CLINICAL INVESTIGATION PLAN

CLINICAL TRIAL NUMBER: 43USSA2110

CCI [redacted]

CLINICAL INVESTIGATION PLAN

A multi-center retrospective chart review to evaluate the safety of Sculptra Aesthetic when used in non-facial areas.

Clinical Trial Number: 43USSA2110

Statements of compliance

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

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

STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	PPD
Sponsor's authorized representatives	PPD Head of Global Clinical Scientists and Clinical Standards
Medical affairs tech expert	PPD Head of Medical Affairs Strategy Ax
Medical expert	PPD Head of Medical Experts Aesthetics
Statistician	PPD Sr. Clinical Data Analyst/Biostatistician
Clinical scientist	PPD Sr Clinical Scientist
Global safety physician	PPD
Vigilance manager	PPD Vigilance Manager Medical Device, Corporate PV
Clinical project manager	PPD

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

SYNOPSIS

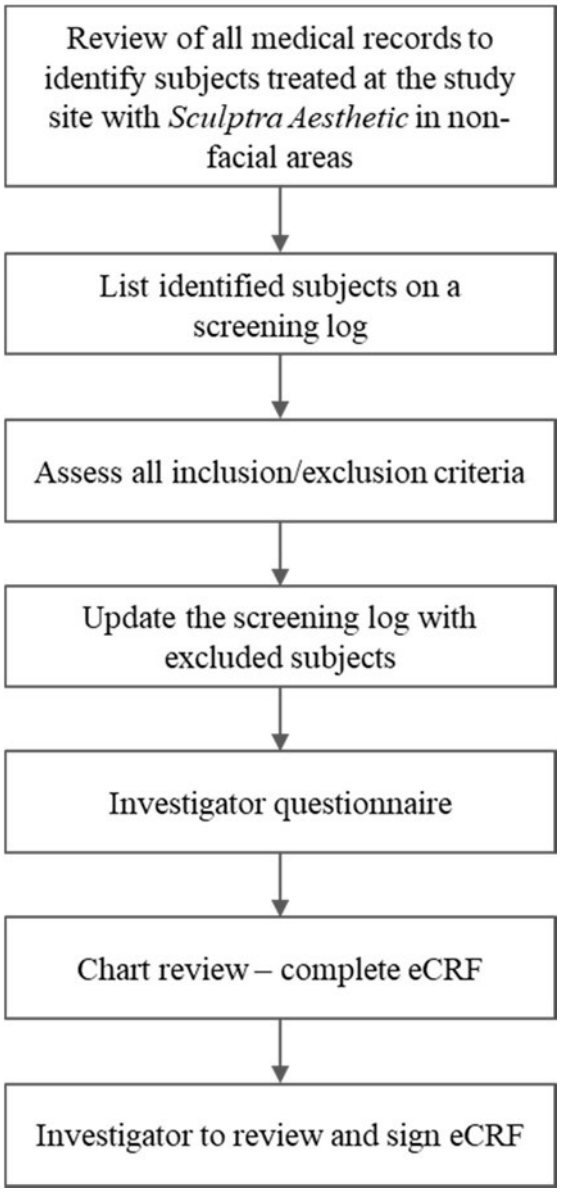
Clinical study title:	A multi-center retrospective chart review to evaluate the safety of *Sculptra Aesthetic* when used in non-facial areas.
Clinical trial number:	43USSA2110
Country(ies) involved :	United States (US)
Planned number of study centers:	8-15 sites
Indication(s):	Non-facial areas
Total number of subjects (planned):	Chart reviews will be performed for approximately 500 subjects.
Clinical study design:	This is a multicenter, retrospective medical chart review to evaluate the safety of *Sculptra Aesthetic* when used in non-facial areas. Sites in the US that have treated approximately 30 subjects or more with *Sculptra Aesthetic* in non-facial areas, during the period January 2018 to December 2020, and has searchable charts with treatments documented, will be considered for participation. Review of medical charts from approximately 500 subjects will be performed. Subjects treated earlier than January 2018 may also be considered for inclusion if needed to reach 500 subjects. Following inclusion, data from all visits/contacts will be reviewed starting from the visit at which the subject had his/her first *Sculptra Aesthetic* treatment in a non-facial area. Chart data will be used to obtain information about demographics, *Sculptra Aesthetic* treatment(s), as well as adverse events (AE)s related to *Sculptra Aesthetic* and to the injection procedure. In addition, the investigator will complete a questionnaire regarding their general use of *Sculptra Aesthetic* in non-facial areas as well as reconstitution and injection procedures.

