Statistical Analysis Plan

Clinical Trial Number: 05DF2209

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Abbreviations and Definitions of Terms

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BOCF	Baseline Observation Carried Forward
CIs	Confidence intervals
CSR	Clinical Study Report
eCRF	electronic case report form
FDA	Food and Drug Administration
FST	Fitzpatrick skin type
GAIS	Global Aesthetic Improvement Scale
GJS	Galderma Jawline Scale
ICH	International Conference on Harmonisation
CCI	[redacted]
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per protocol
PT	Preferred term
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOC	System organ class
CCI	[redacted]
WHODD	World Health Organization Drug Dictionary

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 05DF2209 (v1.0), dated 21 October 2022. No subjects were enrolled prior to Protocol v1.0.

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 prospective, randomized, evaluator-blinded, no treatment controlled, parallel group, multicenter phase IV study to evaluate effectiveness and safety of *Restylane Lyft Lidocaine* for jawline definition. Approximately 140 subjects will be included in the study, randomized (3:1) to *Restylane Lyft Lidocaine* or to No Treatment (control) group.

Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. A follow-up telephone call should be made 72 hours after treatment.

Optional touch-up treatment may be administered 1 month (4 weeks) after initial treatment, if deemed necessary by Treating Investigator and the subject to obtain optimal aesthetic improvement. If optional touch-up is performed, a 72-hour follow-up telephone call and a follow-up visit after 1 month should be scheduled.

Effectiveness and safety data will be collected for up to 12 months after the last treatment for the Treatment group and after baseline for the No Treatment group including follow up visits at 1, 3, 6, 9 and 12 months.

Subjects in the No Treatment group will be offered optional treatment after 12 months (48 weeks) from baseline (Day 1) followed by a safety assessment 2 weeks after the optional treatment. Subjects who decline treatment after 12 months will end their study participation.

The treatment will be performed in accordance with approved Instructions for Use in Canada.

Investigator blinding will be accomplished by having a Treating Investigator administer the treatments and having a Blinded Evaluator, to whom randomization and treatment are concealed, conduct blinded assessments.

1.1.2 Number of Subjects and Randomization

Approximately 140 subjects will be randomized in a 3:1 ratio to treatment with *Restylane Lyft Lidocaine* or no treatment. Randomization numbers will be allocated in ascending sequential order to each subject.

1.2 Study Objectives and Endpoints

1.2.1 Primary Effectiveness Objective and Endpoint

The primary objective of the study is to assess the effectiveness of *Restylane Lyft Lidocaine* versus a no treatment control in Jawline definition by comparing Galderma Jawline Scale (GJS) response rates.

The primary endpoint is the responder rate based on the Blinded Evaluator's live assessment of the GJS at 3 months after last treatment for the Treatment group or after baseline for the No Treatment group.

A responder is defined as a subject with at least 1-point improvement from baseline, on both jawlines concurrently.

1.2.2 Secondary Effectiveness Objectives and Endpoints

The secondary objective is to assess the effectiveness of *Restylane Lyft Lidocaine* for Jawline definition.

Secondary endpoints:

1. Responder rates based on the Blinded Evaluator's live assessment using the GJS at 6, 9 and 12 months after last treatment for the Treatment group or after baseline for the No Treatment group. A responder is defined as a subject with at least 1-point improvement from baseline, on both jawlines concurrently, at each of the timepoints.
2. Proportion of subjects having at least "Improved" on the Global Aesthetic Improvement Scale (GAIS) on both jawlines concurrently, as assessed live by the Subject and Treating Investigator separately at 3, 6, 9 and 12 months after last treatment for the Treatment group and after baseline for the No Treatment group.

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1.2.3 Safety Objectives and Endpoints

To evaluate the safety of *Restylane Lyft Lidocaine* by assessments of adverse events (AEs) by the Treating Investigator throughout the study period.

1. Incidence, intensity, duration, and onset of AEs collected during the study period post treatment.
2. Pre-defined, expected, post-treatment events reported for 28 days from treatment as recorded in the subject diary.

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 for the Treatment group and baseline visit for the No Treatment group. Where applicable, change from baseline will be calculated as the value at a given time point minus the baseline value.

One month is defined as 4 weeks in the study.

1.3.1 Galderma Jawline Scale (GJS)

The GJS is a validated 5-point scale for assessment of jawline. Each score in the GJS is exemplified by photographic images of the scale. The Blinded Evaluator and Treating Investigator will perform live assessment of the subject's left and right jawline separately.

