.5 Prohibited concomitant therapies

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

- Anticoagulants or inhibitors of platelet aggregation that have the ability to prolong bleeding times (e.g. aspirin, non-steroidal anti-inflammatory drugs [NSAIDs]), Omega-3 or Vitamin E should not be used within 14 days before any treatment to avoid increased bruising or bleeding at injection sites. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.
- Chemotherapy, immunosuppressive agents (inhaled corticosteroids allowed) or immunomodulatory therapy (e.g. monoclonal antibodies or antiviral treatment for HIV or Hepatitis C).
- Prescribed corticosteroids or prescription retinoids for topical use in the treatment area or systemic use.
- Planned aesthetic facial plastic surgery (e.g. surgery to either the upper or lower lip, facelift, rhinoplasty, facial liposuction etc.) or cosmetic procedures (e.g. lifting threads, tissue grafting, tissue augmentation with permanent implants, silicone, or fat)
- Treatment/procedure in the face that would interfere with the study injections and/or study assessments or exposes the study subject to undue risk by study participation, e.g.:



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- a. Resurfacing (laser, photomodulation, intense pulsed light (IPL), radiofrequency, ultrasound, chemical peel, dermabrasion, needling, or other ablative/non- ablative procedures)
- b. Needling or mesotherapy
- c. Cryotherapy
- d. Neurotoxin injections (glabella or forehead lines treatment allowed)
- e. Lipolytic injections (e.g. dexycholeic acid or other lipolytic substances)
- f. Planned oral surgery or dental work, such as root canals or sinus surgery, tattoo or piercing in the area to be treated
- Tissue augmenting therapy, contouring or revitalization treatment in the face, except the lips;
  - a. with Collagen or Hyaluronic Acid
  - b. with Calcium Hydroxyapatite (CaHa), Poly L- Lactic Acid (PLLA) or permanent (non-biodegradable)
- Participation in any interventional clinical study.
- The study product contains lidocaine, but additional local anesthesia may be used. Lidocaine should however be used with caution in subjects receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g. certain anti-arrhythmics, as the systemic toxic effects can be additive.

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

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

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#### 4.7 Visits

**Table 1.** Schedule of events, **Group A** (subjects receiving Treatment in 43USSA1812ext)

	Visit 5 <sup>1</sup> Final Study Visit 43USSA1812 <i>Month 12 (±2 weeks) after Baseline</i>	Visit 1 <sup>2</sup> Extension Study Entry Treatment 1 <i>(+2 weeks) after Visit 5</i>	Visit 1a: Telephone Contact <i>72 hours (±24 hrs) after Treatment 1</i>	Visit 2: Month 13 Treatment 2 <sup>6</sup> (Optional) <i>1 month (+2 weeks) after Treatment 1</i>	Visit 2a: Telephone Contact <sup>7</sup> <i>72 hours (±24 hrs) after Treatment 2</i>	Visit 3: Month 14 Treatment 3 <sup>6</sup> (Optional) <i>1 month (+2 weeks) after Treatment 2</i>	Visit 3a: Telephone Contact <sup>7</sup> <i>72 hours (±24 hrs) after Treatment 3</i>	Visit 4: Month 15 Treatment 4 <sup>6</sup> (Optional) <i>1 month (+2 weeks) after Treatment 3</i>	Visit 4a: Telephone Contact <sup>7</sup> <i>72 hours (±24 hrs) after Treatment 4</i>	Visit 5: Month 19 Follow-up <i>7 months (+2 weeks) after ext. Visit 1</i>	Visit 6: Month 21 Follow-up <i>9 months (±2 weeks) after ext. Visit 1</i>	Visit 7: Month 24 Final visit/ Early termination <i>12 months (±2 weeks) after ext. Visit 1</i>
Informed consent		X										
Inclusion/Exclusion criteria		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>				
Demographics incl. weight	X	X <sup>3</sup>								X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test <sup>4,5</sup>		X		X		X		X				
Photography (2D and 3D)	X	X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X	X	X
Sculptra Aesthetic administration		X		X <sup>6</sup>		X <sup>6</sup>		X <sup>6</sup>				
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments <sup>11</sup>	X	X		X		X		X		X	X	X
Visual function assessments <sup>9</sup>	X	X <sup>4,10</sup>		X <sup>4,10</sup>		X <sup>4,10</sup>		X <sup>4,10</sup>		X	X	X
Device deficiencies		X		X <sup>8</sup>		X <sup>8</sup>		X <sup>8</sup>				
Dispense subject diary		X		X <sup>8</sup>		X <sup>8</sup>		X <sup>8</sup>				
Collect subject diary				X <sup>4</sup>		X <sup>4,7</sup>		X <sup>4,7</sup>		X <sup>7</sup>		
Treating Investigator Assessments												
GAIS	X	X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X	X	X
CCI		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>				
	X	X <sup>4</sup>								X	X	X
Blinded Evaluator Assessments												
CCI	X	X <sup>4</sup>								X	X	X
Subject Assessments												
GAIS	X	X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X	X	X
Subject satisfaction questionnaire				X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X	X	X
FACE-Q	X	X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X <sup>4</sup>		X	X	X

