GALDERMA	Title 43USTT1904 Statistical analysis plan - Tear Trough	Doc id MA-42205

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Statistical Analysis Plan

Clinical Trial Number: 43USTT1904

Version: 3.0

APPROVAL SIGNATURE PAGE

Protocol Title: A randomized, evaluator-blinded, parallel group, no-treatment controlled, multi-center study to evaluate the safety and effectiveness of Restylane-L® for correction of Infraorbital Hollows

Sponsor: Q-Med AB, a Galderma affiliate.
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Protocol Number: 43USTT1904

Advanced Clinical Author:
PPD

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

PPD

Signature: PPD

Date: PPD

Table of Contents

1 Study Information

This statistical analysis plan (SAP) describes the effectiveness and safety summaries and analyses that will be performed for Clinical Trial Number (CTN) 43USTT1904, *A randomized, evaluator-blinded, parallel group, no-treatment controlled, multi-center study to evaluate the safety and effectiveness of Restylane-L® for correction of Infraorbital Hollows*, and is based on the study protocol Version 10 dated 15DEC2021.

1.1 Background

1.1.1 Study design

This is a prospective, randomized, evaluator-blinded, no-treatment controlled, parallel group, multi-center US study to evaluate the effectiveness and safety of Restylane-L for correction of Infraorbital Hollows (IOH). Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. Optional touch-up treatment may be administered after 1 month of initial treatment, if deemed necessary by Treating Investigator and subject to obtain optimal aesthetic improvement. Optimal aesthetic improvement is defined as at least 1 grade improvement, from baseline, on the GIHS and best correction that can be achieved as agreed by the Treating Investigator and the subject.

At the month 12 visit, the no-treatment comparator subjects will be offered an optional Restylane-L treatment. The subjects who received Restylane-L at the baseline visit will also be offered an optional additional treatment if optimal aesthetic improvement is not maintained (as determined by the Treating Investigator and subject). For subjects receiving optional treatment at month 12 the effectiveness and safety data will be collected for another 6 months. A subject will be involved in the study for up to 19 months including 30 days screening and 6 months follow-up after optional treatment at month 12. The study flow chart is provided in Appendix A.

1.1.2 Number of subjects and randomization

Approximately 329 subjects will be included (CCI) to treatment with Restylane-L or no treatment. In the treatment group approximately 146 subjects will get injections using needle and approximately 136 subjects using cannula. At least 36 subjects will be Fitzpatrick skin type (FST) IV - VI, with at least 18 of those subjects with FST V – VI. Approximately 47 subjects will be randomized to no-treatment at baseline.

The randomization list will be stratified by FST group (I-III, IV, and V-VI). The FST I-III group will be further stratified by study site. The FST IV and FST V-VI groups will be further stratified at needle or cannula level (needle sites pooled into a needle stratum, and cannula sites pooled into a cannula stratum). Approximately half of the sites will be using needle and the other half will be using cannula for injection.

The Treating Investigator and subjects will not be blinded to study treatments.

1.2 Study objectives

1.2.1 Primary effectiveness objective

The primary objective of the study is to evaluate the effectiveness of Restylane-L (injected using needle or cannula) versus no-treatment control in the correction of Infraorbital Hollows using a Blinded Evaluator's assessment of the Galderma Infraorbital Hollows Scale (GIHS).

1.2.2 Secondary effectiveness objectives

The secondary objectives are to evaluate the effectiveness of Restylane-L (injected using needle or cannula) versus no-treatment control in the correction of Infraorbital Hollows using the following:

- Blinded Evaluator assessment of the GIHS
- Global Aesthetic Improvement Scale (GAIS)

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1.2.3 Safety objectives

The safety objectives are to evaluate AEs and pre-defined, expected post-treatment events reported during the first 28 days after treatment.

1.3 Effectiveness assessments

For all assessments, baseline will be defined as the observation that is closest to, but prior to, the study injection on Day 1. CCI [redacted]

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1.3.1 Galderma Infraorbital Hollows Scale (GIHS)

The GIHS is a four-point scale for assessment of Infraorbital Hollows (Appendix B). Each score in the GIHS is exemplified by Photographic images of the scale. The Blinded Evaluator and Treating Investigator will perform live assessment of the subject´s right and left Infraorbital Hollow separately.

The Blinded Evaluator will perform GIHS at:

- Screening/Baseline visit(s)
- Months 3, 6, 9, and 12 after randomization
- Months 3 and 6 after optional treatment. For assessments at these two visits specifically, the evaluator will be considered unblinded as these assessments are performed on all subjects that elect to receive the optional treatment.

A responder indicator will be created to identify subjects that had at least one-point improvement from baseline, on both sides of the face concurrently. If at any given post-baseline visit, both left side of face GIHS change from baseline score and right side of face GIHS change from baseline score are at least 1, the subject will be considered a responder for that visit.

GIHS change from baseline will be calculated following the formula described above (Section 1.3).

The Treating Investigator will perform GIHS during the following visits:

- Screening/Baseline visit(s)
- Month 1 and 12 after randomization.

The Treating Investigator will only perform the GIHS assessment for the purpose of assessing treatment eligibility. These assessments are not included in any analyses.