Table 1. Galderma Jawline Scale

Grade	Assessment	Description
0	None to Minimal	No to minimal volume deficiency posterior to the jowl along the jawline.
1	Mild	Mild volume deficiency posterior to the jowl along the jawline.
2	Moderate	Moderate volume deficiency posterior to the jowl along the jawline.
3	Severe	Severe volume deficiency posterior to the jowl along the jawline.
4	Very Severe	Extreme volume deficiency posterior to the jowl along the jawline with redundant skin.

1.3.2 Global Aesthetic Improvement Scale (GAIS)

The 7-grade GAIS will be used to assess the aesthetic improvement of the jawline, i.e., improvement from baseline appearance before first treatment by the Treating Investigator and the subject, independently of each other. The GAIS will be assessed by the Treating Investigator and the Subject as specified in the Schedule of Assessments.

The baseline archival photographs (obtained prior to injection at baseline) will be used as a comparison for the GAIS evaluation. The Treating Investigator will assess the GAIS based on the definition in Table 2. The Subject will respond to the question: "*How would you describe the aesthetic improvement of the treatment area today compared to the photograph taken before treatment?*" by using the categorical rating scale.

Table 2. Treating Investigator Global Aesthetic Improvement Scale (GAIS)

Rating	Definition (for Treating Investigator)
Very Much Improved	Optimal aesthetic result for the implant for this subject.
Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
Improved	The appearance is improved from the initial condition.
No Change	The appearance is essentially the same as baseline.
Worse	The appearance is worse than the initial condition.
Much Worse	Marked worsening in appearance from the initial condition.
Very Much Worse	Obvious worsening in appearance from the initial condition.

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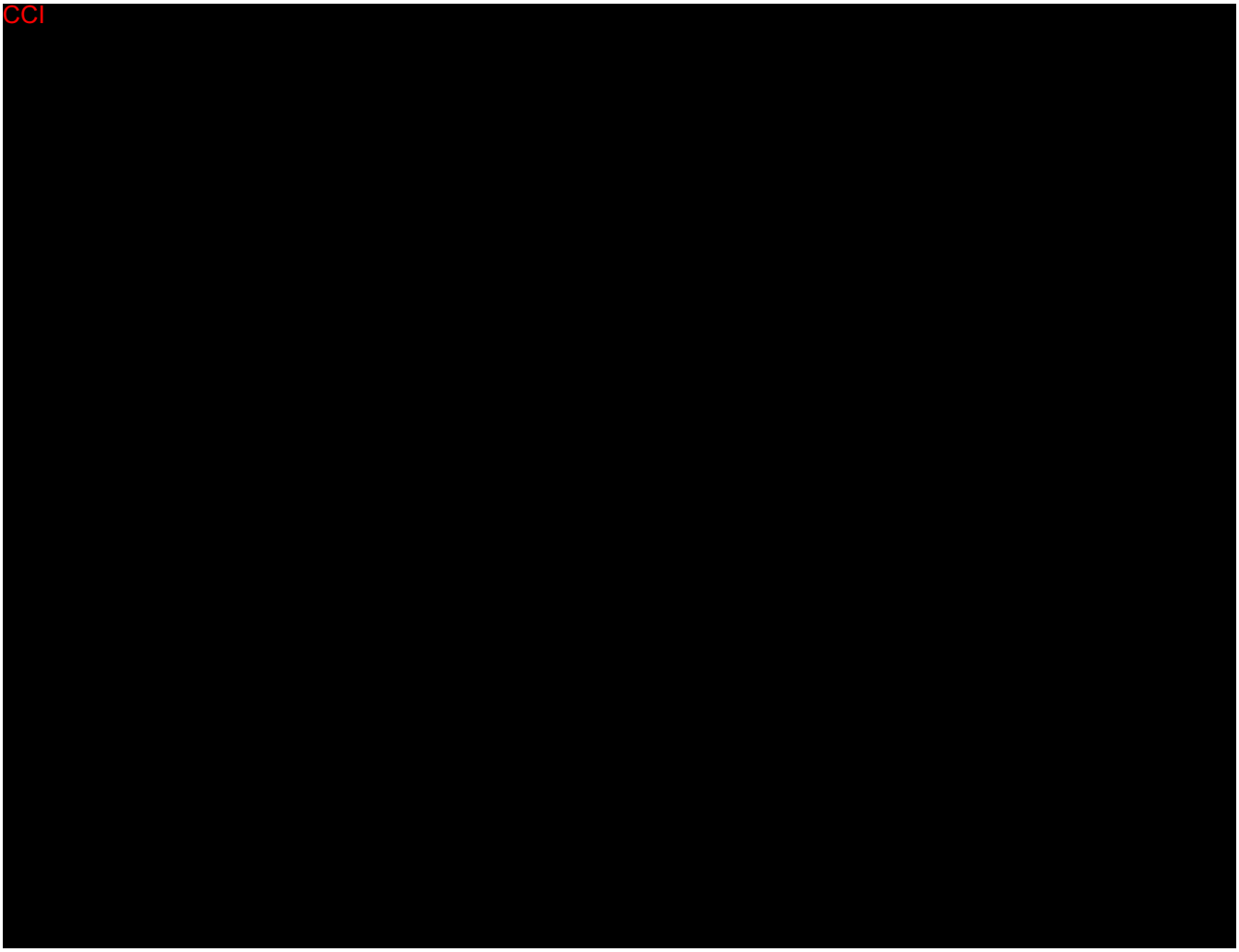