- Visit 5 is identical to Visit 5 outlined and performed in the pivotal study 43USSA1812:
- 43USSA1812ext Visit 1 can be performed at Visit 5 (Month 12, pivotal study) or as a separate visit within 2 weeks of Visit 5 (Month 12, pivotal study).  
When Visit 1 extension occurs on the same day as Visit 5 pivotal (Month 12 in 43USSA1812), assessments already outlined in Visit 5 study protocol 43USSA1812 only need to be performed once.
- Weight only
- Pre-treatment
- Females of childbearing potential



6. If treatment is not performed this is a follow-up visit
7. If applicable (i.e. if treatment was performed at the previous visit)
8. If applicable (i.e. if treatment is performed at this visit)
9. Visual Function assessments include: Snellen visual acuity test, Extraocular muscle function test, Confrontation visual field
10. 30 minutes post treatment
11. Safety assessments include: Cheek firmness, symmetry and function, Device palpability (pre-treatment assessment excluded), Mass formation, Cheek sensation

Abbreviations: GAIS (Global Aesthetic Improvement Scale), CCI (Controlled Clinical Investigation), ET (Early Termination)

**Table 2.** Schedule of events, **Group B** (subjects originally randomized to Treatment Group in 43USSA1812)

	Visit 8 <sup>1</sup> Final Study Visit 43USSA1812 Month 12 ( $\pm 2$ weeks) after Baseline	Visit 1: Extension Study Entry <sup>2</sup> Visit Month 12 ( $\pm 2$ weeks) after Visit 8	Visit 2: Month 19 Follow up Visit 7 months ( $\pm 2$ weeks) after ext. study Visit 1	Visit 3: Month 21 Follow up Visit 9 months ( $\pm 2$ weeks) after ext. study Visit 1	Visit 4: Month 24 Final visit/Early termination Visit 12 months ( $\pm 2$ weeks) after ext. study Visit 1
Informed consent	X	X			
Inclusion/Exclusion criteria	X	X			
Concomitant therapies	X	X	X	X	X
Demographics incl. weight	X	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>
Photography (2D and 3D)	X	X	X	X	X
Adverse event assessments	X	X	X	X	X
Safety assessments <sup>3</sup>	X	X	X	X	X
<b>Treating Investigator Assessments</b>					
GAIS	X	X	X	X	X
CCI	X	X	X	X	X
<b>Blinded Evaluator Assessments</b>					
CCI	X	X	X	X	X
<b>Subject Assessments</b>					
GAIS	X	X	X	X	X
Subject Satisfaction questionnaire	X	X	X	X	X
FACE-Q	X	X	X	X	X

1. Visit 8 is identical to Visit 8 outlined and performed in the pivotal study 43USSA1812
2. 43USSA1812ext Visit 1 can be performed at Visit 8 (Month 12, pivotal study) or as a separate visit within 2 weeks of Visit 8 (Month 12, pivotal study). When Visit 1 extension occurs on the same day as Visit 8 pivotal (Month 12 in 43USSA1812), assessments already outlined in Visit 8 study protocol 43USSA1812 only need to be performed once.
3. Extension study Safety assessments include: Cheek firmness, symmetry and function, Device palpability, Mass formation, Cheek sensation (Visual Function assessment for pivotal study final study visit [Visit 8] only).
4. Weight only

Abbreviations: GAIS (Global Aesthetic Improvement Scale), CCI (Controlled Clinical Investigation), ET (Early Termination)





#### 4.7.1 43USSA1812ext **Visit 1: Entry visit (*all subjects*)**

- The 43USSA1812 Month 12 visit is the final visit in the pivotal study and may also serve as the Entry visit for extension study 43USSA1812ext. The entry visit can also be performed as a separate visit within 2 weeks of 43USSA1812 Month 12 visit. When both visits occur at the same day, assessments need only to be performed once.

The following activities will be performed:

- Informed consent (prior to conducting any extension study specific procedure)
- Assess eligibility for extension study (inclusion and exclusion criteria)

#### **Visit 1: Group A Subjects** (*those receiving Treatment in 43USSA1812ext*):

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

- Review concomitant therapies
- Obtain weight
- Assess and interview for AEs – Investigator
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation.
- Perform Urine Pregnancy test for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for treatment.
- Perform Visual function assessments: Snellen visual acuity test, Extraocular muscle function test and Confrontation visual field
- Obtain Photography 2D and 3D (perform prior to treatment)
- Instruct the subject to complete FACE-Q assessment
- [REDACTED] – Treating Investigator.
- Assess GAIS - Investigator and subject.
- Assess GCWS [REDACTED] – Treating Investigator and Blinded Evaluator (pre-treatment)
- *Sculptra Aesthetic* administration
- Evaluate for device deficiencies
- Dispense diary and instruct subject on daily Diary completion. Remind subject to bring the Diary to the next on-site visit.
- 30 minutes following injection, perform Visual Function Assessments.
- Evaluate the subject for post-treatment AEs- Treating Investigator
- Schedule the next follow up visit (1 month [+2 weeks])