1.3.2 Global Aesthetic Improvement Scale (GAIS)

The GAIS is used to assess the aesthetic improvement of the Infraorbital Hollows. It consists of one question, "*How would you describe the aesthetic improvement of your tear troughs today compare to the photograph taken before treatment?"* rated on a seven-point scale (Appendix C GAIS). Responses can range from 'Very Much Improved' to 'Very Much Worse.'

Both the Treating Investigator and the subject will complete the GAIS, independently, rating their assessment for aesthetic change by comparing the appearance at follow-up visits to baseline photographs (obtained prior to injection at baseline). The Treating Investigator and the subject will complete the GAIS independently. The GAIS will be assessed at:

- Month 1, 3, 6, 9, and 12 after randomization
- Month 1 after optional touch-up
- Month 1, 3, and 6 after optional treatment.

A responder indicator will be created to identify subjects that experienced an improvement in aesthetic appearance of their infraorbital hollows as assessed by the Treating Investigator. If at any given visit the Treating Investigator selects 'Improved,' 'Much Improved,' or 'Very Much Improved' on the GAIS, the subject will be considered a Responder at that visit. A similar responder variable will be created for the GAIS assessed by the subject.

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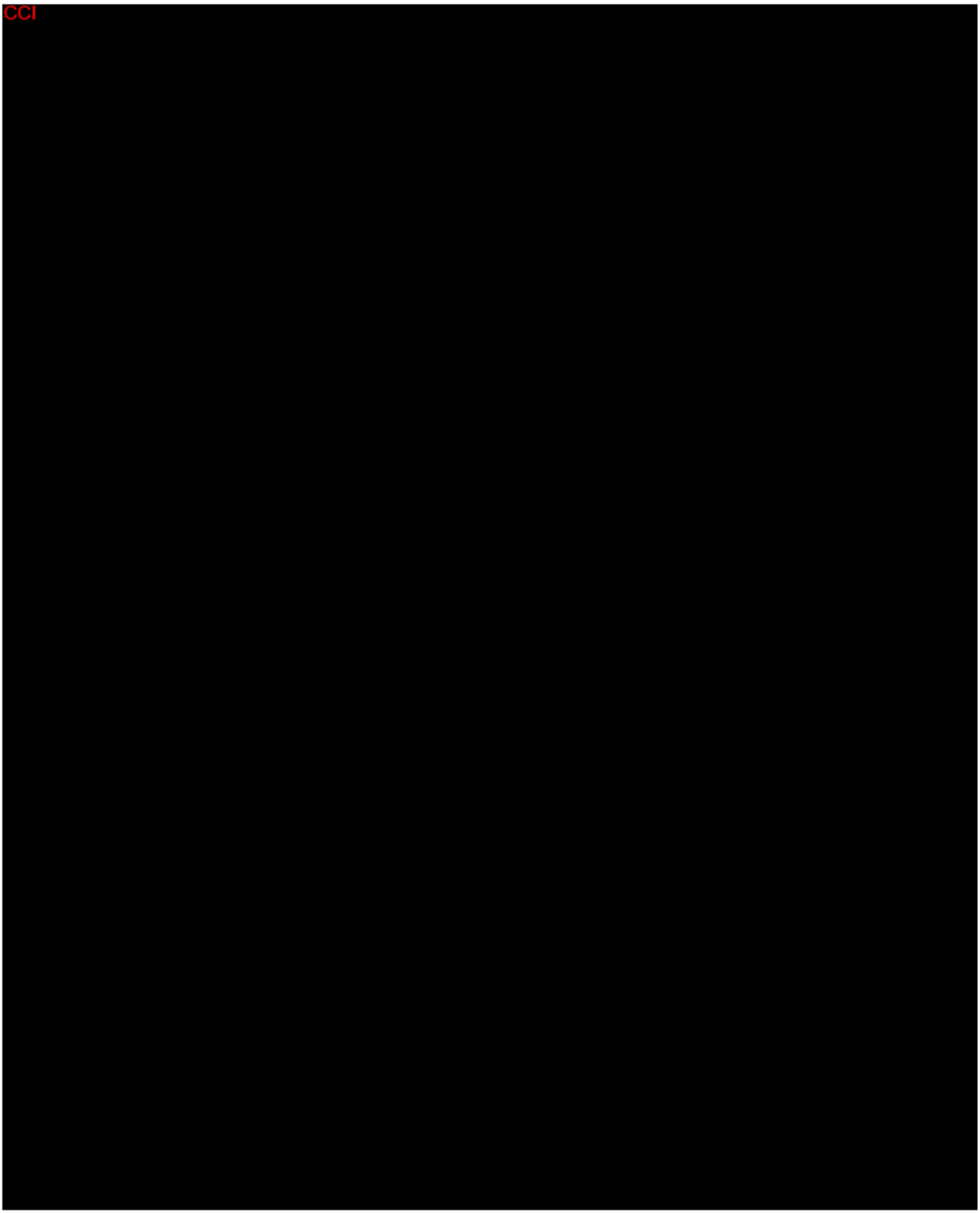

1.4 Effectiveness endpoints

1.4.1 Primary effectiveness endpoint/estimand

The primary endpoint of the study is the Responder rate based on the Blinded Evaluators' live assessment of the GIHS at 3 months after baseline.

A responder is defined as a subject with at least one-point improvement from baseline, on both sides of the face concurrently.