1.4 Safety Assessments

The methods for collecting safety data are described in Section 7 of the protocol. Data to be collected include the following:

- Adverse events.
- Subject diaries to be completed daily for 28 days following each treatment session. The presence and maximum intensity of pre-defined, expected post-treatment events, i.e., bruising, redness, pain, tenderness, lumps/bumps, itching and swelling shall be assessed for the treated area.
- Urine pregnancy test for women of childbearing potential performed at screening and all treatment visits (prior to treatment).
- Device deficiencies assessed at all treatment visits.

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 protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

2.1.1 Programming Conventions

PPD 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 prior to finalization as documented in the Quality Control Plan. 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 included in the analysis datasets that are prepared 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.

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 site number concatenated with subject number, treatment group, assessment dates, and/or time point.

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

- Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified. CIs for responder rates will be calculated via Clopper-Pearson. CIs for the difference (Treatment – No Treatment) in responder rates will be calculated via the normal approximation.
- 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) in each treatment group.
- Date variables will be formatted as DDMMMYYYY for presentation.

2.2 Analysis Populations

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

2.2.1 Safety Population

The Safety population includes all subjects who were treated with *Restylane Lyft Lidocaine* or were randomized to the No Treatment group at baseline. Subjects are analyzed according to the treatment actually received.

2.2.2 Intent-to-Treat (ITT) Population

The ITT population includes all subjects who were randomized. Subjects will be analyzed according to the treatment they were randomized to. All effectiveness variables will be analyzed based on the ITT population.

2.2.3 Per-Protocol (PP) Population

The PP population includes all ITT subjects who complete the visit 4 after baseline and are without any deviations considered to have substantial impact on the primary effectiveness outcome. The primary effectiveness analysis will be repeated using the PP analysis set if there is at least a 10% difference in the number of subjects between the PP and ITT sets.

2.3 Study Subjects

Demographic endpoints, baseline assessments and subject characteristics will be summarized using descriptive statistics by treatment group and overall based on the ITT 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 will be shown in total.

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

The disposition of subjects will be presented by treatment group, and in total, including numbers of subjects who were completed and withdrawn (including primary reason for withdrawal).

The number of subjects expected, completed, withdrawn, and missed will be summarized by scheduled visit, using the following definitions:

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

The end of study status will be listed for all subjects (both completed and withdrawn) individually, including at least subject number, end of study date, and last visit performed. In addition, reason for withdrawal will be provided for withdrawn subjects.

2.3.2 Protocol Deviations

Subjects with any protocol deviations will be summarized by treatment group, overall, and by type.

Depending on the seriousness of a protocol deviation, a subject might be excluded from the PP population, which shall be documented prior to database lock. Since the PP population includes subjects who complete the visit 4 or baseline, the focus will be on major deviations occurring before and at the Month 3 visit which are considered to have a substantial impact on the primary effectiveness outcome, see Table 3 below for list. Reasons for exclusion from the PP population also will be summarized.

Table 3. Major Protocol Deviations Causing Exclusion from Per-Protocol Population

Major Deviation
Month 3 visit out of window by greater than 21 days or earlier than 7 days
Subject did not receive treatment as randomized
GJS by Blinded Evaluator not done at Month 3 (primary endpoint)
GJS by Blinded Evaluator not done at screening or baseline

Table 3. Major Protocol Deviations Causing Exclusion from Per-Protocol Population

Major Deviation
GJS by Blinded Evaluator at baseline is not grade 2 to 4 (moderate or very severe)
Prohibited concomitant treatments/procedures prior to Month 3 visit considered to have substantial impact on primary effectiveness outcome
Prohibited medical history, unstable medical history condition, or medical history condition that worsens prior to Month 3 visit considered to have substantial impact on primary effectiveness outcome

2.3.3 Demographic Characteristics

Age and body mass index will be summarized as continuous variables.