#### **Visit 1: Group B Subjects** (*those originally randomized to Treatment Group in pivotal 43USSA1812 study*):

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

- Review concomitant therapies



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- Obtain weight
- Assess and interview for AEs – Investigator
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability  
(Visual Function assessments performed as part of 43USSA1812 pivotal final study visit only)
- Assess GCWS ([REDACTED])- Blinded Evaluator
- Obtain Photography (2D and 3D)
- GAIS: Perform GAIS assessment - Investigator and Subject.
- Instruct the subject to complete FACE-Q assessment
- [REDACTED] – Treating Investigator.
- Instruct the subject to complete the Subject satisfaction questionnaire
- Assess and interview for AEs – Investigator

**Note:** Visits described below in [Sections 4.7.2 through 4.7.9](#) pertain to **Group A** subjects only. See [Section 4.7.10](#) for **Group B** subjects follow up visits.

#### 4.7.2 Visit 1a, Treatment Follow up 72 hour telephone call (±24 hours)

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

#### 4.7.3 Visit 2, Treatment 2 (1 month [+2 weeks] after Treatment 1)

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



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- Assess whether optimal treatment result has been obtained (as agreed by the Treating Investigator and Subject).
  - If a second treatment is to be performed, confirm eligibility criteria
  - No treatment should be given in the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

For subjects who receive a second treatment:

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

**4.7.4 Visit 2a, Treatment Follow up 72 hour telephone call (±24 hours) – for subjects who received a second treatment only.**

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

**4.7.5 Visit 3, Treatment 3 (1 month [+2 weeks] after Treatment 2)**

- Review the subject's concomitant therapies.
- Collect and review subject diary (only applicable for subjects who received a treatment at Treatment 2 visit).
- Interview for AEs.
- Assess for AEs- Treating Investigator
- Assess GCWS (at rest and dynamic) Treating Investigator (if receiving a treatment at this visit, perform prior to treatment)
- Obtain Photography 2D and 3D (if receiving a treatment at this visit, perform prior to treatment)
- Perform Visual Function Assessments for all subjects (if receiving a treatment at this visit, perform prior to treatment).
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability.



- GAIS: Perform GAIS assessment (if receiving a treatment at this visit, perform prior to treatment) - Investigator and Subject.
- Instruct the subject to complete the Subject satisfaction questionnaire (pre-treatment).
- Instruct the subject to complete Face-Q assessment.
- Assess whether optimal treatment result has been obtained (as agreed by the Treating Investigator and Subject).
  - If a third treatment is to be performed, confirm eligibility criteria
  - No treatment should be given in the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

For subjects who receive a third treatment:

- Prior to any treatment being provided, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive treatment.
- Administer *Sculptra Aesthetic*.
- Evaluate for device deficiencies.
- 30 minutes following injection, perform Visual function Assessments.
- Dispense new subject diary and instruct subject on daily diary completion. Remind subject to bring the diary to the next on-site visit.
- Evaluate the subject for post-treatment AEs – Treating Investigator.
- Schedule the next follow up visit (1 month +2 weeks) after treatment 3 visit

4.7.6 **Visit 3a, Treatment Follow up 72 hour telephone call (±24 hours) – for subjects who received a third treatment only.**

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

4.7.7 **Visit 4, Treatment 4 (1 month [+2 weeks] after Treatment 2)**

- Review the subject's concomitant therapies.
- Collect and review subject diary (only applicable for subjects who received a treatment at Treatment 3 visit).
- Interview for AEs.
- Assess for AEs- Treating Investigator
- Assess GCWS (at rest and dynamic) Treating Investigator (if receiving a treatment at this visit, perform prior to treatment)
- Obtain Photography 2D and 3D (if receiving a treatment at this visit, perform prior to treatment)



- Perform Visual Function Assessments for all subjects (if receiving a treatment at this visit, perform prior to treatment).
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability.
- GAIS: Perform GAIS assessment (if receiving a treatment at this visit, perform prior to treatment) - Investigator and Subject.
- Instruct the subject to complete the Subject satisfaction questionnaire (pre-treatment).
- Instruct the subject to complete Face-Q assessment.
- Assess whether optimal treatment result has been obtained (as agreed by the Treating Investigator and Subject).
  - If a fourth treatment is to be performed, confirm eligibility criteria
  - No treatment should be given in the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

For subjects who receive a fourth treatment:

- Prior to any treatment being provided, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive treatment.
- Administer *Sculptra Aesthetic*.
- Evaluate for device deficiencies.
- 30 minutes following injection, perform Visual function Assessments.
- Dispense new subject diary and instruct subject on daily diary completion. Remind subject to bring the diary to the next on-site visit.
- Evaluate the subject for post-treatment AEs- Treating Investigator.
- Schedule the next follow up visit month 7 (+2 weeks) after Visit 1

4.7.8 **Visit 4a, Treatment Follow up 72 hour telephone call (±24 hours) – for subjects who received a fourth treatment only.**

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

4.7.9 **Visits 5, 6, and 7: Follow-up, Month 19 (+2weeks), 21 (±2 weeks), and 24 (±2 weeks)**

- Obtain weight measured at clinic.
- Review the subject's concomitant therapies.
- Collect and review subject diary (only applicable for subjects in the treatment group who received a treatment at Treatment 4 visit).
- Obtain 2D and 3D Photographs.

