GALDERMA
EST. 1981

[redacted]

[redacted]

A copy of the following document is included:

Statistical Analysis Plan version 2.0	Effective 15 March 2021

[redacted]

GALDERMA
EST. 1981

[redacted]

GALDERMA
EST. 1981

[redacted]

Effective date: 2022-03-08 18:10

Statistical Analysis Plan

Clinical Trial Number: 43USSA1812ext

Effective

Version: 2.0

[redacted]

Revision History

Version	Date	Revision Author	Comments

[redacted]

GALDERMA
EST. 1981

[redacted]

GALDERMA
EST. 1981

CCI [redacted]

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

SIGNATURE PAGE

PPD

[redacted]

Table of Contents

[redacted]

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 43USSA1812ext, dated 29 July 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 12-month extension of the prospective, randomized, evaluator- blinded, no-treatment controlled study 43USSA1812.

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

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

A summary or comparison by treatment group means by Group A vs. Group B status.

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

1.1.2 Number of Subjects

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

1.2 Study Objectives

The objectives are to evaluate the long-term effectiveness and safety of *Sculptra Aesthetic* in the correction of cheek wrinkles.

1.3 Effectiveness Assessments

For all assessments, the baseline visit (hereafter referred to as the "pre-treatment visit") will be defined as the observation that is closest to but prior to study treatment. In other words, the pre-treatment visit for Group A will occur after the pivotal study, but before treatment in the extension study (e.g. Month 12 pre-treatment). For Group B, the pre-treatment visit will be the same as what was used in the pivotal study (e.g. Day 1).

Change from pre-treatment will be calculated for each group as the value at a given time point minus the pre-treatment value. Note that the first visit in the extension study, the Study Entry Visit, is equivalent to the pre-treatment visit for Group A, but this is not true for Group B.

CCI

The severity of cheek wrinkles will be assessed live by the Blinded Evaluator using the validated 5-graded GCWS during the study. The GCWS scale is a validated photograph-based outcome instrument.

CCI

The severity of cheek wrinkles will be assessed live by the Blinded Evaluator using the validated 5-graded GCWS during the study. The GCWS scale is a validated photograph-based outcome instrument.

1.3.3 Global Aesthetic Improvement Scale (GAIS)

The 7-graded GAIS will be used to live assess the aesthetic improvement of cheek wrinkles by the Treating Investigator and the subject, by comparing to a photograph taken at the pre-treatment visit before the first treatment. The Treating Investigator and the subject will, independently of each other, respond to the question: "
by using the respective categorical scale below. (Table 2).

CCI

1.3.4 Subject Satisfaction Questionnaire

Subject satisfaction with treatment result will be assessed by using a subject satisfaction questionnaire (Section 7.4 of the protocol).

1.3.5 FACE-Q "Satisfaction with Cheeks"

The FACE-Q is a patient-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. There are five questions in which the patients will respond with how satisfied they are with their cheeks (higher = more satisfied).

1.3.6 Return to Social Engagement

Subjects will record the date and earliest time he/she felt comfortable to return to social engagement following treatment in a subject diary. Diaries are only given to Group A. Return to social

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

[redacted]

1.4 Effectiveness Endpoints

Pre-treatment refers to the Month 12 (pre-treatment) visit for Group A subjects (originally randomized to control group in pivotal study 43USSA1812). For Group B, pre-treatment refers to Day 1 which occurred during the 43USSA1812.

Effectiveness endpoints include the following:

1. Responder rate based on the GCWS [redacted], as assessed live by the Blinded Evaluator at Months 19, 21 and 24. *A responder is defined as a subject with at least 1 grade improvement from pre-treatment on both cheeks concurrently.*

2. Responder rate based on the GCWS [redacted] as assessed live by the Blinded Evaluator at Months 19, 21 and 24. *A responder is defined as a subject with at least 1 grade improvement from pre-treatment on both cheeks concurrently.*

3. Percentage of subjects having at least "Improved" according to the GAIS on both sides of the face combined, as assessed live by the subject and the Treating Investigator separately, at all visits following Month 12 in the pivotal study 43USSA1812.