Gender identity, sex at birth, race (including Asian subgroups), ethnicity, Fitzpatrick Skin Type (FST) score, childbearing potential, and baseline GJS (Blinded Evaluator) on the left and right side will be summarized as categorical variables.

2.3.4 Medical History, Medications, and Procedures

Prior and concomitant medications, vaccines, and procedural anesthetics will be coded using the World Health Organization Drug Dictionary (WHODD). Medical history, prior cosmetic treatments/procedures, and concomitant procedures/treatments will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Prior medications/procedures are the medications/procedures with stop dates prior to first study treatment session or randomization date for No Treatment group.
Medications/procedures after the first study treatment session for Treatment group and after randomization date for No Treatment group will be considered concomitant.

Subjects reporting medical history, prior cosmetic treatments/procedures, and concomitant procedures/treatments will be summarized by System Organ Class (SOC) and Preferred Term (PT). Procedural anesthetics will only be listed.

Subjects reporting concomitant medications and vaccines 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 preferred name. Prior medications will only be listed.

2.4 Effectiveness Analysis

2.4.1 Datasets Analyzed

The ITT population is primary for all effectiveness analyses. The primary effectiveness analysis will be repeated using the PP analysis population if there is at least a 10% difference in the number of subjects between the PP and ITT populations.

2.4.2 Handling of Missing Data

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

For the ITT analysis of the Blinded Evaluator GJS Responder rate at Month 3 after last treatment for Treatment group (primary endpoint), missing values will be assumed to be

missing due to lack of effect. Therefore, the primary method of imputation will use the baseline observation carried forward (BOCF) method. Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the observed cases, as well as worst-case (No Treatment group imputed as responder, Treatment group imputed as non-responder) and best-case (Treatment group imputed as responder, No Treatment group imputed as non-responder) imputation in the ITT set.

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

Descriptive statistics of all safety data will be performed on observed cases in the Safety population.

2.4.3 Primary Effectiveness Analysis

Responder rate for each treatment based on the GJS, as assessed live by the Blinded Evaluator at 3 months after last treatment for the Treatment group and after baseline for the No Treatment group, will be the primary effectiveness endpoint. A responder will be defined as a subject with at least 1 grade improvement from baseline, on both jawlines concurrently.

The null hypothesis will be that there is no relationship between responder rate and treatment group (i.e., the responder rate is the same in treated and untreated subjects). The alternative hypothesis will be that there is a relationship between responder rate and treatment group (i.e., the responder rate is different in treated subjects compared to untreated subjects).

The estimates of the responder rate in each group will be presented as well as the difference in responder rates. Corresponding confidence intervals for responder rates (via Clopper-Pearson) and the difference in responder rates (via normal approximation) along with the p-value (via Fisher's exact test) for the difference will also be presented. For a significant result, the two-tailed p-value of the comparison of responder rates between the treated and untreated subjects at 3 months using the Fisher's exact test needs to be smaller than 0.05.

A forest plot of the treatment difference in Month 3 responder rates for the GJS will be provided.

2.4.4 Secondary Effectiveness Analysis

(i) To assess the effectiveness of *Restylane Lyft Lidocaine* for Jawline definition, the following will be presented:

The responder rate on the GJS as assessed live by the Blinded Evaluator at 6, 9 and 12 months after last treatment for the Treatment group and after baseline for the No Treatment group will be presented as well as the difference in responder rates between groups. Corresponding confidence intervals for responder rates and the difference in responder rates will also be presented. A bar plot of the percentage of responders by visit will be produced for Blinded Evaluator and presented by treatment group.

The responder rates based on the GAIS as assessed by the investigator and the subject, respectively, at each visit will be calculated and presented along with their 95% confidence intervals for each treatment group. The difference in responder rate between the two groups will be presented along with a 95% confidence interval.

In addition, the GJS and GAIS (for subject and investigator) will be presented with number of subjects and percentage for each category of the scales for each visit by treatment group.

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2.4.5 Subgroup Analyses

Supgroup analyses will be performed on age groups: less than or equal to median age, greater than median age. The statistical testing performed on the primary and secondary efficacy analyses will be repeated by age group.