- Interview for AEs
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability.
- Perform Visual function assessments: Snellen visual acuity test, Extraocular muscle function test and Confrontation visual field
- Assess for AEs –Treating Investigator
- Assess GAIS - Investigator and subject.
- Assess GCWS [REDACTED] – Blinded Evaluator.
- [REDACTED] – Treating Investigator.
- Instruct the subject to complete the Subject satisfaction questionnaire.
- Instruct the subject to complete Face-Q assessment.

#### **For Group B Subjects Only**

##### **4.7.10 Visits 2, 3 and 4; Follow-up, Months 19 (+2 weeks), 21 (±2 weeks), and 24 (±2 weeks)**

- Obtain weight measured at clinic.
- Review the subject's concomitant therapies.
- Obtain 2D and 3D Photographs.
- Interview for AEs
- Perform safety assessments: Cheek sensation, Cheek firmness, symmetry and function, Mass formation and Device Palpability
- Assess for AEs- Treating Investigator
- Assess GAIS - Investigator and subject.
- Assess GCWS [REDACTED] –Blinded Evaluator.
- [REDACTED] – Treating Investigator.
- Instruct the subject to complete the Subject satisfaction questionnaire.
- Instruct the subject to complete Face-Q assessment.

##### **4.7.11 Unscheduled Visits**

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

## **5 Subjects**

### **5.1 Subject information and informed consent**

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



It is the responsibility of the Investigator or his/her authorized designee to give each subject, prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study, e.g. explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the IRB. The subject shall be informed that the participation is confidential and voluntary and that the subject has the right to withdraw from the study at any time, without any 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 Investigator or his/her authorized designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries. The data will not contain any information that can be used to identify any subject.

Photographs collected during the study will be analyzed and stored in a database by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study. The subjects will be recognizable on the photographs, but their names will not be disclosed.

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

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

## 5.2 Inclusion criteria

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

1. Subject completed Month 12 of study 43USSA1812
2. Subjects willing to comply with the requirements of the extension of the study and providing a signed written informed consent.

For subjects eligible for treatment in the extension study:

3. Female subjects who are exempt from birth control requirements must be postmenopausal for at least 1 year; if the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test at the extension study entry visit and prior to all injection visits. Acceptable forms of effective birth control methods include:

- Combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 28 days prior to enrollment
- Hormonal or copper intrauterine device (IUD) inserted at least 28 days prior to Enrollment
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository
- Bilateral tubal ligation prior to Enrollment
- Vasectomized partner (in monogamous relationships) for at least 3 months prior to Enrollment
- Strict abstinence (at least one month prior to enrollment and agrees to continue for the duration of the study or use acceptable form of birth control).



### 5.3 Exclusion criteria

For Group A subjects eligible for treatment in the extension study, the exclusion criteria for study 43USSA1812 applies. The presence of any of the following exclusion criteria will exclude a subject from treatment in the extension study:

1. Known/previous allergy or hypersensitivity to any of the *Sculptra Aesthetic* constituents.
2. Known/previous allergy or hypersensitivity to lidocaine and other local anesthetics, e.g. amide-type anesthetics or topical anesthetics agents.
3. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions.
4. Previous tissue augmenting therapy, contouring or revitalization treatment in the face, except the lips, with any of the following fillers (other than *Sculptra Aesthetic* treatments as part of 43USSA1812) prior to enrollment in the extension study:
  - a. Collagen, Hyaluronic Acid – 12 months
  - b. Calcium Hydroxyapatite (CaHa), Poly L- Lactic Acid (PLLA) or permanent (non-biodegradable)- Prohibited
5. Previous treatment/procedure in the face in the previous 6 months that, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the study subject to undue risk by study participation, e.g.:
  - a. Resurfacing (laser, photomodulation, light, radiofrequency, ultrasound, chemical peel, dermabrasion, or other ablative/non- ablative procedures)
  - b. Needling or mesotherapy
  - c. Cryotherapy
  - d. Neurotoxin injections
  - e. Lipolytic injections (e.g. dexychoic acid or other lipolytic substances)
  - f. Dental work, such as root canals or sinus surgery,

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

6. Presence of any disease or lesions near or on the area to be treated, e.g.
  - a. Inflammation, active or chronic infection in or near the treatment area
  - b. Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes zoster/ herpes simplex and acanthosis
  - c. Scars or deformities
  - d. Cancer or precancerous condition (e.g. actinic keratosis or actinic cheilitis)
7. History of severe elastosis and/or excessive sun exposure that in the opinion of the Treating Investigator, could affect the safety and effectiveness outcome of the study.
8. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation (e.g. aspirin or other NSAIDs), Omega-3, or vitamin E within 14 days before





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treatment. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.