Target Medical Records:	Subjects treated at the site with *Sculptra Aesthetic* for non-facial areas. Treatment should consist of at least 2 vials in total and at least 2 different treatment sessions (i.e. injections), out of which at least one treatment session should have been performed before December 31, 2020. The Investigator and all other injectors at the respective site will review the medical charts and complete the Injector questionnaire to define their general use of *Sculptra Aesthetic* in non-facial areas as well as reconstitution and injection procedures (name of injector/profession, date of completion of questionnaire, period of use, treatment area, dilution media/volume, additives used, total volume, standing time of reconstituted *Sculptra Aesthetic*, injection depth, reason for treatment, injection tools). Data from all visits/contacts of the included subjects will be reviewed starting from the visit at which the subject had his/her first *Sculptra Aesthetic* treatment in a non-facial area. The following information will be collected from eligible subjects: • Demographic data (date of birth, gender, ethnicity, race) • Relevant medical conditions/surgical procedures • Relevant non-pharmacological treatments and other procedures (including aesthetic treatments) administered in conjunction with *Sculptra Aesthetic* treatment in non-facial areas, or as treatment for an AE related to *Sculptra Aesthetic* treatment in non-facial areas. • Treatment and follow-up data (date of treatment, name of injector, area treated, number of vials used, procedure used) • Additional information on treatment and reconstitution data if other procedure than the general procedure defined in the Injector questionnaire was used (dilution media/volume, additives used, total volume, standing time of reconstituted *Sculptra Aesthetic*, injection depth, reason for treatment, injection tools) • Photos available pre and post treatment (Yes/No) • Treatment related AEs including medical interventions to resolve AEs if applicable
Primary objective and endpoint:	Objective To evaluate the safety of *Sculptra Aesthetic* when used in non-facial areas. Endpoint AEs related to the product or injection procedure reported in the medical chart.
Secondary objectives and endpoints:	Not applicable.
Subgroup analysis:	Subgroup analyses may be performed if appropriate.
Clinical study duration:	First subject in (first chart reviewed) April 2022 / last subject in (last chart reviewed), June 2022. Approximately 3 months for collection of all subject data.
Inclusion criteria:	1. Subjects who have been treated at the site with *Sculptra Aesthetic* in non-facial areas. 2. Treatment should consist of at least 2 vials in total, in at least 2 different treatment sessions, out of which at least 1 treatment session should have been performed before December 31, 2020. 3. Subjects with available information about treatment dates and treatment procedures.

Exclusion criteria:	1. Subjects that have actively asked not to be involved in a study or registry. 2. Other conditions that in the Investigator's opinion would exclude the subject from participation; the condition should be recorded. *Treatment with Sculptra Aesthetic in the face is not a reason for exclusion.*
Study product(s) and treatment of subjects:	*Sculptra Aesthetic* used in clinical practice.
Statistical method:	In general, all variables (including AEs; treatment procedure) will be presented by means of descriptive statistics, as appropriate.
Sample size:	No formal sample size calculation is performed for this study. The sample size of 500 subjects is judged to be sufficient for evaluating the safety of *Sculptra Aesthetic* when used in non-facial areas.