The primary estimand is then the difference in proportions of GIHS responders at Month 3 in the Restylane-L group versus a No Treatment control group in subjects who are randomized at baseline and did not have a remote month 3 GIHS assessment.

1.4.2 Secondary effectiveness endpoints/estimands

Secondary effectiveness endpoints include:

(i) Blinded Evaluator Assessment of GIHS

Responder rate based on the Blinded Evaluators' live assessment of the GIHS, at 6, 9, and 12 months after baseline and at 3 and 6 months after optional treatment.

A responder is defined as a subject with at least one-point improvement from baseline, on both sides of the face concurrently, at each of the timepoints separately.

The estimand is then the difference in proportions of GIHS responders at Months 6, 9, and 12 (before treatment) after baseline and the proportions of GIHS responders at Months 3 and 6 after optional treatment in the Restylane-L group versus a No Treatment control group in subjects who are randomized at baseline.

(ii) GAIS

Number and proportion of subjects having at least "Improved" on the GAIS, as assessed live by the Subject and Treating Investigator separately at all follow-up visits after baseline.

The estimand is the proportions of GAIS responders, assessed separately by Treating Investigator and subject, at each follow-up visit up until Month 12 (before treatment), and the proportions of GAIS responders at Months 3 and 6 after optional treatment in the Restylane-L group versus a No Treatment control group in subjects who are randomized at baseline.

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1.5 Safety assessments

For details regarding the safety assessments, please refer to the Clinical Study Protocol (CSP) Section 8.

1.5.1 Adverse events

Adverse events (AEs) are to be monitored throughout the course of the study. All AEs reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version in force at the time of database freeze) and classified by MedDRA preferred term (PT) and system organ class (SOC).

A two-point scale ("Yes" or "No" response) will be used for the causality assessments. The Treating Investigator should be asked to indicate a response to each of the following questions in the eCRF:

- *"Do you consider that there is a reasonable possibility that the event may have been caused by the study product?"*
- *"Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"*

If any of these questions is answered with a 'Yes,' the AE will be considered related. These assessments will also be reviewed by the Sponsor.

<u>Adverse Events of Special Interest (AESI)</u>

Due to the injection location of this study, AESIs will be considered and collected. All incidences of visual disturbances, regardless of relationship to study product or seriousness, will be considered as a potential AESI. These include, but are not limited to, the following: Any change in vision, any loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving eyes, any change in Snellen visual acuity including change of one line or greater.

1.5.2 Vision Function Assessment

Vision function assessments include Snellen visual acuity test, extraocular muscle function test, and confrontation visual field. Vision function assessments will be performed both before and 30 minutes after any study injection.

1.5.3 Subject Study Diary

Subjects will complete a 28-day symptom diary, starting on the day of injection, for each treatment (initial, optional touch-up, optional re-treatment).

1.5.4 Laboratory assessments

For all women of childbearing potential, a urine pregnancy test is required prior to receiving any study injections.

1.6 Safety endpoints/estimands

The Safety endpoints/estimands for this study include:

- **(vii) Incidence and intensity of all AEs collected during the whole study**
- **(viii) Incidence, intensity, and duration (number of hours) of pre-defined, expected post-treatment events collected using a subject diary for 28 days after treatment**

2 Statistical Methods

2.1 General methods

All tables, listings, and figures will be programmed using CCI . Data collected in this study will be documented using summary tables and subject data listings created by using the CCI . Confidence intervals (CI) and p-values will be 2-sided and performed at a significance level of 5%, unless otherwise specified. Data for all subjects in the clinical database will be included in the data listings. Calculated (derived) variables will be listed as appropriate. Any changes from the SAP will be detailed in the clinical study report.

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum, and maximum). Categorical variables will be presented in frequency tables with number and percent of observations for each level. Missing counts for all variables will be presented for informational purposes only and will not be included in percentage calculations.

Study days will be calculated relative to the first injection of study drug, for subjects randomized to Restylane-L, and date of randomization for subjects randomized to No Treatment. Day 1 will be the first day of study drug administration (for subjects randomized to the Restylane-L group) or Baseline visit (for subjects randomized to No Treatment) in the study. Baseline will be the last assessment prior to the first injection of study drug (for subjects randomized to Restylane-L) or day of randomization (for subject randomized to No Treatment) unless otherwise indicated. The Screening Visit 1 (Day -30 to Day -1) will be considered the visit prior to first injection of study drug (for subjects randomized to Restylane-L) or randomization visit (for subjects randomized to No Treatment). Because the Screening visit and Baseline visit (Day 1) may be performed on the same day, the Screening visit can also be Day 1.

Adverse events, cosmetic/aesthetic procedures and implant history events, medical history events, and concomitant treatments/procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1 or higher. Prior/concomitant medications and procedural anesthetics will be coded using the World Health Organization (WHO) Drug Dictionary Global, 1 Sep 2019 B3 or higher.

In general, all analyses will be summarized by injection tool and treatment group (Restylane-L Needle, Restylane-L Cannula, Restylane-L (pooled), No Treatment), unless otherwise stated in Section 2.4 or Section 2.5.

2.1.1 Visit Windows

Study visits are expected to occur according to the protocol schedule in Appendix G. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative study day (in relation to randomization date) of all dates will be presented. There will not be any windowing for unscheduled visits in the analysis, and unscheduled visits will not be included in any analyses. Unscheduled visits, if any, will be presented in listings only.