4. Percentage of subjects responding in each response category for each question in the subject satisfaction questionnaire at all visits following Month 12 in the pivotal study 43USSA1812.

5. Change from pre-treatment in subject satisfaction using the Satisfaction with Cheeks FACE-Q questionnaire with Outcome Rasch transformed total scores as well as proportion of subjects in each response category for each of the individual questions at all visits following Month 12 in pivotal study 3USSA1812.

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

[redacted]

1.4.1 Exploratory Effectiveness Endpoints

[redacted]

1.5 Safety Assessments

The methods for collecting safety data are described in Section 8 of the Clinical Study Protocol.

1.6 Safety Endpoints

Safety endpoints include:

1. Incidence, intensity, time to onset and duration of adverse events collected throughout the study period.

2. Incidence, intensity and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days from each treatment.

3. Safety assessment by a qualified staff member at all visits according to predefined methods:
   - Cheek firmness, symmetry and function
   - Device palpability (pre-treatment assessment excluded for those receiving treatment in the extension study))
   - Mass formation
   - Cheek sensation
   - Visual Function Assessments (Group A subjects only)

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

CCI [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

[redacted]

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 CCI 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 (SD), median, minimum (min), and maximum (max). 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.
- Confidence intervals will be two-sided and constructed at the 95% confidence level.

2.1.3 Data Transformations

The Rasch transformation scoring of the FACE-Q will be reported (Section 4).

2.1.4 Handling of Missing Data

Number of missing values will be summarized and reported as appropriate.

All effectiveness endpoints will be evaluated based on the observed cases.

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

2.2 Analysis Populations

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

2.3 Study Subjects

Demographic endpoints and subject characteristics will be summarized using descriptive statistics 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 who are eligible to enter the extension study will be reported in total and by study center.

The number of subjects who enter the extension study, complete the study, and withdraw will also be summarized in total and by study center. The primary reasons for not participating in the study or completing the study will be summarized by reason.

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 occurring during the extension study, as well as type of deviation, will be summarized by treatment group (Group A or Group B), overall and by site. Separate summaries will be provided for COVID-19 related protocol deviations.

2.3.3 Demographic and Pre-treatment Characteristics

Pre-treatment age, weight, and body mass index (BMI) will be summarized as continuous variables.

Gender, age category (≥55 vs <55), race, ethnicity, Fitzpatrick skin type, pre-treatment GCWS [redacted] for both Blinded Evaluator and Treating Investigators, reporting for each side of the face) will be summarized as categorical variables.

Demographics will be summarized for each treatment group.

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, and prior and concomitant procedures/non-pharmacological treatments will be coded according to MedDRA.

[redacted]

Prior medications/procedures are the medications/procedures with stop dates prior to the Month 12 visit. Medications/procedures will be considered concomitant as follows:

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

Subjects reporting medical history, cosmetic treatments/procedures, and prior and concomitant procedures/non-pharmacological treatments will be summarized by system organ class (SOC) and Preferred Term (PT). A separate summary of medical history occurring in at least 5% of subjects will be provided.

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 analyses will be performed on the extension population.

2.4.2 Efficacy Analyses

Pre-treatment refers to the Month 12 (pre-treatment) visit for Group A subjects (originally randomized to control group in pivotal study 43USSA1812). For Group B, pre-treatment refers to Day 1 which occurred during the 43USSA1812.

Effectiveness endpoints will be analyzed by treatment group as follows:

- The following proportions will be summarized and report exact 2-sided 95% confidence intervals (Clopper-Pearson method):
    - GCWS [redacted] responder rate, as assessed live by the Blinded Evaluator at Months 19, 21 and 24. A responder is defined as a subject with at least 1 grade improvement from pre-treatment on both cheeks concurrently. Summaries will be provided overall, by age group (<55 vs. ≥55), and Fitzpatrick skin type (FST) group (I-III vs. IV-VI).
    - Percentage of subjects having at least "Improved" according to the GAIS on both sides of the face combined, as assessed live by the subject and the Treating Investigator separately, at all visits following Month 12 in the pivotal study 43USSA1812.
- Percentage of subjects responding in each response category for each question in the subject satisfaction questionnaire at all visits following Month 12 in the pivotal study 43USSA1812

[redacted]

(no confidence intervals will be provided).