9. Treatment with chemotherapy, immunosuppressive agents (inhaled corticosteroids allowed), immunomodulatory therapy (e.g. monoclonal antibodies or antiviral treatment for HIV or Hepatitis C) within 6 months before treatment.
10. Use of topical corticosteroids or topical prescription retinoids (in the treatment area) within 1 month of enrollment into the extension study or systemic retinoid treatment within 6 months of enrollment into the extension study.
11. Previous surgery including plastic surgery, lifting threads, tissue grafting or tissue augmentation with permanent implants, silicone or fat, or tattoo, affecting the treatment area.
12. History of cancer or previous radiation near or on the area to be treated.
13. HIV positive or active hepatitis.
14. History of or active collagen diseases such as systemic lupus erythematosus, rheumatic arthritis, polymyositis, dermatomyositis, skin or systemic scleroderma.
15. Tendency to form keloids, hypertrophic scars, or any other healing disorder.
16. Presence of piercing, beard or facial hair that could interfere with study evaluation.
17. Abnormal result on functionality, sensation, symmetry, mass formation or palpation assessments in the treatment area.
18. Abnormal result on extraocular muscle function test or confrontational visual field assessment.
19. Presence of a dental, oral, or facial condition which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment, e.g. has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities.
20. Woman who is pregnant (confirmed by positive urine pregnancy test/serum pregnancy test), breast-feeding or intend to become pregnant over the duration of the study.
21. Any medical condition that, in the opinion of the Treating Investigator, would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease that may interfere with the outcome of the study).
22. Other condition preventing the subject from entering the study in the Treating Investigator's opinion, e.g. subjects failing pretreatment safety assessments, subjects not likely to avoid other cosmetic treatments in the treatment area, subjects anticipated to be unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.
23. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), or employees and close relatives of employees at the Sponsor company.
24. Participation in any interventional clinical study throughout the duration of the study.



#### 5.4 Subject number

Prior to any study procedures being conducted, the subject must sign the informed consent form. Each subject who has signed the informed consent form will keep the same subject number as in study 43USSA1812. 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.

For the duration of the clinical study, each subject will be identified using the subject number for all documentation and discussion.

#### 5.5 Withdrawal of subjects

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

The withdrawal criteria are:

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

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

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

If a subject is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses. Subjects who receive product and are withdrawn or discontinued from the study will not be replaced. For AEs still ongoing at the time of withdrawal, see [Section 8.6.11](#).

## 6 Study Products

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

## 6.1 Investigational product

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

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

Each vial of *Sculptra Aesthetic* contains:

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

Investigational Study Product	
Trade Name or Equivalent	<i>Sculptra Aesthetic</i>
Treatment Substance	Poly-L-lactic acid (PLLA)
Concentration	367.5 mg
Packaging	Single use vial
Storage Conditions	Store at room temperature, up to 30°C (86°F). DO NOT FREEZE. Refrigeration is not required.  Upon reconstitution, <i>Sculptra Aesthetic</i> can be stored for up to 72 hours at temperatures between 5- 30°C.
Reconstitution Volume	8 mL SWFI
Additional Anesthetic	1 mL of Lidocaine Hydrochloride 2% added to vial immediately prior to injection
Recommended Maximum Volume per treatment session	<ul style="list-style-type: none"> <li>• Maximum of 18 mL (2 vials) of <i>Sculptra Aesthetic</i> will be administered per treatment session</li> <li>• Maximum of 9 mL (1 vial) per cheek, evenly distributed within the treatment area.</li> </ul>
Frequency intervals	Four (4) injection sessions with 1-month (+2weeks).
Reconstitution needle size	18G
Injection needle size	25G

<b>Mixing Instructions</b>	Immediate use after mix
<b>Injection Technique</b>	Bolus, fanning, cross-hatching, linear threading injection technique or other techniques at the discretion of the Treating Investigator
<b>Injection Depth</b>	Subdermal regions
<b>Treatment Area</b>	<p>Within the following borders:</p> <ul style="list-style-type: none"> <li>• Superior border - from top of tragus to top of alar crease</li> <li>• Medial border - from top of the alar crease, along the nasolabial fold (NLF) to the inferior border of the mandibular ramus</li> <li>• Inferior border - from medial border at mandibular ramus to angle of mandibular ramus</li> <li>• Lateral border - from angle of mandibular ramus to top of tragus</li> </ul>

## 6.2 Reference product

Not applicable.

## 6.3 Additional products and materials

The following will be supplied by the study sites:

- 18 G sterile needles (for reconstitution)
- 25 G sterile needles (for injection)
- 2% Lidocaine HCl. (Only the 3 Lidocaine products listed below should be used and only for the treatment group).
  - 2% Lidocaine HCl- Hospira with 0.1% Methyl paraben
  - 2% Lidocaine HCl- West Ward with 0.1% Methyl paraben
  - 2% Lidocaine HCl- West Ward without preservatives
- Sterile Water for Injection (SWFI), United States Pharmacopeia (USP)
- Single use 5 mL sterile syringes
- Single use 1 mL or 3 mL sterile syringes
- Antiseptic (such as alcohol)

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



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## 6.4 Packaging, labeling, and storage

### 6.4.1 Investigational product

*Sculptra Aesthetic* is supplied as a sterile freeze-dried preparation for injection in a clear glass vial, which is sealed by a penetrable stopper, covered by an aluminum seal with a flip-off cap. Each carton of *Sculptra Aesthetic* contains one vial of poly-L-lactic acid, sodium carboxymethylcellulose, non-pyrogenic mannitol.