STUDY FLOW-CHART

Figure 1. Study flow chart



ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CTA	Clinical Trial Agreement
eCRF	Electronic Case Report Form
e.g.	For Example (Latin: exempli gratia)
FAS	Full Analysis Set
FDA	Food and Drug Administration
G	Gauge
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act of 1996
i.e.	That is (Latin: id est)
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
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. An Investigator should be a Physician.
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
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or term	Explanation
mL	Milliliter
PI	Principal Investigator. A qualified person responsible for conducting the clinical investigation at an investigation site. If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.
PLLA	Poly-L-lactic acid
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
Study Site	Institution or center where the study is carried out
US	United States
WHO	World Health Organization

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1. BACKGROUND INFORMATION

Poly-L-lactic acid (PLLA) has been used for more than 30 years in a variety of medical devices, including pins, plates, and screws for reconstructive surgery; intrabone and soft-tissue implants; and as vectors for the sustained release of bioactive compounds. PLLA has also been used in soft tissue augmentation since 1999 in Europe and since 2004 in the United States (US).[1]

PLLA is a synthetic, biocompatible, biodegradable polymer. For its use in soft tissue augmentation, it is supplied as a lyophilized powder containing PLLA microparticles. PLLA generates a desired subclinical inflammatory tissue response that leads to encapsulation of the microparticles, stimulation of collagen production, and fibroplasia. Over time, the PLLA degrades, the inflammatory response wanes, and collagen production increases. This response leads to generation of new volume and structural support that occurs in a gradual, progressive manner, and which can last for years.[2]

Sculptra Aesthetic has been approved for facial use in US since 2004.[3] *Sculptra Aesthetic* is an injectable implant containing microparticles of PLLA, indicated for use for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles for use in immune-competent subjects, and for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.[4]

Injection procedure-related adverse events (AE)s may occur like for all injectable substances. The most common of these AEs for *Sculptra Aesthetic* includes bruising, edema, discomfort, hematoma, inflammation and erythema, which are generally transient and resolve spontaneously. Serious adverse events (SAE)s have rarely been reported.[3, 4, 5]

For further information, see *Sculptra Aesthetic* Instructions for Use (IFU).[4]

1.1 Study rationale and justification for design

It is known that the PLLA is used off-label in clinical practice for treatment of various non-facial locations, but there are relatively few publications on non-facial use.

Since the approval of *Sculptra Aesthetic* in 2004, the sterile water for injection (SWFI) volume used for reconstitution of *Sculptra Aesthetic* has gradually increased in clinical practice. Current recommendation is 5 or 8 mL of SWFI, see IFU.[4] 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 recommended volume, and usually in combination with anesthetic solutions like lidocaine 2%.[6, 7]

The purpose of this study is to collect real-world safety data for *Sculptra Aesthetic* when used in non-facial areas.

1.2 Relevant previous data

1.2.1 Non-clinical documentation

The non-clinical data are summarized in the Summary of safety and effectiveness data report.[3]

1.2.2 Clinical documentation

Please refer to the IFU.[4] The IFU summarize the adverse effects experienced with *Sculptra Aesthetic* injections.

2. STUDY DESIGN

2.1 Overall design

This is a multicenter, retrospective medical chart review to evaluate the safety of *Sculptra Aesthetic* when used in non-facial areas.

Sites in the US that have treated approximately 30 subjects or more with *Sculptra Aesthetic* in non-facial areas during the period January 2018 to December 2020, and has searchable charts with treatments documented, will be considered for participation.

Review of medical charts from approximately 500 subjects will be performed. Primarily subjects receiving treatment with *Sculptra Aesthetic* in non-facial areas between January 2018 and December 2020 will be included in the study. Subjects treated earlier than January 2018 may thereafter also be considered for inclusion if needed to reach 500 subjects.

