Statistical Analysis Plan

Clinical Trial Number: 43USSA1705

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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 Protocol 43USSA1705 (v3.0), dated 15 OCT 2018.

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 randomized, multicenter, evaluator-blinded study to evaluate the safety and effectiveness of Sculptra Aesthetic for correction of nasolabial folds.

Eligible subjects will be treated with a single regimen of Sculptra Aesthetic on both sides of the face, starting at the baseline visit. A single regimen consists of up to 4 injection sessions with 4-week (+7 days) intervals. Subjects will be treated with either Sculptra Aesthetic reconstituted with 8 mL of sterile water for injection (SWFI) or with Sculptra Aesthetic reconstituted with 5 mL of SWFI.

Subjects will be randomized (2:1) to either treatment with Sculptra Aesthetic reconstituted with 8 mL of SWFI or to treatment with Sculptra Aesthetic reconstituted with 5 mL of SWFI.

At least eight (8) subjects will be Fitzpatrick skin type (FST) IV and at least eight (8) subjects will be FST V-VI. [redacted]

Clinical study participation for each subject is up to approximately 52 weeks from screening to the final follow-up visit.

1.1.2 Number of Subjects

The study is planned to enroll approximately 80 subjects at approximately 5 centers in the United States.

1.2 Study Objectives

1.2.1 Safety Objective

The objective is to evaluate the safety of Sculptra Aesthetic as a single regimen for correction of Nasolabial Fold (NLF) contour deficiencies [redacted]

1.2.2 Effectiveness Objective

The objective is to evaluate the 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. Likewise, change from baseline will be calculated as the value at a given time point minus the baseline value.

1.3.1 [redacted] Scale ([redacted]

The [redacted] is a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds. [redacted]

[redacted] 8.

[redacted]

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1.3.5 Subject Diary

A subject diary will be dispensed to all subjects for daily completion for 28 days beginning on the injection day for each treatment with direct questioning f[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Effectiveness Endpoints

1.4.1 Primary Effectiveness Endpoint

Change from baseline on both sides of the face as assessed by the Blinded Evaluator using [redacted] at 48 Weeks after the first treatment session.

1.4.2 Secondary Effectiveness Endpoints

Secondary effectiveness endpoints include:

- Change from baseline on both sides of the face as assessed by the Blinded Evaluator using [redacted]
- Response to treatment using the [redacted] Scale ([redacted] at Weeks 16, 24, 32, 40 and 48. [redacted]
- [redacted]: Nasolabial Folds Questionnaire at Baseline and at Weeks 24, 32, 40 and 48.
- Subject satisfaction score [redacted] Weeks 16, 24, 32, 40 and 48.
- [redacted]

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.
- Incidence, intensity, time to onset and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days from each treatment.
- [redacted]

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.

For the study to be deemed successful, the following criteria need to be met:

- The primary effectiveness endpoints (change from baseline in [redacted] at Week 48 as assessed by the Blinded Evaluator) should be statistically significantly < 0 on both sides of the face in the treatment group

- The confidence intervals around the point estimates of the primary effectiveness endpoints in the treatment group should overlap with those of the reference group
- Acceptable safety profile in the treatment group.

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 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 analysis population sample size (i.e. number of subjects).
- Date variables will be formatted as ddMMMYYYY for presentation.

2.1.3 [redacted]

[redacted]

2.2 Analysis Populations

The statistical analyses will be performed based on the following subject populations.

[redacted] Sensitivity analyses will include only randomized subjects (Section 2.4.3 and Section 2.5.2).

2.2.1 Intent-to-Treat Effectiveness Population

The Intent-to-treat (ITT) population includes all subjects who were randomized, or FST IV-VI subjects receiving Sculptra Aesthetic re-constituted with 8 mL of SWFI without randomization. All primary and secondary effectiveness variables will be analyzed based on the ITT population.

2.2.2 Per-Protocol Effectiveness Population

The Per-Protocol (PP) population includes all ITT subjects who have no protocol deviations considered to have a substantial impact on the primary effectiveness outcome, and will be analyzed according to the randomization scheme. If the PP population contains less than 90% of the subjects in the ITT population, a sensitivity analysis of the primary effectiveness endpoint will be performed based on the PP population.

2.2.3 Safety Population

The safety population includes all subjects who were administered the investigational product, and will be analyzed according to as-treated principle. All safety data will be summarized based on the safety population.