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

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

“CAUTION – Investigational Device. Limited by Federal Law to Investigational Use.”

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

Detailed product information is provided in the study IFU.

### 6.4.2 Reference product

Reference product is not applicable.

### 6.4.3 Product accountability

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

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

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

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

Any malfunctioning investigational products shall be reported as described in [Section 8.7.3](#).

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

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

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

## 6.5 Treatment

### 6.5.1 Treatment procedure

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

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

The investigational product is reserved for use by doctors trained in the appropriate injection technique. Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections should be observed at all times including the use of disposable gloves during the injection procedure. All traces of make-up in the treatment area should be removed prior to any injection. The treatment site should be cleaned with a suitable antiseptic solution. An ice pack can be applied on the site for a short period. Topical or local injection anesthesia may be used to further reduce pain on injection. If (topical or local) anesthetic or ice is used, the area should be cleaned after anesthetic is removed. The use of anesthetic or ice should be recorded in the source documentation and on the eCRFs.

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

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

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

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

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

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

Lateral border - from angle of mandibular ramus to top of tragus Injection technique

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

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

- Antegrade linear threading: also called push-ahead technique as some product is pushed ahead of the needle. Once the needle is in place, the product is injected ahead while inserting the needle in the tissue.
- Retrograde linear threading: the needle is threaded into the tissue at the appropriate depth, and the product is injected as a straight line on withdrawal of the needle



- Bolus: multiple aliquot injections of the product is injected along a line or regions of the tissues
- Fanning: a number of linear threads to spread the product over a wider area
- Cross-hatching: combines multiple injections of linear threading that crisscross at right angle to provide volume in a square shape

#### 6.5.2 Treatment regimen (dose and interval)

Eligible subjects from the 43USSA1812 Control group (Group A) who enroll into the extension at the Month 12 Visit will receive a single regimen of *Sculptra Aesthetic*. A single regimen consists of up to 4 injection sessions with 1-month (+2 weeks) intervals. The first treatment will be administered at the Extension study Visit 1 (same day as 43USSA1812 final study visit, or  $\leq 14$  days of this visit). Sufficient amount of study product, as determined by the Treating Investigator, should be injected to achieve optimal correction:

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

Treatment will stop when optimal correction has been achieved and subsequent visits will be follow-up visits. Treatment will not be performed if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

#### 6.5.3 Post-treatment care

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

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

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

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

#### 6.5.4 Post-trial provisions

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

#### 6.5.5 Treatment compliance

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

## 7 Effectiveness Assessments

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



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The methods for collecting effectiveness data are:

- GCWS ( )
- Photography 2D and 3D
- GAIS
- Subject Satisfaction Questionnaire,
- FACE-Q “Satisfaction with Cheeks”
- Return to social engagement after treatment recording
- 

## 7.1 CCI

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

Figure 2 GCWS

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## 7.2 (GCWS)

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

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## 7.3 Global Aesthetic Improvement Scale (GAIS)

The 7-graded GAIS will be used to live assess the aesthetic improvement of cheek wrinkles by the Treating Investigator and the subject, by comparing to a photograph taken at the baseline visit before the first treatment. The Treating Investigator and the subject will, independently of each other, respond to the question: “How would you describe the aesthetic improvement today compared to the photograph taken before treatment?” by using the respective categorical scale below.

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#### 7.4 Subject Satisfaction Questionnaire

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

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### 7.5 FACE-Q “Satisfaction with Cheeks”

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



#### FACE-Q™ - SATISFACTION WITH CHEEKS

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

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### 7.6

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

### 7.7 Return to social engagement

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

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

Did you feel comfortable to return to social engagement today?

- Yes or No

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

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

7.8

after treatment  
based on review of baseline photographs and live assessment by responding to the following  
questions:

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## 7.9 Photography

Photographs shall be taken at the time points indicated in the Schedule of Events. For subjects being treated, this should occur prior to the first injection of the study product and before each additional treatment. Camera equipment will be provided by the Sponsor or their designee and standardized photographs should be taken. Instructions for photography are provided in a separate photography manual. Baseline photographs may be used as a reference in the assessment of GAIS by the Treating Investigator and subject. Photographs may also be taken to document AEs at the Treating Investigator's discretion. Any personnel who were not previously trained in the photographic equipment and technique will be trained in the same manner as for study 43USSA1812, prior to extension study start.

## 8 Safety Assessments

Safety assessments for this study include an evaluation and an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an AE, a subject diary,

pregnancy tests, cheek firmness, function and symmetry, device palpability (pre-treatment assessment excluded for those in Group A), mass formation, cheek sensation and visual function assessments (Group A only).

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

Each subject should be questioned about AEs at each visit following enrollment (i.e. Informed consent). Definition and Reporting requirements are found in [Section 8.6](#).

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

It is the responsibility of the Treating Investigator to determine severity of the AE and relatedness of the event to the study product and/or injection procedures. Adverse Events must be reported as outlined below in [Section 8.6.5](#).