2.1.2 Multiple Comparisons/Multiplicity

Multiplicity will be adjusted for in the primary effectiveness subgroup analysis and is further detailed in Section 2.4.3.2.

For all secondary effectiveness endpoints, no correction for multiplicity will be done; p-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of the results.

2.2 Analysis Populations

There will be three analysis populations defined for this study:

- Modified Intention-to-treat (mITT) Population – Includes all subjects who are randomized and will be analyzed according to the randomization scheme; subjects with a GIHS Month 3 assessment via a remote visit (i.e. remote office visit and/or GIHS assessment done remotely) will be excluded
- Intention-to-treat (ITT) Population - Includes all subjects who are randomized at baseline and will be analyzed according to the randomization scheme determined at baseline
- Per protocol (PP) Population - Includes all subjects in mITT who complete 3 months after baseline visit without any deviations considered to have substantial impact on the primary effectiveness
- Safety Population - Includes all subjects who are treated with Restylane-L or randomized to the control group, and will be analyzed according to as-treated principle

2.3 Study subjects

2.3.1 Subject disposition

The disposition of subjects will be presented by treatment group (Restylane-L, No Treatment) and in total, including number of subjects that were:

- Screened, including screen failures
- Enrolled
- Randomized
- Study Completers
- Early withdrawals/discontinuations
- Restylane-L group (Needle or Cannula) or No Treatment group
- ITT population
- PP population
- Safety Population

Specifically, the number and percentage of subjects in each of the specified categories above will be presented. The discontinuation reason as specified on the electronic case report forms (eCRFs) will also be summarized by number and percent.

All withdrawn/discontinued subjects and inclusion/exclusion data will be presented by subject in data listings.

2.3.2 Protocol deviations

Subjects with protocol deviations will be listed individually, including subject number and observed deviation. The following are considered protocol deviations for this study:

- SAE Reporting
- Study Product Use

- Missed Procedure
- Eligibility
- Photography
- Informed Consent
- Missed Visit
- Prohibited Medication or Procedure
- Out of Window Visit
- Remote Visit, all assessments done
- Remote Visit, all assessments not done

Depending on the seriousness of the deviation, a subject might be excluded from the PP population, which shall be documented in a listing prior to database lock.

For this study, the protocol deviations that will exclude subjects from PP are identified (but not limited to) in Table 1 below. Deviations from the SAP will be documented in the CSR.

Table 1. Protocol deviations

	Deviation
*	Any subject that conducts their Month 3 visit significantly out-of-window
*	Any subject that misses the primary endpoint visit (Month 3)
*	Any subject not treated according to the assigned treatment
*	Any subject that does not complete the GIHS at the primary endpoint visit (Month 3)
*	Any subject that do not have Grade 2 or 3 on the Blinded Evaluator GIHS at baseline
*	Any subject with more than 1 grade difference in Blinded Evaluator GIHS between the left and right side at baseline
*	Any subject with prohibited concomitant treatments/procedures prior to Month 3 visit considered to have a substantial impact on the primary effectiveness outcome.
*	Any subject with a prohibited medical history, unstable medical history, or medical history that worsens prior to Month 3 visit considered to have a substantial impact on the primary effectiveness outcome

2.3.2.1 Out of Window visit duration

When a subject performs a planned study visit outside of the protocol-specified visit windows (Appendix G), the subject has an out of window study visit, which is considered a type of protocol deviation for this study. Knowing a subject's Screening visit (Visit 1a) and Baseline visit (Visit 2) and using the protocol-specified visit windowing, one can calculate a subject's target study visit window date range for each planned study visit. Then, by comparing a subject's actual study visit date to the target study visit window date range, one can calculate the days over/under the actual study visit was in relation to the target study visit date, or study visit out of window duration.

The duration, in days, a study visit is out of window will be summarized by treatment group, overall, and by visit. Out of window visit durations will also be presented by site as well. Duration will be split into the following below categories. Duration categories will include both days before and days after the target planned visit date.

- +/- 1-2 days
- +/- 3-7 days
- +/- 8-20 days
- +/- 21 or more days

The number and percentage of subjects within each out of window duration category will be presented descriptively. For the overall analysis, percentages will be calculated using the number of subjects with an out of window visit at the respective visit as the denominator; for the by site analysis, percentages will be calculated using the number of subjects at the respective site as the denominator.

2.3.3 Demographic characteristics

Demographic assessments for this study include:

- Age (years)
  - Age groups using a median split
- Height (in)
- Weight (lbs.)
- BMI (kg/m^2)
  - BMI groups using a median split
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- FST score (I, II, III, IV, V, VI)
- Blinded Evaluator GIHS, both sides of face (0, 1, 2, 3)

The demographic and baseline characteristic analyses will be presented by treatment group and overall and will be based on the ITT population using the appropriate descriptive statistics for continuous and categorical variables. Age, height, weight, and BMI will be analyzed as continuous variables. Gender, race, ethnicity, FST score and GIHS scores will be analyzed as categorical variables.

Demographics and baseline characteristics will be presented by subject in a data listing.