2.3 Study Subjects

Demographic endpoints and subject characteristics will be summarized using descriptive statistics by treatment group and overall based on the Safety population using the Observed Cases (OC). There are no planned inferential statistical analyses of demographic endpoints or subject characteristics.

2.3.1 Subject Disposition

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

The number of subjects in each study population (i.e. ITT, PP, and Safety) will be summarized by study center and in total.

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

- Randomized and unrandomized (i.e. unrandomized FST IV-VI subjects),
- 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 any protocol deviations will be summarized overall, by site, and by type.

Depending on the seriousness of the deviation, a subject might be excluded from the PP population, which shall be documented prior to database lock. Reasons for exclusion from the PP population will be summarized.

2.3.3 Demographic Characteristics

Age, BMI and baseline [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

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). Medical history, allergen history (food, environmental, and drug), and prior and concomitant procedures/non-pharmacological treatments will be coded according to MedDRA.

Prior medications/procedures are the medications/procedures with stop dates prior to study treatment. Medications/procedures after the study treatment will be considered concomitant.

Subjects reporting medical history, allergen history, cosmetic treatments/procedures, and prior and concomitant procedures/non-pharmacological treatments will be summarized by system organ class (SOC) and Preferred Term (PT).

Subjects reporting prior and 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.

2.4 Effectiveness Analysis

2.4.1 Datasets Analyzed

All effectiveness variables will be analyzed based on the ITT population. A sensitivity analysis of the primary effectiveness endpoint may be performed based on the PP population. Summary statistics will be computed for each effectiveness endpoint using the Observed Cases (OC) with no imputation for missing data. Inferential statistical analyses will account for missing data as appropriate (SAP Section 2.4.2 below).

2.4.2 Handling of Missing Data

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

For ITT analyses of the primary endpoint, missing values will be imputed using the baseline observation carried forward (BOCF) method. The impact of missing data on the primary endpoint will be evaluated by performing a sensitivity analysis based on the observed cases in the ITT population.

All other effectiveness endpoints will be evaluated based on the observed cases in the ITT population.

[redacted], if at least 3 of the scale's 5 items are answered, the sum score to be used in the Rausch transformation will be computed as the mean of the completed items times 5.

2.4.3 Primary Effectiveness Analysis

For the 8 mL treatment groups the mean change from baseline in [redacted] as assessed by the Blinded Evaluator at Week 48 (denoted as μ) will be evaluated using a one-sided Student's t-test. Thus H_0: $\mu \geq 0$ will be tested against H_1: $\mu < 0$ in the right and left side of the face separately. In other words; the null hypothesis of no mean change in [redacted] (or possibly a worsening) as compared with baseline will be tested against the alternative hypothesis of an improvement from baseline in [redacted]. The test will be performed at the 2.5% significance level. Both right and left sides of the face will need to be statistically significantly less than 0 for the treatment to be judged effective. Results will include one-sided p-values and two-sided 95% confidence intervals for the mean change from baseline for both treatment groups. In order to confirm that there are comparable treatment effects in the two groups, there should be an overlap of the confidence intervals. A figure of these confidence intervals will be given.

As a sensitivity analysis, the above will be repeated using only randomized subjects.

Further, separate summaries and analyses will be created for each skin type and for each site. Consistency across skin types and sites will be explored by using an analysis of variance model. Separate models will be run with effects for 1) treatment, skin type, and treatment by skin type interaction, and 2) treatment, site, and treatment by site interaction.

2.4.4 Secondary Analysis

For the two treatment groups, exact confidence intervals based on the binomial distribution will be calculated for the proportion of responders on the [redacted] and [redacted], as defined below.

[redacted]

The proportion of responders based on [redacted] as assessed by the Blinded Evaluator at Weeks 16, 24, 32, 40, and 48 will be calculated and summarized by treatment group along with their two-sided 95% confidence intervals.

In addition, the change from baseline in [redacted] at Weeks 16, 24, 32, and 40 based on the Blinded Evaluator's assessment, for the right and left side of the face separately, will be calculated and summarized by treatment group.

Scores for the Treating Investigator at baseline and at each treatment visit will be listed only.