For inclusion to the study, the treatment should consist of at least 2 vials in total and at least 2 different treatment sessions (i.e. injections), out of which at least one treatment session should have been performed before December 31, 2020. The reconstitution volume may differ from instructions in the IFU for *Sculptra Aesthetic*, which recommends reconstitution in 5 mL or 8 mL sterile water for injection.

Following inclusion, data from all visits/contacts will be reviewed starting from the visit at which the subject had his/her first *Sculptra Aesthetic* treatment in a non-facial area. Chart data will be used to obtain information about demographics, *Sculptra Aesthetic* treatment(s), as well as AEs related to *Sculptra Aesthetic* and to the injection procedure. In addition, the investigator will complete a questionnaire regarding their general use of *Sculptra Aesthetic* in non-facial areas as well as reconstitution and injection procedures. See Figure 1. Study flow chart.

Before and after pictures for potential publication/podium presentations may be collected from a few subjects.

2.2 Risks and benefits

This study is a retrospective chart review; no subjects will be exposed to any investigational product because of study participation, therefore there is no anticipated direct risk for the subjects. There is a potential risk of breach of confidentiality of the medical record information and associated privacy of the subject. This risk will be minimized by removing direct subject identifiers in the study database and limiting access to information contained in the chart review files.

The benefit of this study will be the achievement of more knowledge about the real-world safety profile for *Sculptra Aesthetic* using higher reconstitution volume than currently labeled.

2.3 Study duration

First subject in (first chart reviewed) April 2022 / last subject in (last chart reviewed), June 2022. Approximately 3 months for collection of all subject data.

3. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESIS

3.1 Primary objective and endpoints

Primary objective

To evaluate the safety of *Sculptra Aesthetic* when used in non-facial areas.

Endpoint

AEs related to the product or injection procedure reported in the medical chart.

3.1.1 Secondary objectives and endpoints

Not applicable.

3.1.2 Subgroup analysis

Subgroup analyses may be performed if appropriate.

4. STUDY POPULATION

Chart reviews will be performed for approximately 500 subjects.

4.1 Informed consent

As this is a retrospective chart review, a waiver of consent will be requested from the Institutional Review Board (IRB) (see Section 10.1.2).

Before and after pictures for potential publication/podium presentations may be collected from a few subjects. Informed consent will be collected from these subjects. After adequate verbal and written information, and before collection of pictures, the Informed Consent Form (ICF) must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. A copy of the subject information sheet, including the signed ICF, will be provided to the subject. The date of informed consent must be recorded in the source documentation and in the electronic Case Report Form (eCRF). The subject information sheet and the signed ICF should be filed by the investigator for possible future audits and/or inspections.

4.2 Subject screening and enrollment

Investigators must keep a record of all patients that were considered for enrolment even if they were not subsequently enrolled. This information is necessary to verify that the patient population was selected without bias (the International Conference on Harmonization [ICH] guideline for Good Clinical Practice [GCP] 8.3.20). All potentially eligible subjects must be documented on a screening log.

Based on the inclusion and exclusion criteria, investigators will screen all potentially eligible subjects on the screening log by reviewing their medical chart, starting from December 31, 2020 and going backwards in consecutive order, and any reason for non-inclusion will be documented. Subjects eligible for the study will be allocated a subject number in consecutive order. Each subject will be identified using the subject number for all documentation and discussion. A subject identification log is required to be kept in the Investigator file

4.3 Inclusion criteria

For inclusion in the study, subjects must fulfil all of the following criteria:

1. Subjects who have been treated at the site with *Sculptra Aesthetic* in non-facial areas.
2. Treatment should consist of at least 2 vials in total, in at least 2 different treatment sessions, out of which at least 1 treatment session should have been performed before December 31, 2020.
3. Subjects with available information about treatment dates and treatment procedures.

4.4 Exclusion criteria

Subjects who fulfill any of the following criteria must not be included in the study:

1. Subjects that have actively asked not to be involved in a study or registry.
2. Other conditions that in the Investigator's opinion would exclude the subject from participation; the condition should be recorded.

