Statistical Analysis Plan

Clinical Trial Number: 43USSA1705ext

Effective

Open label Extension study for 43USSA1705 (A randomized, evaluator-blinded, multi-center study to evaluate the safety and effectiveness of Sculptra Aesthetic for correction of nasolabial folds)

Revision History

Version	Date	Revision Author	Comments
[redacted]	[redacted]	[redacted]	[redacted]

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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 the open label extension for Protocol 43USSA1705, named Protocol 43USSA1705ext (v3.0), dated 02 MAR 2020.

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 48-week prospective, open-label follow-up study, with the aim to evaluate the long-term safety and effectiveness of treatment with Sculptra Aesthetic for correction of Nasolabial Fold (NLF) contour deficiencies. Participation will be limited to the five sites who participated in the 43USSA1705 study.

Eligible subjects in 43USSA1705 were treated with a single regimen of Sculptra Aesthetic [redacted]

[redacted]. Subjects will enter this extension study upon completion of the 43USSA1705 study and perform follow-up visits at [redacted] after baseline (i.e. Day1/first treatment session in the 43USSA1705 study).

1.1.2 Number of Subjects

Approximately 60 subjects will be recruited from five US sites [redacted]. Since this is an extension study, no sample size calculation is needed.

1.2 Study Objectives

1.2.1 Safety Objective

The objective is to evaluate the long-term safety of Sculptra Aesthetic as a single regimen [redacted]

1.2.2 Effectiveness Objective

The objective is to evaluate the long-term effectiveness of Sculptra Aesthetic as a single regimen for correction of NLF contour deficiencies [redacted]

1.3 Effectiveness Assessments

For all assessments, baseline will be defined as the observation that is closest to but prior to study treatment on Day 1 in study 43USSA1705. Likewise, change from baseline will be calculated as the value at a given time point minus the baseline value.

1.3.1 [redacted]

[redacted] is a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds. Scoring of fold severity is based on visual assessment of the length and apparent depth of the wrinkle at a certain time-point. Scoring of the left and right nasolabial folds separately [redacted] will be based on visual live assessment by the Evaluator at defined time points, and not on a comparison to the baseline appearance.

[redacted] will be assessed at [redacted] after baseline.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

1.3.2 [redacted]

The aesthetic improvement of the nasolabial folds will be assessed by the Investigator and the subject, independently of each other. [redacted]

[redacted]

[redacted] will be assessed by the Investigator and Subject at [redacted] after baseline. The following categorical scales will be used (Table 2).

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] is a patient-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. [redacted].

1.3.4 [redacted]

[redacted] ne.

1.4 Effectiveness Endpoints

- Change from baseline on both sides [redacted] as assessed by the Evaluator [redacted] after baseline.
- Responder rate using [redacted] at [redacted] after baseline.

  [redacted].
- Responder rate using the [redacted] at [redacted] after baseline.

  [redacted]
- [redacted] at [redacted] after baseline.
- [redacted] at [redacted] 2 and [redacted] after baseline.

1.5 Safety Assessments

The methods for collecting safety data are described in Section 7 of the Clinical Study Protocol.

1.6 Safety Endpoints

Safety endpoints include incidence, intensity, time to onset, and duration of adverse events collected throughout the study period.

2 Statistical Methods

2.1 General Methods

Any change made to the finalized SAP before database lock will result in a SAP amendment. Otherwise, the change will be documented in the Clinical Study Report (CSR).

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

2.1.1 Programming Conventions

[redacted] 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 Standard Data Tabulation Model (SDTM) datasets. Analysis Data Model (ADaM) datasets will be developed from the SDTM datasets for use 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.

All study data from the eCRFs as well as derived variables will be provided in 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 study center number concatenated with subject number, assessment dates, and/or time point.

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 number of subjects.
- Date variables will be formatted as DDMMMYYYY for presentation.

2.1.3 Data Transformations

The [redacted] will be reported (Section 4).

2.2 Analysis Populations

Only one population will be defined: The Extension population. The Extension population includes all subjects entering the extension study. This would include all subjects who are signing the extension study informed consent.

2.3 Study Subjects

Demographic endpoints and subject characteristics will be summarized using descriptive statistics using the Observed Cases. There are no planned inferential statistical analyses of demographic endpoints or subject characteristics.

2.3.1 Subject Disposition

The number of subjects enrolled will be shown in total and by study center.

The disposition of subjects will be summarized, including numbers of subjects who were:

- Completed,
- Withdrawn (including primary reason for withdrawal).