[redacted]

The proportion of improved subjects based on [redacted] at Weeks 16, 24, 32, 40, and 48, will be calculated and summarized by treatment group along with their two-sided 95% confidence intervals. The proportions will be calculated separately for the subject's assessment and for the Treating Investigator's assessment. [redacted] In addition, the number and percent of subjects in each response category will also be summarized.

[redacted] scores will be summarized by treatment group at Week 24, 32, 40 and 48. The number and percent of subjects in each response category for each question will also be summarized.

Subject Satisfaction

Answers on the subject satisfaction questionnaire will be summarized.

[redacted]

2.5 Safety Analysis

Safety endpoints will be summarized using descriptive statistics by treatment group based on the safety population using the Observed Cases (OC). There are no planned inferential statistical analyses of safety endpoints.

2.5.1 Treatment Administration, Procedural Anesthetics, and Injection Concomitant Procedures

The number and percentage of subjects receiving one administration of Sculptra, two administrations, three administrations, and four administrations will be summarized by treatment group.

Other treatment administration endpoints that will be summarized by treatment group and treatment session include (but are not limited to):

- Injection volume.
- Injection method.
- Depth of injection.

The number of subjects with any procedural anesthetics will be summarized by type and location. The number of subjects with any injection concomitant procedures will be summarized.

2.5.2 Adverse Events

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).
- Subjects with at least one AE of special interest (in total as well as serious AEs).
- Number of subjects who did not have an AE.

As a sensitivity analysis, the above will be repeated using only randomized subjects.

Apart from the summary table described above, all other adverse event tables will be summarized in total and by treatment session: the first treatment session will include all AEs with a date of onset on or after the first treatment date but before the date of the second treatment or through the end of the trial if a subject receives only one treatment; the second treatment session will include all AEs with a date of onset on or after the second treatment date but before the date of the third treatment or through the end of the trial if a subject receives only two treatments, etc.

Study product or injection procedure-related AEs, as well as AEs unrelated to study product or injection procedure will be summarized by System Organ Class (SOC), Preferred Term (PT) and maximum intensity.

In addition, for study product or injection procedure-related AEs, the number of days to onset and the duration of event will be summarized by SOC and PT.

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

Actions taken for study product or injection procedure-related AEs will also be summarized.

Serious AEs, AEs of special interest, and AEs with late onset (i.e. AEs with onset > 21 days after most recent treatment) will be listed.

For subject counts, a subject will only be counted once per SOC and once per PT 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.

Further, separate summaries of the study product or injection procedure-related AEs, by treatment session and maximum intensity, will be created for each skin type and for each site, by SOC and PT.

[redacted]

2.5.4 Subject Diary Symptoms

Diary data will be presented for each diary separately. The 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 severity. Number of days with the event will be presented by treatment group and category: 1, 2-7, 8-14, and 15-28.

2.5.5 Other Safety Analyses

Nodules and papules assessments will be summarized.

Device deficiencies and vision function assessments will be listed.

2.6 Interim Analysis

Since the Sponsor is not blinded to treatment in this study, available data may be analyzed prior to study completion.

2.7 Determination of Sample Size

In the pivotal study report on which PMA P030050 Supplement 2 was based, [redacted] was used for effectiveness assessment. The change from baseline in [redacted] at Month 9 post treatment (which should approximately correspond to Week 48 in the current study, in case all four treatments are done) was -0.74 in the Sculptra group and the standard deviation was 0.57. However, the primary effectiveness endpoint was calculated differently in the pivotal study; the median of the left and right averages from three different evaluators was used. Since no averaging or use of the median of different measurements is done in the current study, the standard deviation is expected to be larger than in the pivotal one. Hence a standard deviation of 1 is assumed for these sample size calculations. Furthermore, with an assumed population change from baseline of -0.74, 90% power and one-sided test at the 2.5% significance level, at least 22 subjects are needed. With a drop-out rate of 15% at Week 48, at least 26 will need to be included to the treatment group. However, it was judged that 60 subjects would need to be included to the treatment group in order to provide a reasonable amount of safety data.

For the reference group, the rationale for sample size is based on effectiveness only. With 17 evaluable subjects, the study is adequately powered (80% power using a one-sided test at the 2.5% significance level) to detect a statistically significant change from baseline in [redacted] at Week 48, using the same assumptions for standard deviation and change from baseline as for the treatment group. With a drop-out rate of 15% at Week 48, at least 20 subjects need to be included to the reference group.

2.8 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.

4 [redacted]

[redacted]

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