Treatment with Sculptra Aesthetic in the face is not a reason for exclusion.

4.5 Study termination and discontinuation of subjects

The Sponsor will suspend or terminate the study when so instructed by the Regulatory Authority (RA) in US, the US Food and Drug Administration (FDA) or the IRB, 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 enrollment or non-compliance with the Clinical Investigation Plan (CIP) or applicable regulatory requirements.

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

Discontinuation of subjects will not be applicable as this is a retrospective chart review study.

5. STUDY INTERVENTION

Not applicable. As this is a retrospective chart review study no study products will be provided.

6. CHART REVIEW

As this is a retrospective chart review study, there will be no study specific subject visits. Data from all visits/contacts of the included subjects will be reviewed starting from the visit at which the subject had his/her first *Sculptra Aesthetic* treatment in a non-facial area. The site study personnel or other delegated representative will record the information retrieved from the chart review in the eCRF.

6.1 Eligibility

Eligibility criteria should be checked during screening as specified in sections 4.2, 4.3 and 4.4.

6.2 Injector questionnaire

The Investigator and all other injectors at the respective site will review the medical charts and complete the Injector questionnaire, which defines their general use of *Sculptra Aesthetic* in non-facial areas as well as reconstitution and injection procedures, for each area of the body. The following data will be captured:

- Name of injector, profession
- Date of completion of questionnaire
- Period during which the procedure was generally used
- Treatment area
- Dilution media, volume used
- Use of lidocaine or another added ingredient
- Total volume of liquid added to reconstitute *Sculptra Aesthetic*
- Storage time of reconstituted *Sculptra Aesthetic* before use
- Injection depth
- Reason for non-facial *Sculptra Aesthetic* treatment (volume, sagging/loose skin/laxity, cellulite [dimples/depressions/undulations], skin quality/texture, scar, skin firmness, wrinkles)
- Injection tool; needle/cannula (including Gauge [G], length and brand)
- Use of injection guidance tool (e.g.; ultrasound guided injections, AccuVein® [near-infrared light])

6.3 Demography

The following demographic and baseline characteristic data will be captured in the eCRF:

- Date of birth
- Gender
- Ethnicity
- Race

6.4 Medical conditions/surgical procedures

History of relevant medical conditions and/or surgical procedures should be documented in the eCRF using medical terminology.

6.5 Non-pharmacological treatments

History of relevant non-pharmacological treatments and other procedures (including aesthetic treatments) administered in conjunction with *Sculptra Aesthetic* treatment, or as treatment for an AE related to *Sculptra Aesthetic* treatment, should be documented in the eCRF using medical terminology.

6.6 *Sculptra Aesthetic* treatment and follow-up

The dates of all *Sculptra Aesthetic* treatment will be identified. One *Sculptra Aesthetic* treatment form in the eCRF should be completed for each treatment session. The following data (as available) should be collected from the medical charts and recorded in the form:

- Date of treatment
- Name of injector
- Area treated
- Number of vials used
- Procedure used; general procedure defined in the Injector questionnaire or other procedure.

If other procedure than the general procedure defined in the Injector questionnaire (section 6.1) was used, following additional information will be recorded:

- Dilution media, volume used
- Use of lidocaine or another added ingredient
- Total volume of liquid added to reconstitute *Sculptra Aesthetic*
- Storage time of reconstituted *Sculptra Aesthetic* before use
- Injection depth
- Reason for non-facial *Sculptra Aesthetic* treatment
- Injection tool; needle/cannula (including G, length and brand)
- Use of injection guidance tool (e.g.; ultrasound guided injections, AccuVein® [near-infrared light])

To capture safety data, all follow-up visits after the initial *Sculptra Aesthetic* treatment will be recorded by date and any AEs related to *Sculptra Aesthetic* treatment recorded in the charts will be captured as defined in Section 8.1.4.