2.3.4 Medical and surgical history

All summaries will be done by treatment group based on the ITT population. History of relevant or clinically significant surgical events and medical conditions, including any prior dermatological/cosmetic procedures or implants, will be collected. Medical History will be coded according to MedDRA; the version used will be noted as a footnote in the tables and listings.

The number and percent of subjects reporting medical history, and the number of events will be summarized by system organ class (SOC) and preferred term (PT). System organ class and PTs will be presented in descending frequency first, and then alphabetically if there are ties. Each subject

will contribute at most one count per summarization category. In other words, if a subject has more than one medical history event with same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than one medical history event for a SOC, the subject will be counted only once in that SOC and PT. For the event level analyses, counts of each respective event will be presented.

Prior dermatological/cosmetic procedures or implants will also be presented and will follow the same methods specified above.

Medical history information and prior dermatological/cosmetic procedures or implants will be presented by subject in a data listing.

2.3.5 Concomitant medication/procedures

All summaries will be done by treatment group based on the Safety Population. Concomitant medications/therapies/procedures for this study are defined as any existing medications/ therapies/ procedures ongoing at the time of the screening visit, any changes to existing medications/ therapies (such as dose or formulation) during the course of the study, or any new medications/therapies received by the subject since the screening visit. Concomitant medications/therapies will be coded using the World Health Organization (WHO) Drug Dictionary; concomitant procedures will be coded according to MedDRA. The versions used for the coding will be noted as a footnote in the tables and listings.

The number and percent of subjects reporting concomitant medications/therapies, and number of drugs, will be summarized by the WHO Drug Dictionary Anatomical Therapeutic Chemical 3rd level (ATC-3) and the preferred name. If the 3rd level term is not available, the next available level (e.g., ATC-2) will be used. In addition, the number and percent of subjects reporting a concomitant medication/therapy, and the number of drugs will be summarized by reason. Concomitant medications that started due to an AE will be summarized separately.

ATC-3 and preferred name will be presented in descending frequency first, and then alphabetically if there are ties. Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one medication with same preferred name, the subject will be counted only once for that preferred name. Similarly, if a subject has more than one medication for an ATC-3 level, the subject will be counted only once in that ATC-3 level and preferred name. For the number of drugs, counts of each respective medication will be presented.

Concomitant procedures will also be presented, and will follow the same methods specified for medical history (Section 2.3.4).

Concomitant medications/procedures will be presented by subject in a data listing.

2.4 Effectiveness analysis

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2.4.1 Datasets analyzed

The mITT population will be used for the primary effectiveness analysis. All secondary effectiveness analyses will be based on the ITT population.

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2.4.2 Handling of missing data

In general, the number of missing values will be summarized and reported as appropriate in all outputs. The primary analysis will be performed using MI as the primary imputation method. The MI methods are detailed in Appendix H.

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2.4.3 Primary effectiveness analysis

The primary effectiveness analysis will be done using the mITT Population. To evaluate the effectiveness of Restylane-L versus no-treatment control in the correction of Infraorbital Hollows, the GIHS responder rates (defined in Section 1.3.1) at Month 3 after baseline will be compared using the CMH test stratified by injection tool at the 5% significance level (2-sided).

The null hypothesis will be that there is no relationship between GIHS responder rate and treatment group (i.e. the responder rate is the same in both Restylane-L and no treatment groups). The alternative hypothesis will be that there is a relationship between responder rate and treatment group (i.e. the responder rate is different in the two groups). For a significant result, the two-sided p-value of the comparison of GIHS responder rates between the treated and untreated subjects at Month 3 using the CMH test needs to be smaller than 0.05.

The estimates of the GIHS responder rates in each treatment group will be presented as well as the difference in responder rates (Restylane-L responder rate – No Treatment responder rate). Corresponding 95% CI for the treatment group GIHS responder rates and the difference in responder rates along with the p-value for the difference will also be presented. The normal approximation (Wald) method will be used to calculate the 95% CI for the individual treatment group GIHS responder rates as well as the 95% CI for the difference in responder rates.

