Statistical Analysis Plan

Clinical Trial Number: 43USSA2110

Revision History

Version	Date	Comments
V1.0	01SEP2022	1. Initial version.

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1 Study Information

1.1 Background

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from Clinical Investigational Plan (CIP) 43USSA2110 (v2.0), dated 27 APR 2022. No subjects were entered prior to CIP v2.0.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

1.1.1 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. 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.

1.1.2 Number of Subjects and Randomization

Approximately 8-15 sites will be included, with a minimum 1 injector per site. Chart reviews will be performed for approximately 500 subjects.

This study is not randomized.

1.2 Study Objectives

1.2.1 Primary Objective

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

1.2.2 Secondary Objectives

Not applicable.

1.3 Effectiveness Assessments

Not applicable.

1.4 Effectiveness Endpoints

Not applicable.

1.5 Safety Assessments

The methods for collecting safety data are described in Section 8 of the CIP. Data to be collected include the following:

- Adverse events (AEs)
- Pregnancy

1.6 Safety Endpoints

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

1.7 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]).

2 Statistical Methods

2.1 General Methods

Any change made to the finalized SAP before database lock will result in an SAP amendment. Otherwise, changes will be documented in the Clinical Study Report (CSR). However, if additional supportive or exploratory analyses are requested after SAP approval, this will not require amendment of the SAP, but these additional analyses will be described in the CSR.

Some of the analyses detailed here may be more explicit or in some respects different from those stated in the CIP. In case of differences, this SAP supersedes the statistical sections in the CIP.

2.1.1 Programming Conventions

EMB Statistical Solutions will have responsibility for performing analyses. All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

The electronic case report form (eCRF) data for all subjects will be provided in analysis datasets. The analysis datasets will be used in table and figure production.

2.1.2 Reporting Conventions

The formats for the tables, listings, and figures described in this SAP will be provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the CSR.

Study data from the eCRFs as well as derived variables will be provided in injector/subject data listings. An indication of specific listings for each data type will not be indicated in the text of subsequent SAP sections. Data listings supplied as part of the CSR will be sorted by site number concatenated with subject number and assessment dates.

The following conventions will be applied to all data presentations and analyses:

- Quantitative variables will generally be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum. Unless otherwise specified, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data.
- Categorical variables will be summarized by the number and percentage of subjects (and number of events where appropriate) within each category. Unless otherwise specified, the percentage will be presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as ‘0’ rather than ‘0 (0)’.

- All summary tables will include the analysis population sample size (i.e., number of subjects).
- Date variables will be formatted as DDMMMYYYY for presentation.

2.1.3 Handling of Missing Data

Only observed data will be included in summaries, no imputation of missing data will be performed.

2.2 Analysis 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.

2.3 Study Subjects

Demographic endpoints and subject characteristics will be summarized using descriptive statistics based on the FAS population using observed cases. There are no planned inferential statistical analyses of demographic endpoints or subject characteristics.

2.3.1 Subject Disposition

The number of subjects screened and screen failures will be summarized in total. The number of subjects in the FAS will be summarized by study site and in total.

2.3.2 CIP Deviations

Subjects with any CIP deviations will be listed by subject. CIP deviations of each category will be summarized overall and by site.

2.3.3 Demographic Characteristics

Age will be summarized as a continuous variable. Gender, race, and ethnicity will be summarized as categorical variables.

2.3.4 Medical and surgical history, concomitant medication/procedures

All summaries will be presented overall based on the FAS population.

Relevant medical conditions and/or surgical procedures and relevant non-pharmacological treatments will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Medications administered as treatment for an AE related to *Sculptra Aesthetic* treatment will be coded using the World Health Organization's (WHO) Drug Dictionary / WHO Anatomical Therapeutic Chemical (ATC) Class Level 3 (if Level 3 is not available, the highest class available will be used) and WHODD generic name. If a reported medication cannot be coded with a generic name, the lowest available higher-level dictionary term will be used instead. If a medication cannot be coded on a lower level than the anatomical main group (ATC level 1), that medication will be presented as 'Not codable' under that therapeutic subgroup/anatomical main group.

The number and percent of subjects reporting medical history, and the number of events will be summarized by system organ class (SOC), in total and for ongoing events.

The number and percent of subjects reporting concomitant medications taken due to an AE, and the number of drugs, will be summarized. Also, the number and percent of subjects, and the number of drugs, will be summarized by ATC code.

2.4 Injectors

2.4.1 Injectors by Site

The number of injectors will be summarized by site, by profession and overall.

2.4.2 Injector Questionnaire

The number of injectors reporting use of *Sculptra Aesthetic* in each treatment area, number of vials, dilution media and volume, other ingredient added, reconstitution volume and time before use, and administration characteristics including depth of injection, reason for treatment, injection tool and other tools used will be provided.

All information collected on the Injector Questionnaire will be listed by site and injector.

2.5 Effectiveness Analysis

Not applicable.

2.6 Safety Analysis

Safety endpoints will be summarized using descriptive statistics. There are no planned inferential statistical analyses of safety endpoints.

2.6.1 Treatment Administration and Procedural Anesthetics

Treatment administration endpoints will be summarized for each treatment session by treatment area and overall. These include (but are not limited to): area treated, number of vials used, dilution media/volume used, use of lidocaine injection volume, injection method, and depth of injection.

If 'general procedure used' was captured for a given subject, the information described on the Injector Questionnaire will be used for summaries and listings.

Additionally, the number and percentage of subjects that received treatment in each treatment area and the number and percentage of subjects that received 2, 3, 4, etc. treatments will be summarized.

2.6.2 Related Adverse Events (AEs)

All related AEs will be coded according to MedDRA and summarized by System Organ Class (SOC), Preferred Term (PT). The time to onset and duration of each related AE will be derived. Time to onset (days) will be derived as the AE start date minus most recent treatment date. Duration will be derived as stop date minus start date plus 1.

An overall summary of related AEs will be provided. This 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 with at least one AE with late onset, and number of events (in total as well as serious).

- Number of subjects who did not have an AE reported in the chart.

The following will be provided summarized by SOC and PT for related AEs:

- Number of subjects and number of events.
- Number of subjects and number of events by maximum intensity.
- Number of events by action taken.
- Number of days to onset and duration of event summarized as continuous variables.

For subject counts, a subject will only be counted once per SOC and once per PT at the worst severity in cases where multiple events are reported for a subject within SOC or PT. For event counts, subjects with multiple events in a category will be counted for each event.

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

2.6.3 Other Safety Data

All follow-up visits occurring after treatment will be listed by subject.

Chart review verification information will be listed by subject.

2.7 Interim Analysis

There are no planned interim analyses for this study.

2.8 Determination of 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.

2.9 Changes in the Analysis Planned in the CIP

There have been no substantial changes from the statistical methods described in the CIP.

3 Reference List

There are no other references beyond those that are included in the CIP.

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SIGNATURES PAGE

Date	Signed by
2022-09-02 13:29	PPD
Justification	Approved by Owner

2022-09-02 14:10	PPD
Justification	Approved by Technical Expert

2022-09-07 17:09	PPD
Justification	Approved by Project Manager