Photos available pre- and post-treatment will be collected if the subject has signed an informed consent for collection of photos.

7. EFFECTIVENESS ASSESSMENTS

Section is not applicable.

8. SAFETY ASSESSMENTS

AEs and SAEs related to the *Sculptra Aesthetic* or the injection procedure in non-facial areas will be identified by review of the medical charts and reported within the study. Events resulting from treatment in facial areas and not previously reported to the Sponsor or RA, will be reported as spontaneous post marketing reports.

8.1 Adverse events

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

This definition includes:

a) events related to *Sculptra Aesthetic*

b) events related to the procedures involved

8.1.2 Assessment of severity

Severity is a clinical determination of the intensity of an AE and not the severity of a disease. The investigator should classify the intensity of the event according to the following definitions:

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

8.1.3 Definition of a serious adverse event

Each AE shall be assessed by the Investigator for seriousness (Yes or No) of the event. SAEs should be recorded in a SAE form.

A SAE is an AE that:

a) led to death,

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

   a. a life-threatening[II] illness or injury, or

   b. a permanent impairment of a body structure or body function, or

   c. hospitalization or prolonged hospitalization[III], or

   d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

   e. chronic disease

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

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

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

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

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

8.1.4 Recording instructions

All AEs and SAEs identified by the Investigator during the medical chart review and assessed as related to the product or injection procedure in conjunction with *Sculptra Aesthetic* treatment in non-facial areas, should be collected and documented in the AE/SAE form in the eCRF.

Following information should be recorded for all AEs and SAEs:

- Event term (recorded in standard medical terminology and avoiding abbreviations)
- Affected area
- Start date (first day with symptoms)
- Stop date (last day with symptoms)
- Intensity (mild, moderate, or severe according to definition in Section 8.1.2)
- Seriousness (serious or not serious)
- Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests)
- Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable)

For SAEs following additional information should be recorded:

- Date when AE became serious (SAE onset date)
- Course of event
- Classification of seriousness
- Information on if the AE has been reported to the Sponsor or RA previously.

The AE/SAE form must be signed and dated by the Investigator.

8.1.5 SAE reporting

If an SAE, assessed as suspected related, is discovered during the medical chart review an SAE form should be completed and reported to the Sponsor.

The Investigator shall report any related SAE to the Sponsor immediately but not later than 24 hours of awareness of the event. This report should be made by recording the SAE in the eCRF. If not possible to complete the report in the eCRF, a paper form can be completed, signed and sent to the Sponsor via:

E-mail:	PPD
Or fax:	PPD

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

Surface mail for providing complementary information: PPD

The report must be completed as detailed as far as possible, but in case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information:

- Site identification
- Subject identification (age, gender, initials, subject number)
- AE description
- Date when AE occurred
- Name of treating physician
- Name of study product including batch number

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the Sponsor. 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, including possible treatments for the SAE
- AE form
- Medical history
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

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

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.

If the SAE has not been reported as part of standard post market surveillance, the Sponsor will report the event to FDA in accordance with national regulations (21 CFR 803).

8.2 Pregnancy

Pregnancy itself is not regarded as an AE. Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect shall be reported on the exposure in utero report form to the Sponsor immediately but no later than 24 hours after the Investigator's awareness, using the contact details specified in section 8.1.5. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, and has been assessed as related to treatment with *Sculptra Aesthetic*, shall be handled and reported as SAEs to the Sponsor within the study according to procedure defined in 8.1.5.

9. STATISTICAL DESIGN AND ANALYSIS

9.1 General

The principal features of the statistical analysis of the study data are described in this section. More details of the planned statistical analysis will be described in a separate Statistical Analysis Plan (SAP) that will be finalized prior to database lock. Any deviations from the SAP will be documented in the clinical investigation report.

All statistical analyses, including summary tables and data listings, will be performed using SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC, US).

In general, all variables will be presented by means of descriptive statistics and figures, as appropriate. Continuous variables will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum, while categorical variables will be presented using number of subjects and percentages.