These numbers will be summarized by study center. The number of subjects expected, completed, missed, and withdrawn will be summarized by scheduled visit.

- Expected = all subjects minus withdrawn subjects.
- Completed = subjects that showed up at that visit.
- Missed = expected subjects minus completed subjects.
- Withdrawn = all subjects who have withdrawn up to that visit.

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

2.3.2 Protocol Deviations

Subjects with deviations will be summarized and listed individually. Summaries will be by COVID-19 related deviations and overall. Listings will include subject number and observed deviation.

2.3.3 Demographic Characteristics

Age, body mass index (BMI) and [redacted] will be summarized as continuous variables. Gender, race, ethnicity, Fitzpatrick skin type, and childbearing potential will be summarized as categorical variables.

2.3.4 Medical History, Medications, and Procedures

Medical history and cosmetic history were captured in the pivotal study, and will be summarized for the Extension population.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). Concomitant procedures/non-pharmacological treatments will be coded according to Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant therapies are defined as follows:

- Any therapy ongoing at the time of V11/Week 48.
- Any changes to existing therapies (such as changes in dose or formulation) during the course of the study, or
- Any new therapies started after V11/Week 48.

Subjects reporting concomitant medications will be summarized separately, by WHODD Anatomical Therapeutic Chemical (ATC) Class Level 3 (if Level 3 is not available, the highest class available will be used) and WHODD generic name. Additionally, concomitant medications taken due to adverse events will be summarized separately.

Prior and concomitant procedures will be listed.

2.4 Effectiveness Analysis

2.4.1 Datasets Analyzed

All effectiveness variables will be analyzed based on the Extension population.

2.4.2 Handling of Missing Data

The number of missing values will be summarized and reported as appropriate.

All effectiveness endpoints will be evaluated based on Observed Cases.

2.4.3 Effectiveness Analysis

The baseline value is defined as the observation that is closest to but prior to study treatment at the baseline visit/first treatment in the 43USSA1705 study. Change from baseline is calculated as the value minus the baseline 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 baseline throughout the study will be presented for the Extension population.

[redacted]

The change from baseline in [redacted] at each follow-up visit based on the Evaluator's assessment, for the right and left side of the face separately, will be calculated using descriptive statistics. In addition, the number and percent of subjects in each response category will be presented. The [redacted] be calculated along with their two-sided exact 95% confidence interval.

[redacted]

The proportion of improved subjects based on [redacted] at each follow-up visit will be calculated along with their two-sided exact 95% confidence intervals. The proportions will be calculated separately for the subject's assessment and for the Investigator's assessment. [redacted] In addition, the number and percent of subjects in each response category will be presented.

[redacted]lds

[redacted] scores will calculated and presented at all follow-up visits using descriptive statistics. The number and percent of subjects in each response category for each question will also be presented.

Subject satisfaction

Subject satisfaction will be presented using descriptive statistics as appropriate for each follow-up visit.

2.5 Safety Analysis

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

2.5.1 Adverse Events

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

A summary of all AEs (number and percentage of subjects with at least one event and number of events) will be provided, which will include:

- Subjects with at least one AE (in total as well as serious AEs).
- Subjects with at least one study product or injection procedure-related AE (in total as well as serious AEs).
- Subjects with at least one unrelated AE (in total as well as serious AEs).
- Number of subjects who did not have an AE.

The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT, and severity.

In addition, for related AEs the number of days to onset from last treatment (in the 43USSA1705 study) and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median.

- Time to onset of an AE will be derived as the start date minus the date of the most recent treatment. If the start date is missing, it will be assumed that the AE started on the first day of the extension study.
- Duration of an AE will be derived as the stop date minus the start date + 1. Missing stop dates will not be imputed and therefore no duration will be calculated in these cases.

Action taken for related AEs will also be summarized. Non-related AEs will be summarized by SOC, PT, and intensity.

These summaries will be performed for:

- The whole period from baseline [redacted] to the end of the extension study [redacted]
- The period from baseline to the end of the 43USSA1705 study ([redacted]
- The period from start of the extension study [redacted] to the end of the extension study [redacted]

Serious AEs that starts during the extension study will be listed.

2.5.2 Subgroup analyses

Subgroup analyses will be performed for adverse events (number and percent of subjects with related adverse events as well as number of events by SOC, PT, and severity) on subgroups defined by study center and FST group (I-III, IV, and V-VI) respectively.

2.6 Interim Analysis

No interim analysis is planned.

2.7 Changes in the Analysis Planned in the Protocol

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

3 Reference List

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
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Date	Signed by
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Effective