- Change from pre-treatment in subject satisfaction using the Satisfaction with Cheeks FACE-Q questionnaire with Outcome Rasch transformed will be summarized with descriptive statistics and 2-sided exact 95% confidence intervals (via t-distribution). Total Rasch transformed scores as well as proportion of subjects in each response category for each of the individual questions at all visits following Month 12 in pivotal study 43USSA1812.

- Time to return to social engagement after treatment (based on subject diaries, Group A only) will be analyzed using Kaplan-Meier methods. The median time to return to social engagement will be estimated and Kaplan-Meier plots will be created.

2.4.3 Exploratory Effectiveness Endpoints

- [redacted]

- [redacted]

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 Treatment Administration, Procedural Anesthetics, and Injection Concomitant Procedures

Treatment administration endpoints that will be summarized by treatment session (Group A only) 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 Pre-Defined Expected Post-Treatment Symptoms (Subject Diary, Group A only)

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

[redacted]

2.5.3 Adverse Events (AEs)

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

Typically, only AEs that occur during the extension period will be summarized. A summary of all related AEs that includes those occurring from the pivotal study to end of the extension study will be provided for Group B only.

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

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

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

Adverse events will also be summarized by the following subgroups:

- Study Center
- Age Group (<55 years vs. ≥55 years)
- FST Skin Type
- Injection Technique (including techniques of Bolus, Fanning, Cross Hatching, Linear Antegrade, etc. and all observed combinations of these [e.g. Bolus * Fanning, Bolus * Linear Retrograde, Cross Hatching * Fanning * Linear Retrograde, etc.]).
- Pre-Treatment CCI

Adverse events of special interest (all incidences of visual disturbances, regardless of relationship to study product or seriousness) will be summarized. Adverse events related to study product or injection procedure will be summarized by session.

2.5.4 Other Safety Analyses

Visual function will be summarized by visit, along with each visit's change from pre-treatment (Group A only), and 95% confidence intervals, via t-distribution, will be provided for the change.

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

The incidence of nodules, papules, and granuloma (defined as AEs with system organ class containing "nodule", "papule", or "granuloma") will be summarized, including the time to onset from the pre-treatment visit as well as the duration.

Weight and BMI will additionally be summarized at each visit along with change from the pre-treatment visit.

2.6 Interim Analysis

There are no planned interim analyses for this study.