All statistical analyses will be descriptive.

9.2 Analysis data sets and populations

All analyses will be performed on the full analysis set (FAS), i.e. subjects fulfilling all inclusion criteria and none of the exclusion criteria.

9.3 Coding

'Relevant medical conditions and/or surgical events', 'Relevant non-pharmacological treatments administered in combination with Sculptra' and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Medications will be coded according to the to the World Health Organisation's (WHO) drug dictionary / WHO Anatomical Therapeutic Chemical (ATC) classification system and presented by therapeutic subgroup (ATC level 2) and chemical substance (ATC level 5). If a reported medication cannot be coded with a Preferred Name, the lowest available higher-level dictionary term will be used instead. If a medication cannot be coded on a lower level than the therapeutic subgroup or the anatomical main group (ATC level 1), that medication will be presented as 'Not codable' under that therapeutic subgroup/anatomical main group.

9.4 Effectiveness analysis

Section is not applicable.

9.5 Safety analysis

All AEs will be summarized by system organ class (SOC) and Preferred Term (PT) and intensity if available. The number of days to onset and the duration of the event will be summarized by SOC and PT using mean, SD, min, max and median statistics if available. The summary will include:

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

Serious AEs and AEs with onset >21 days after most recent treatment will be listed.

9.6 Subgroup analyses

Subgroup analyses may be performed if appropriate. The subgroup analyses will be descriptive in nature.

9.7 Handling of missing data

Data will be presented using observed cases only.

9.8 Interim analysis

No interim analysis is planned for this study.

9.9 CIP deviations

CIP deviations will be listed including subject number and observed deviation. Deviations from the statistical plan will be documented in the Clinical Study Report.

9.10 Sample size

No formal sample size calculation is performed for this retrospective chart review. The sample size of 500 subjects is judged to be sufficient for evaluating the safety of *Sculptra Aesthetic* when used in non-facial areas.

10. ETHICS AND GENERAL CLINICAL STUDY CONDUCT

10.1 Ethical considerations

10.1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the CIP, 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.[8]

The study shall follow the international standard for clinical study of medical devices for human subjects, ISO 14155:2020 or later updates as applicable for US regulations, and the ICH guideline for GCP (E6[R2]) as applicable for medical device.

10.1.2 Application to independent ethics committee and/or regulatory authorities

This is a retrospective chart review of subjects treated with *Sculptra Aesthetic* for any non-facial indication. A waiver of informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be requested from the IRB.

A waiver of consent is requested for this retrospective chart as the following criteria are met:

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Each enrolled subject's medical records will be reviewed by the PI or designee for demographics, treatment data, other non-facial aesthetic treatment and treatment related AEs. Information will be collected on individual data collection sheets and stored in a password-protected database/eCRF. A code will be used to protect subject confidentiality. The key to the code will be kept separate for the data. At the completion of the data analysis the key to the code will be destroyed.

As this is a retrospective chart review, application for approval from the RA (FDA) is not required.

It is the responsibility of the PI to obtain approval of the CIP/CIP amendment(s) from the 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 shall be followed.

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

10.2 Personnel training

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. All personnel involved in the study shall be listed together with their function in the study on a signature and delegation log.

10.3 Data management and documentation

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.

The database, the data entry screens, and program will be designed in accordance with the CIP and the eCRF specification. Data validation will be performed by computerized logical checks and manual review.

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.

10.3.1 Data entry and collection

A 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and should be completed electronically for each screen failure as well as enrolled subjects.

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified for the site. Study data should be entered directly from the source documents, which are to be defined at each study center before inclusion of the first subject. Source documents are all documents used by the investigator or hospital that relate to the patient's medical history, that verifies the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the study. They include laboratory notes, memoranda, material dispensing records, patient files, etc.

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

The study data is the sole property of the Sponsor and should 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.