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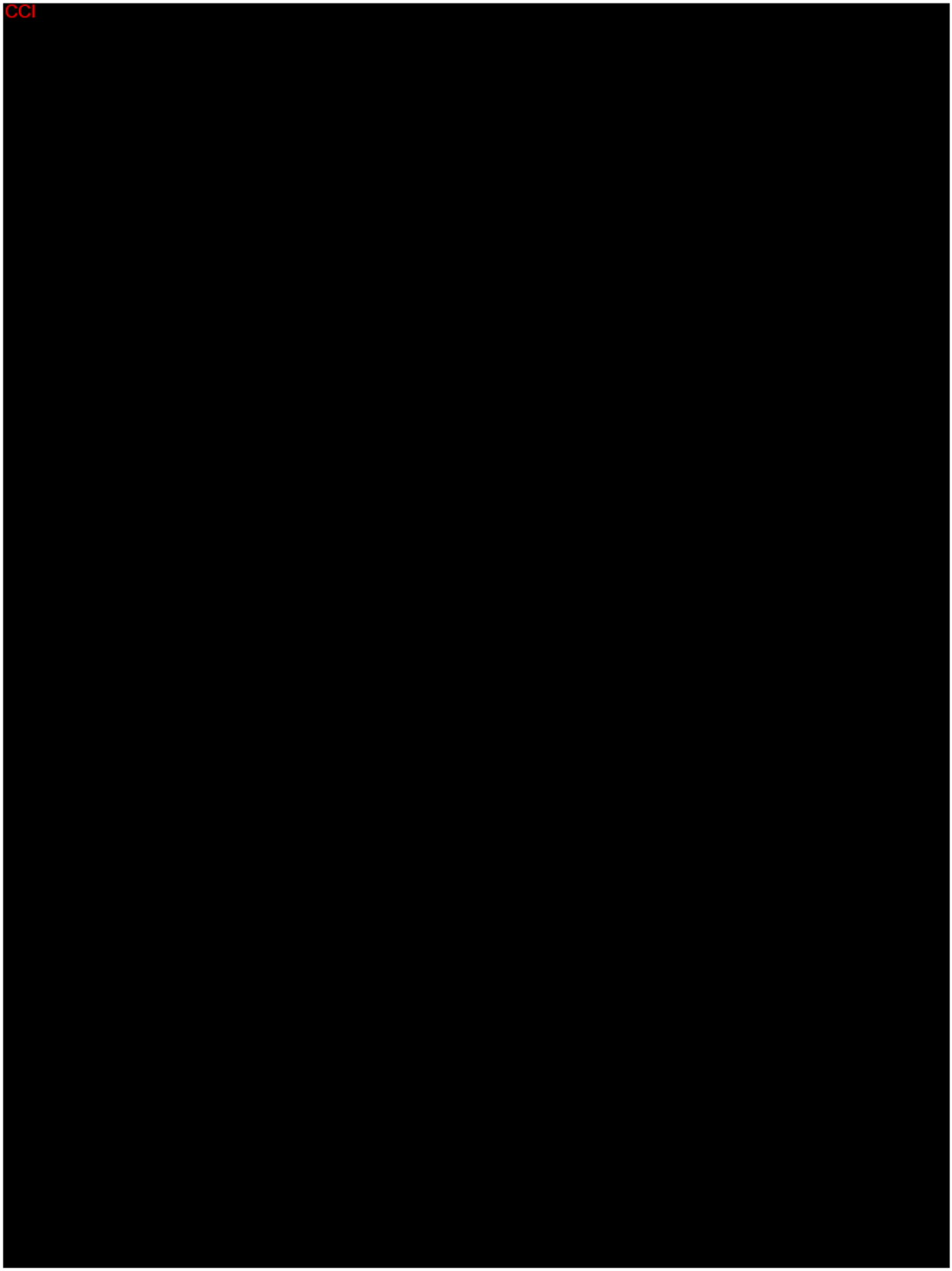

2.4.4 Secondary analysis

All secondary endpoint analyses will be conducted using the ITT Population. In general, "by treatment group" refers to the Restylane-L Needle, Restylane-L Cannula, Restylane-L (pooled), and the No Treatment group.

2.4.4.1 GIHS

Responder rates based on the GIHS determined by the Blinded Evaluator (described in Section 1.3.1) will be analyzed using the CMH test stratified by injection tool. This test will use the ITT Population on the observed cases following the methods described in Section 2.4.3 and will be presented by visit. No correction for multiplicity will be done; p-values (if generated) will only be provided for ease of interpretation of the results.

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2.4.4.2 GAIS

GAIS aesthetic improvement (overall appearance), as determined separately by the Treating Investigator and Subject, will be presented in frequency tables. The response rates (defined in Section 1.3.2) based on the GAIS as assessed by the Treating Investigator will be calculated and presented, separately, by treatment group. The actual GAIS ratings of the Treating Investigator will also be presented similarly and by visit.

The methods described above will be repeated for the GAIS results as determined by the Subject.

GAIS results, including both responder (Yes/No) and the actual GAIS ratings of the Treating Investigator and Subject, will be presented by treatment and subject in data listing.

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2.5 Safety Analysis

All safety analyses will be performed based on the safety population set. In general, "by treatment group" refers to the Restylane-L Needle, Restylane-L Cannula, Restylane-L (pooled), and the No Treatment group.

2.5.1 Extent of exposure

Injection Characteristics

Injection characteristics include, for each treatment (initial, touch-up, re-treatment), injection administration, procedural anesthetics, and post-injection concomitant procedures used. The

following parameters will be summarized descriptively for the infraorbital hollows combined, for each treatment separately:

- Number of subjects treated
- Total number of syringes used
- Needle used (Co-pack, Other, Needle group only)
- Cannula used (25G x 1.5 in, 27G x 1.5in; Cannula group only)
- Injection method (Linear antegrade, Linear retrograde, Fanning, Micro-bolus, Serial puncture, Other)
- Injection depth (Supraperiosteal, Other)

The following parameters will be summarized for each treatment separately, by treatment group:

- Procedural Anesthetics (No, Yes)
- Type of Anesthetics (Topical, Local Injection)
- Injection Concomitant Procedures (None, Massage, Ice Pack, Other)

If a subject receives more than one injection for a given treatment period, only the injection given closest to the protocol-specified injection visit (Appendix G) will be presented in the injection characteristics summary.