2.7 Determination of Sample Size

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

2.8 Changes in the Analysis Planned in the Protocol

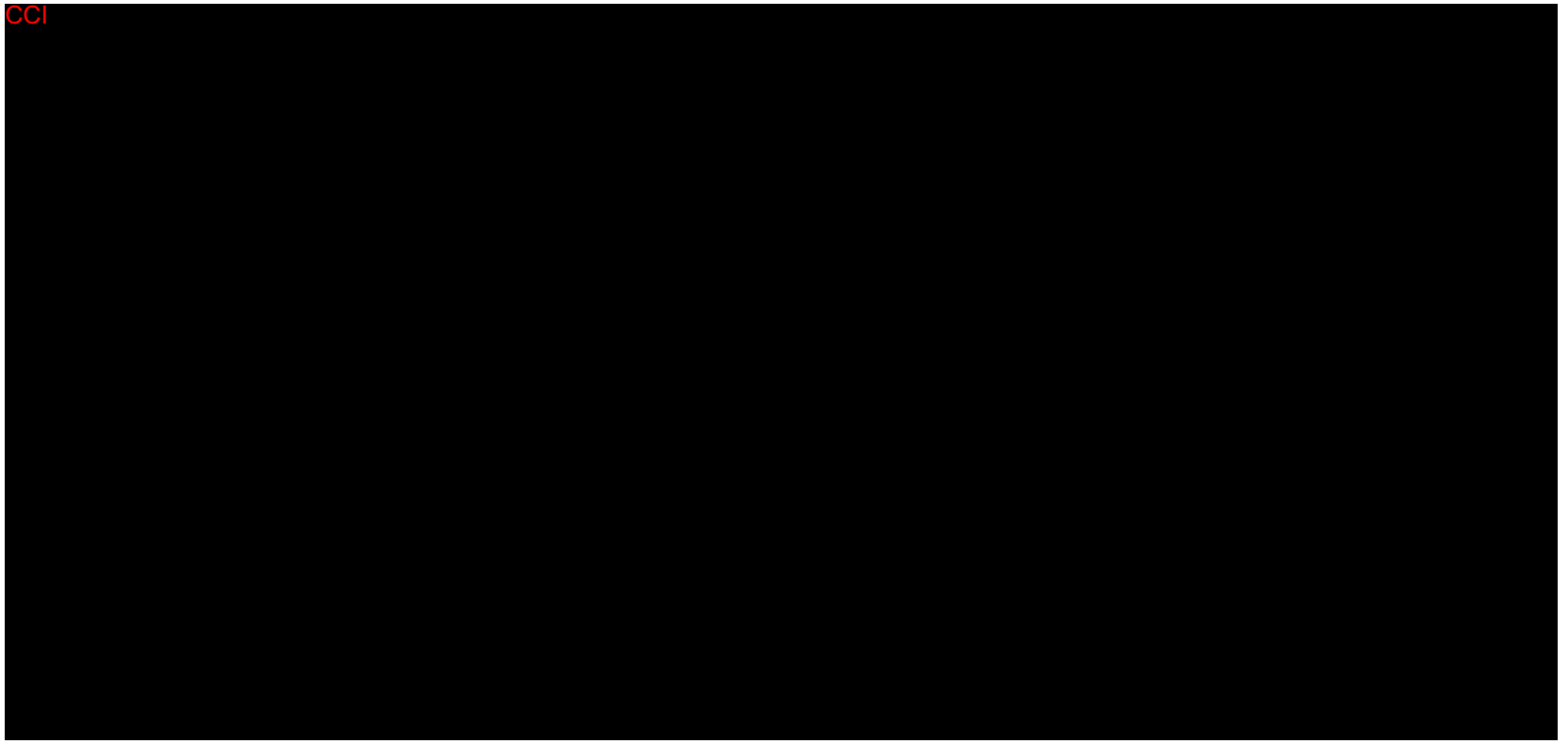
There have been no substantial changes from the statistical methods described in the protocol.

3 Reference List

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

4 Rasch Transformation of FACE-Q

CCI



5 Schedule of Events (Treatment and Control Groups)

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

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

1. *Visit 5 is identical to Visit 5 outlined and performed in the pivotal study 43USSA1812.*
2. *43USSA1812ext Visit 1 can be performed at Visit 5 (Month 12, pivotal study) or as a separate visit within 2 weeks of Visit 5 (Month 12, pivotal study). When Visit 1 extension occurs on the same day as Visit 5 pivotal (Month 12 in 43USSA1812), assessments already outlined in Visit 5 study protocol 43USSA1812 only need to be performed once.*
3. *Weight only*
4. *Pre-treatment*
5. *Females of childbearing potential*
6. If treatment is not performed this is a follow-up visit
7. If applicable (i.e. if treatment was performed at the previous visit)
8. If applicable (i.e. if treatment is performed at this visit)
9. Visual Function assessments include: Snellen visual acuity test, Extraocular muscle function test, Confrontation visual field
10. 30 minutes post treatment
11. Safety assessments include; Cheek firmness, symmetry and function, Device palpability (pre- treatment assessment excluded), Mass formation, Cheek sensation

Abbreviations: GAIS (Global Aesthetic Improvement Scale), GCWS ([redacted]ET (Early Termination)

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

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

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

Abbreviations: GAIS (Global Aesthetic Improvement Scale), GCWS ([redacted]), ET (Early Termination)

Effective date: 2022-03-08 18:10

SIGNATURES PAGE

Date	Signed by
2022-03-02 08:44	PPD
Justification	CCI [redacted]

2022-03-02 09:05	PPD
Justification	CCI [redacted]

2022-03-08 18:10	PPD
Justification	CCI [redacted]

Effective

Version: 2.0

[redacted]