2.5 Safety Analysis

Safety endpoints will be summarized using descriptive statistics by treatment group based on the Safety population using observed cases. There are no planned inferential statistical analyses of safety endpoints.

Subjects in the No Treatment group who elect for an optional treatment will also be included in the Treatment Administration and Adverse Events summaries.

2.5.1 Treatment Administration, Post-injection Care, and Procedural Anesthetics

Injection volume, injection method(s), depth of injection and needle and cannula size will be summarized for each treatment session by treatment area for each treatment group.

Injection volume overall, number of syringes, needles and cannulas will be summarized by treatment session for each treatment group.

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

2.5.2 Adverse Events (AEs)

AEs will be summarized relative to the treatment session timing using the following categories:

- No Treatment at Baseline: Subjects who receive no treatment at baseline, include AEs before any optional *Restylane Lyft Lidocaine* treatment at Month 12.
- Initial Treatment with *Restylane Lyft Lidocaine*: Subjects who were initially treated with *Restylane Lyft Lidocaine* at Baseline.
- Optional Treatment at 12 Month Visit: Subjects who received no treatment at baseline and were treated with *Restylane Lyft Lidocaine* at the 12 month visit. Includes AEs that occur after optional treatment.

- Total *Restylane Lyft Lidocaine*: Includes all subjects who were initially treated with *Restylane Lyft Lidocaine* at baseline or treated at the optional 12 month visit.

All AEs will be coded according to MedDRA and summarized by System Organ Class (SOC), Preferred Term (PT), and treatment. The number of subjects with at least one event, associated percentage, and number of events will be provided.

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.

The number of subjects with AEs related to study product or study product injection procedure and unrelated AEs will be presented by SOC, PT, and maximum intensity. Action taken for related AEs will also be summarized by SOC and PT using number of events.

Serious AEs (SAEs) will be listed.

For AEs related to study product or study product injection procedure, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, standard deviation, median, minimum, and maximum. Days to onset of an AE will be derived as the start date minus the date of most recent treatment session. Duration of an AE will be derived as the stop date minus the start date + 1.

For the purpose of deriving days to onset and duration, the following date imputation rules will be used.

Start Date

- If start date is completely missing, or if month and day are missing and year is the same year as baseline (randomization for No Treatment group, first treatment administration for Treatment group), it will be assumed that the AE started at baseline.
- If the start date is missing the day, the baseline day will be used provided the imputed date is on or after the subject's randomization date; otherwise, the day of randomization will be used.
- If the start date is missing the month, the randomization month will be used.
- If the start date is missing the year, the baseline year will be used provided the imputed date is on or after the subject's randomization date; otherwise, the subsequent year after randomization will be used.

End Date

- If end date is completely missing, it will be assumed that the AE is still ongoing and will not be imputed.
- If the end date is missing the day, the last of the month will be used (i.e. UNK-JAN-2022 becomes 31-JAN-2022)
- If the end date is missing the month, the subsequent month after the start date will be used.
- If the end date is missing the year, the year of randomization will be used, provided the imputed date is after the start date; otherwise, the subsequent year after start date will be used.

Adverse events with a completely missing start date will be considered treatment-emergent unless the event has a stop date prior to the date of the first dose of study drug. All AEs will be listed by treatment and subject. Dates will be presented as collected in the listings.

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 SAEs),
- number of subjects with at least one related AE and number of events (in total as well as SAEs),
- number of subjects with at least one unrelated AE and number of events (in total as well as SAEs),
- number of subjects who did not have an AE.

2.5.3 Pre-defined, Expected, Post-treatment Events

The number and percentage of subjects reporting each pre-defined, expected, post-treatment symptom, as collected in the 28-day diary, will be presented in total and by maximum intensity for each treatment session. Summaries will be presented for each jawline separately and for both combined (using worst intensity). The number of days with the event for each treatment session will be similarly presented by day category (1, 2-7, 8-14 and 15-28 days). The percentage of subjects with each event also will be plotted for each treatment session by day.

2.6 Interim Analysis

No formal interim analysis will be performed. However, analysis of data could take place at a time point after the last collection of primary endpoint data.

2.7 Determination of Sample Size

2.7.1 Sample Size

A total sample size of approximately 140 subjects will be included in this study. For the responder rate in GJS, a Fisher's exact test using a 5% two-sided significance level will have approximately 90% power to demonstrate difference between a responder rate of 70% in the *Restylane Lyft Lidocaine* group, and a responder rate of 35% in the no treatment control group when the sample sizes are 105 and 35, respectively. Accounting for 10% dropouts, approximately 140 subjects need to be randomized in a 3:1 ratio.