Roles and rights of the study site personnel for data collection, entering of study data into the eCRF and data sign off shall be determined before start and specified in a delegation log.

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 PI or authorized study staff must verify that all data entries in the eCRFs are accurate and correct. The PI shall electronically sign off the study data. By signing, the signee takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

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. 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 authorized designee. This will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records shall be electronically signed by the PI to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means

of the PI's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

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.

10.3.2 Source documentation

The eCRF is essentially considered a data entry form and does not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents at the site that relate to the subject's medical history, that verify the existence of the subject and the eligibility criteria etc.

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

These shall be made available for review by the monitor at each monitoring visit.

10.3.3 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 PI are responsible for complying with all requirements pursuant to national legislation in which the Institution and the PI are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The Institution and PI are jointly responsible for providing sufficient information as applicable to subjects participating in the collection of before and after pictures to enable them to give their informed consent 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. Should a subject be provided an informed consent, they may withdraw their 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 European Union (EU) 2016/679 (General Data Protection Regulation; GDPR) and the regulation EU 2017/745 (Medical Devices Regulation; MDR) on the protection of individuals with regard to the processing of personal data and. For the purposes of the study, the Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

10.3.4 Archiving / record keeping

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

All records pertaining to the study, including signed eCRFs, ICFs, source documents, and other study documentation must be retained for as long as is specified in the CTA. Measures should be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

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.

10.4 CIP deviations

The PI is not allowed to deviate from the CIP and no up-front waivers from the CIP will be issued. 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 of the subject or the scientific integrity of the study to the Sponsor (within 24 hours following detection) as well as the IRB if required by national regulations.

10.5 Quality control / quality assurance

10.5.1 Clinical Monitoring

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. Specific details about monitoring in the study will be outlined in a separate monitoring plan.

10.5.2 Audits / inspections

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

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

10.6 CIP amendments

The PI and other study 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 amendment.

10.6.1 CIP amendment history

Not applicable, this is the first submitted version.

10.6.2 CIP history

Not applicable, this is the first submitted version.

10.7 Financing, indemnification and insurance

This is a Galderma fully sponsored study. The CTA between sponsor and investigational study sites 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.

The Sponsor´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.

10.8 Publication policy

The PI's, Institution's, and CCI 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 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[V]. 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 CCI to take primary responsibility for the overall work as primary author.

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

11. REFERENCES

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4. Sculptra Aesthetic Instructions for Use: QMS-10261 Instructions for Use Sculptra Aesthetic, US, V6.0
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8. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

SIGNED AGREEMENT OF THE CLINICAL INVESTIGATION PLAN

Clinical trial number: *43USSA2110*

Clinical study title: *A multi-center retrospective chart review to evaluate the safety of Sculptra Aesthetic when used in non-facial areas*

I, the undersigned, have read and understand the clinical investigation 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 (IFU) will serve as a basis for co-operation in this study.

Principal Investigator Signature	Date
Printed Name	Title
Institution	Study Center Number

Sponsor signatures

The CIP is electronically signed in the document management system within the CCI quality management system by the representatives listed below.

Head of Clinical Project Management
PPD

Medical Affairs Tech Expert
PPD

Medical Expert
PPD

Statistician
PPD

Clinical Scientist
PPD

Scientific Writer
PPD

GALDERMA EST. 1981	Title **43USSA2110 Sculptra Chart Review CIinical Investigation Plan**	Doc id **MA-50102**

SIGNATURES PAGE

Date	Signed by
2021-12-17 15:21	PPD
Justification	Compiled by
2021-12-17 19:46	PPD
Justification	Approved by Owner
2021-12-20 06:49	PPD
Justification	Approved by Technical Expert
2021-12-21 13:51	PPD
Justification	Approved by Technical Expert
2021-12-22 13:08	PPD
Justification	Approved by Technical Expert
2022-01-03 12:10	PPD
Justification	Approved by Medical Affairs