Injection Volume Administered

The injection volume (mL) administered throughout the study will be presented descriptively by the following timepoints, by group (where applicable):

- Initial treatment – The amount of study product injected into subjects at the baseline visit (for subjects randomized to Restylane-L) or at the Month 12 visit (for subjects randomized to No Treatment).
- Optional Touch-up – The amount of study product injected into subjects at the Month 1 visit. Only applicable to subjects randomized to Restylane-L.
- Initial treatment + Touch-up – The cumulative sum of study product injected into subjects for the initial and touch-up treatments, regardless of how many treatments a subject received. This will be presented for both treatment groups.
- Re-Treatment – The amount of study product injected into subjects at the Month 12 visit. Only applicable to subjects randomized to Restylane-L.
- Total injected volume – The cumulative sum of study product injected into subjects across every potential injection timepoint, regardless of how many injections a subject got. This will be presented for both treatment groups.

If a subject receives more than one injection for a given treatment period, their total volume from all injections will be summarized in the 'Total injected volume' timepoint. Only the injection given closest to the protocol-specified injection visit (Appendix G) will be presented in each respective timepoint section described above.

All injection volume, injection characteristics, procedural anesthetics, and injection concomitant procedures data will be presented by treatment and subject in data listings.

2.5.2 Adverse events

All AE data will be summarized by needle, cannula, and no treatment separately. Only AEs occurring after first injection, for subjects randomized to Restylane-L or after randomization for subjects randomized to No Treatment, or AEs that worsened, will be included in analysis. AEs occurring before, if any, will only be listed in subject data listings.

All AE endpoints will be presented by the timepoint in which they occurred, defined as:

- No Treatment at Baseline: For subjects randomized to No Treatment, an AE which starts between date of randomization up until the time of their first injection.
- Initial Treatment with Restylane-L: For subjects randomized to Restylane-L, an AE which starts on or after their baseline injection up until their optional retreatment (including optional touch-up); for subjects randomized to No Treatment, an AE which starts on or after their optional initial treatment.
- Retreatment with Restylane-L: For subjects randomized to Restylane-L, an AE which starts on or after their optional retreatment.

Missing dates, severity, relationship, and seriousness will be imputed as described in Section 2.4.2. Adverse Events will be summarized by SOC and PT. The MedDRA version used for the coding will be noted as a footnote in the tables and listings.

A summary of AEs will be provided, which will include the number and percentage of subjects and number of events with the following categories of:

- Any AE
- Any Serious AE
- Any AE related to study product or injection procedure
- Any Serious AE related to study product or injection procedure
- Any AE unrelated to study product or injection procedure
- Any Serious AE unrelated to study product or injection procedure
- Any AESI
- Any Serious AESI
- Number of subjects who did not have an AE

Summaries of related AEs (including the total number of events, number and percentage of subjects) will be displayed by treatment grouping specified above according to the following:

- All AEs related to study product or injection procedure by SOC, PT, and maximum intensity (mild, moderate, or severe)
- All AEs related to study product or injection procedure by SOC, PT, and duration of event
- All AEs related to study product or injection procedure by SOC, PT, and number of days to onset of event
- All AEs by SOC, PT, and action taken (none, medical treatment, non-pharmacological treatment, subject withdrawn)
- All AEs unrelated to study product or injection procedure by SOC, PT, and maximum intensity (mild, moderate, or severe)

For the subject level analyses, the number and percentage of subjects who experienced at least one of the events listed above will be summarized overall and for each SOC and each PT. System organ class and PTs will be presented in descending frequency first (by treatment group), and then alphabetically if there are ties. Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one AE with same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than one AE for a SOC, the subject will be counted only once in that SOC and PT. For the event level analyses, the counts of each respective event will be presented. In general, percentages) will be calculated using the number of subjects in the Safety population for the denominator.

For the "action taken" summary specifically, subjects will be only counted in 'None' category if no other action was taken. For the onset/duration summaries, number of days to onset and duration of event will be summarized by SOC and PT, using mean, SD, minimum, maximum, and median statistics. Time to onset of an AE will be derived as the start date minus the date of most recent treatment. Duration of an AE will be derived as the stop date minus the start date + 1. Imputation rules for partial/completely missing dates are specified below. Missing stop date will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of AEs that were ongoing at the end of the study will be given.

All reported AEs will be listed in data listings including time to onset, duration of AE, action taken (if applicable) and severity. By-subject listings also will be provided for all subjects for the following: Pre-treatment and AEs, AE severity, AEs related to study product or injection procedure, serious adverse events (SAEs), AEs leading to discontinuation of study drug, action taken, and resolution or outcome.

Handling of Missing/Partial Dates

While every effort will be made to obtain complete information on every reported AE, the following imputation rules will be followed for any respective missing AE data:

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2.5.3 Pre-defined, Expected, Post-Treatment Events

Number and percentage of subjects reporting each pre-defined, expected, post-treatment symptom (i.e. Pain, Tenderness, Redness, Bruising, Swelling, Itching, Lumps/Bumps for each side of face), as collected in the 28-day diary, will be presented in total and by maximum severity (Tolerable, Affects daily activities, Disabling). Number of days with the event will be summarized by treatment period using the following categories: 1, 2-7, 8-13, and 14-28 days. If a subject completes more than one diary for a given treatment period, only the first diary (i.e. the diary with earlier entry dates) will be summarized in the table.

All subject diary data will be presented by treatment and subject in a data listing.