2.8 Changes in the Analysis Planned in the Protocol

The definition of the Safety Population was updated to include subjects who were randomized to the No Treatment group.

3 Reference List

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

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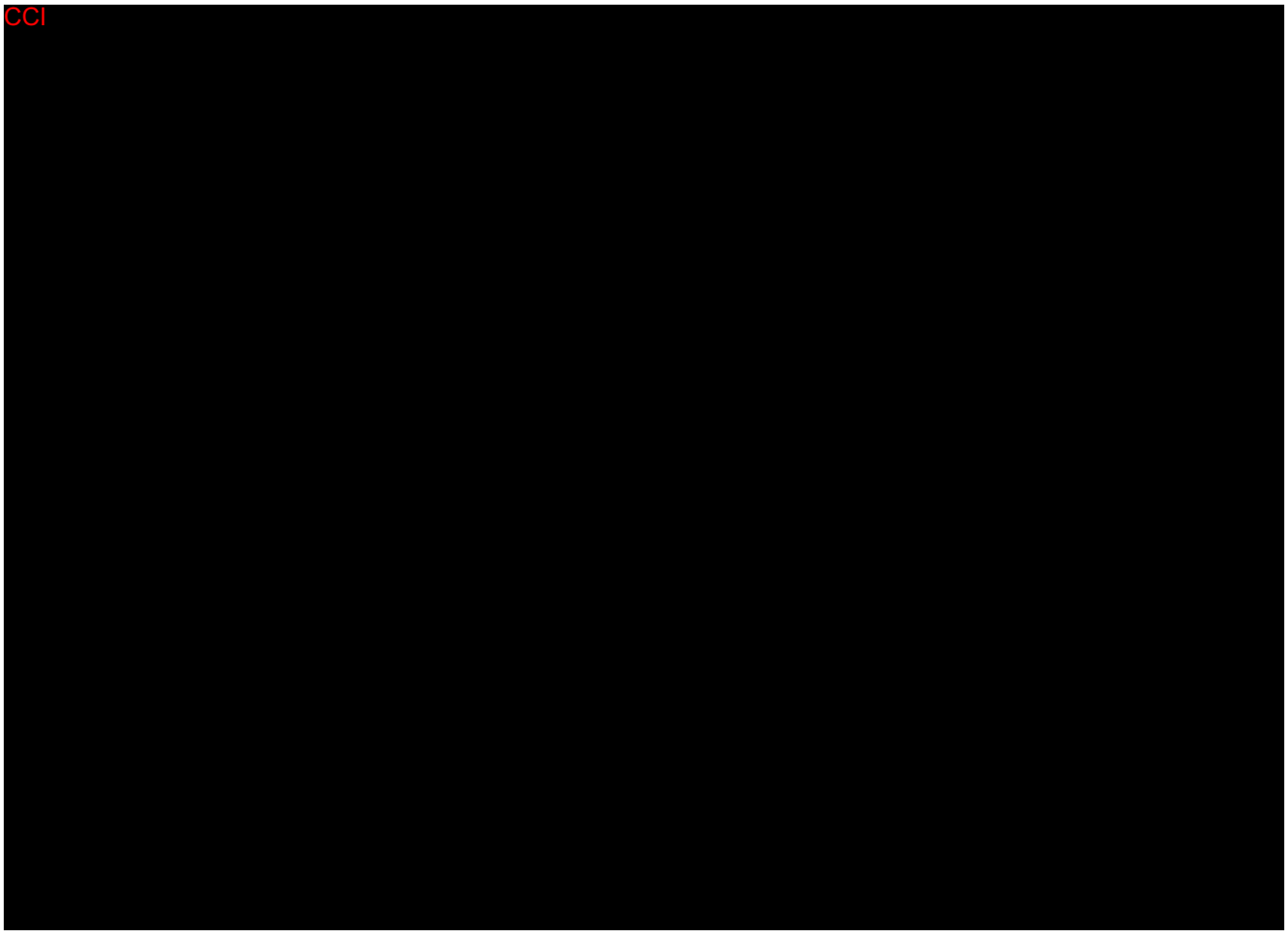

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SIGNATURES PAGE

Date	Signed by
2023-10-18 13:21	PPD
Justification	Approved by Technical Expert

2023-10-19 10:32	PPD
Justification	Approved by Owner