### 8.2 Subject Diary Data

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

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

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

### 8.3 Laboratory assessments

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

### 8.4 Visual Function assessments

Visual function assessments will only be performed for subjects receiving treatment in the extension study (Group A). These assessments will be performed both prior to and post injection of the study product at all treatment visits and will also be performed at each follow up visits. The post-treatment



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assessments should be performed 30 min after the injections are completed. In the event of blindness or any significant ophthalmic sign or symptom, subjects are to undergo immediate evaluation by an ophthalmologist or a retina specialist. All incidences of visual disturbances, regardless of relationship to study product or seriousness, are considered Adverse Events of Special Interest (AESIs) and include but are not limited to the following: any loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving eyes. AESI's should be reported (using the Adverse Event Clarification Form) within 24 hours of awareness. Please refer to recording instructions in [Section 8.6.6](#).

#### 8.4.1 Snellen visual acuity test

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

#### 8.4.2 Extraocular muscle function test

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

#### 8.4.3 Confrontation visual field

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

### 8.5 **Other safety assessments – All Subjects**

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

#### 8.5.1 Cheek sensation

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

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



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

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

#### 8.5.2 Cheek firmness, symmetry and function

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

#### 8.5.3 Mass formation

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

#### 8.5.4 Device palpability- All Subjects

Device palpability will be assessed at post treatment visits for Group A subjects and at all physical visits for those in Group B, and will assess whether or not the palpability is the normal expected feel. An unexpected feel is to be recorded as an adverse event.

### 8.6 Adverse events

#### 8.6.1 Definition of an adverse event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons<sup>1</sup>, whether or not related to the study product.

This definition includes:

- a) events related to the investigational product or the reference product
- b) events related to the procedures involved

#### 8.6.2 Definition of a serious adverse event

A serious adverse event (SAE) is an AE that:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
  - 1. a life-threatening<sup>2</sup> illness or injury, or

<sup>1</sup> For users or other persons, this definition is restricted to events related to the investigational product.

<sup>2</sup> 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



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2. a permanent impairment of a body structure or body function, or
  3. in-patient or prolonged hospitalization<sup>3</sup>, or
  4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to fetal distress, fetal death, or a congenital abnormality or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (see [Section 8.6.5](#)).

#### 8.6.3 Definition of unanticipated adverse effect

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

#### 8.6.4 Recording instructions

Each subject with an AE occurring after enrollment through study exit should be fully recorded in the source document(s) for further transcription into the eCRF. Each subject should be questioned about AEs at each study visit following enrollment. The question asked should be: "Since your last clinical visit; have you had any health problems?" Information on AEs can also be obtained from signs and symptoms detected during each examination or from a laboratory test, observations made by the study site personnel, subject diaries, or spontaneous reports from the subjects or their relatives.

When an AE is related to a device deficiency (refer to [Section 8.7](#)), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form, provided separately in the investigator file, and the eCRF.

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

- a) Event term (recorded in standard medical terminology and avoiding abbreviations)
- b) Affected area
- c) Start date (first day with symptoms)
- d) Stop date (last day with symptoms)
- e) Intensity (mild, moderate, or severe according to definition in [Section 8.6.4.1](#))
- f) Seriousness (serious or not serious, according to definition in [Section 8.6](#))
- g) Causal relationship to study product or study product injection procedure (yes or no)
- h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
- i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

were more severe. (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

<sup>3</sup> Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).



The pre-defined, expected post-treatment events shall be assessed separately. These events shall be collected daily by subjects in a diary for up to 28 days after each treatment.

#### 8.6.4.1 Intensity

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

- Mild:** Awareness of symptoms or signs, but easily tolerated (acceptable)  
**Moderate:** Enough discomfort to interfere with usual activity (disturbing)  
**Severe:** Incapacity to work or to do usual activity (unacceptable)

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

#### 8.6.4.2 Causal relationship and seriousness

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

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

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

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

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

#### 8.6.5 Reporting of adverse events

Adverse event reporting on each subject shall start upon enrollment in the extension study.

The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

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

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

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

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

The following information should be provided when reporting an AESI:

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



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

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

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

#### 8.6.7 Reporting of serious adverse events

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

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

- CTN 43USSA1812ext
- Subject identification (age, gender, subject number)
- Date when AE occurred
- Date when AE became serious
- Adverse event description
- Name of investigator and original reporter (if other than Investigator)
- Name of study product (investigational product or no-treatment)\
- Treatment specification

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

Supporting documentation to be provided with the SAE report:

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

E-mail for SAE reporting: CCI

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed to the CRO. A copy of the fully completed SAE form shall be kept at the site. The blinded evaluator should perform live effectiveness assessments only and not discuss the treatment or any potential adverse events with the patient.

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

The Sponsor is responsible for reporting to the RA, if applicable and according to national regulations.

#### 8.6.8 Stopping Rule

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

If the Sponsor's investigation concludes:

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

#### 8.6.9 Reporting of unanticipated adverse device effects

The Investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during the study as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (see US requirement 21 CFR 812.150 (a.), for contact details, see [Section 8.6.7](#)).

#### 8.6.10 Follow-up of unresolved events ongoing at termination of the study

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

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

All adverse events with a causal relationship to the study products or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor. The report should as a minimum include the information described in [Section 8.6.4](#). The report can be sent via e-mail according to contact details specified in [Section 8.6.7](#).

#### 8.6.12 Pregnancy

Pregnancy itself is not regarded as an AE.



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

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge be submitted to the Sponsor according to contact details specified in [Section 8.6.7](#). The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

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

#### 8.6.13 Anticipated adverse events

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

### 8.7 Device deficiencies

#### 8.7.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety<sup>4</sup>, or performance.

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

#### 8.7.2 Recording instructions

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

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

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

#### 8.7.3 Reporting of device deficiencies

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

E-mail for device deficiencies reporting:

CCI

<sup>4</sup> Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

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A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the CRO within 24 hours after the Investigator's awareness (for contact information, see [Section 8.6.7](#)). If the form is completed within an eCRF system, refer to the eCRF completion guidelines.

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

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

## 9 Data Handling and Management

### 9.1 Data management

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

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

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

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

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

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

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

#### 9.2.1 Data entry

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

#### 9.2.2 The query process

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

#### 9.2.3 User identification

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

#### 9.2.4 Audit trail

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

### 9.3 Source documents

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

The Investigator is responsible for maintaining source documents. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary. Source documents shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected.





All supportive documentation submitted with the eCRF, such as laboratory or hospital records, shall be clearly identified with the CTN and subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

#### 9.4 Record keeping and access to source data

The PI/Institution shall permit study-related monitoring, audits, IRB review, and RA inspections and shall provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed informed consent forms and detailed records of study product accountability). The records shall be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records shall be documented and the Sponsor shall be informed in writing.

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

#### 9.5 Document and data retention

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

After study completion and database lock, a security sealed CD with electronic study data shall be provided by the eCRF vendor for archiving.

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

### 10 Statistical Methods

#### 10.1 General

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

All study data will be listed in subject data listings.

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

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

#### 10.2 Analysis populations

Only one population will be defined: The extension population and it includes all subjects entering the extension study.



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

Demographic endpoints and subject characteristics for the extension population will be presented using descriptive statistics.

### 10.4 Effectiveness analysis

Pre-treatment is defined as Month 12 (pre-treatment) for Group A subjects and Day 1 in pivotal study 43USSA1812 for Group B subjects.

Change from pre-treatment is calculated as the value *minus* the pre-treatment value.

Exact confidence intervals will be used for the proportions, i.e. they will be based on the binomial distribution. For the presentation of effectiveness data, all time points from pre-treatment through the end of the extension study will be presented for the extension population. Group A data may be compared to Group B data descriptively.

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Responder rate based on the CCI, as assessed live by the Blinded Evaluator at Months 19, 21 and 24 will be analyzed as effectiveness endpoints.

A responder is defined as a subject with at least 1 grade improvement from pre-treatment on both cheek concurrently.

#### GAIS

Responder rate based on the GAIS, as assessed live by the subject and Treating Investigator separately at Month 19, 21 and 24 will be analyzed as effectiveness endpoints.

A responder is defined as a subject having at least "Improved" according to the GAIS on both sides of the face combined.

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

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

#### Other effectiveness endpoints

All other effectiveness endpoints will be analyzed by the means of standard descriptive statistics, including 95% confidence intervals.

### 10.5 Safety analysis

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

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

AEs related to study product or injection procedure and unrelated AEs will be presented by maximum intensity, SOC and PT. For related AEs, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized by SOC and PT. Serious AEs will be listed.

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

- number of subjects with at least one AE and number of events (in total as well as serious AEs)





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

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

#### 10.6 Handling of missing data

All effectiveness endpoints will be evaluated based on observed cases.

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

#### 10.7 Data monitoring committee

Not applicable to this study.

#### 10.8 Withdrawals and deviations

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

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

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

#### 10.9 Sample size

Since this is an extension study, no sample size calculation required. Approximately 150 subjects will be enrolled in this study.

### 11 Protection of personal data

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

The Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the study subject should be made aware of this exception in the informed consent. The Institution and Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

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

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



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

## 12 Quality Control and Quality Assurance

### 12.1 Quality control

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

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

### 12.2 Quality assurance

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

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

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

### 12.3 Changes to the clinical investigational plan

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

## 13 Financing, Indemnification, and Insurance

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



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#### 14 Publication Policy

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

The aim is to submit the results of this study for publication in the public database ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved<sup>5</sup>. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

#### 15 Suspension or Premature Termination

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

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

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

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



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## Appendix 1

### Investigator Signature Page

#### Signed Agreement of the Clinical Investigational Plan

CTN: 43USSA1812ext

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

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

#### Principal Investigator

\_\_\_\_\_  
Printed name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Study site



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## SIGNATURES PAGE

Date	Signed by
2020-07-28 20:54	PPD
Justification	CCI
2020-07-29 08:09	PPD
Justification	CCI
2020-07-29 11:06	PPD
Justification	CCI
2020-07-29 18:26	PPD
Justification	CCI

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