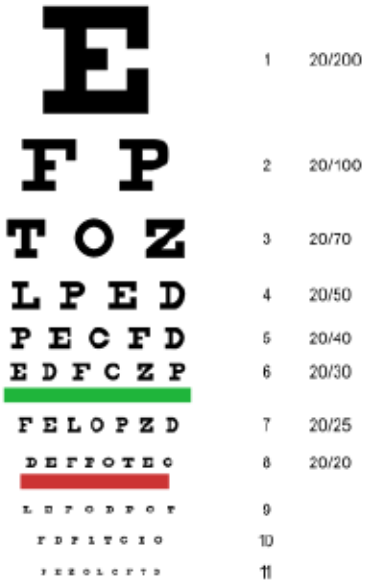
2.5.4 Vision Function Assessment

For the extraocular muscle function test and confrontation visual field vision function assessments (specified in Section 1.5.2) the number and percentage of subjects reporting normal and abnormal test results will be presented by treatment group and by visit.

For Snellen visual acuity test, subjects that experience a worsening of 1+ line change in at least one eye during the course of the study will be summarized by eye, treatment group, and visit. Only subjects that experience a worsening line change will be considered in the analysis; the number and percentage of subjects that experience a worsening of 1+ line change in at least one eye during the course of the study will be presented. The number of subjects with a non-missing Snellen assessment at a respective visit will be used as the denominator.

A 1+ worsening line change in Snellen visual acuity is when a subject moves up at least one line of letters on the Snellen Eye Chart (Figure 1). For example, if a subject's visual acuity at baseline is 20/40 for the left and right eyes and then at Visit 3 is 20/70 for the left eye and 20/50 in the right eye, the subject experienced a 2-line worsening for the left eye and a 1-line worsening in the right eye.

Figure 1. Snellen Eye Chart



The visual function assessment data will also be presented by treatment and subject in data listing. This listing will only include subjects with a change in visual function as determined by any of the three vision assessments.

2.5.5 Laboratory Assessments

The pregnancy test data will be presented by treatment and subject in a data listing.

2.5.6 Device Deficiencies

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Any reported device deficiency will be presented by subject in a data listing.

2.6 Interim Analysis

There are no interim analyses planned for this study.

2.7 Determination of Sample Size

Due to the public health emergency related to the COVID-19 pandemic during 2020, steps have been taken to ensure patient and practitioner safety in alignment with FDA Guidance dated May 11, 2020 (Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency). Most notably, in partnership with clinical sites and the IRB, optional remote assessment procedures for efficacy and safety endpoints has been implemented to ensure safety and respect localized and elective restrictions. Therefore, the sample size has been increased during the conduct of the study to ensure a sufficient number of subjects in the mITT population used in the assessment of the primary effectiveness endpoint.

The study was initially planned to enroll a total sample size of approximately 238 subjects; approximately 204 randomized to treatment with Restylane-L (~102 injected using needle, and ~102 injected using cannula) and approximately 34 randomized to no treatment.

Based on information on missing data and the number of remote visits performed at study sites so far, the study is now planned to enroll approximately 329 subjects; approximately 282 will be randomized to treatment with Restylane-L (~146 will be injected using needle, and ~136 will be injected using cannula) and approximately 47 will be randomized to no treatment in order to achieve the required number of mITT subjects in each stratum.

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2.8 Changes in the Analysis from Previous Protocol Versions

Refer to Section 2.4 for a brief background on changes in the analyses specified in the SAP that differ from previous versions of the Protocol. Protocol Version 10.0 now matches the SAP.

2.9 Change History

The table below outlines the changes made to the SAP since the previous version.

Table 3. Changes from Previous Version

Version	Date	Description of Changes
2.0	06 OCT 2020	• Increased the number of subjects to be randomized • Added the mITT analysis population • Included the new COVID-19 protocol deviation categories • Updated the planned protocol deviation analysis • Updated the primary analysis method to be conducted using the mITT population • CCI [redacted] • CCI [redacted] • Updated the missing data sensitivity analyses to include: CCI [redacted], BOCF, ITT observed cases, tipping analysis using the mITT population, tipping point analysis using the ITT population • Added type of Month 3 visit (onsite, remote) as another subgroup analysis of the primary endpoint • Updated the sample size calculation
3.0	16 DEC 2021	• Updated the MI methods for CMH test (Appendix H) • Updated primary analysis and secondary GIHS analysis method to be the CMH test CCI [redacted]

		• Updated Snellen Visual Acuity analysis • Added Section 2.3.2.1 to describe out of window visit duration analysis • Added information to Table 2 • Added handling of data for injection characteristics, extent of exposure, and diary analyses for subjects injected multiple times in a treatment period. • CCI [redacted] • Included information on statistical methods updates in section 2.4 • Updated secondary analysis to present Months 3 and 6 after optional treatment as descriptive only • Updated tipping point analysis method to CMH

3 Reference List

1. Bohdana Ratitch, et al. "Combining Analysis Results from Multiply Imputed Categorical Data", 2013, PharmaSUG Proceedings, Paper SP-03

GALDERMA	Title 43USTT1904 Statistical analysis plan - Tear Trough	Doc id MA-42205

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5 Appendix B. GIHS

6 Appendix C. GAIS Response Categories

Rating (Treating Investigator and Subject	Definition (only 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.

GALDERMA	Title 43USTT1904 Statistical analysis plan - Tear Trough	Doc id MA-42205

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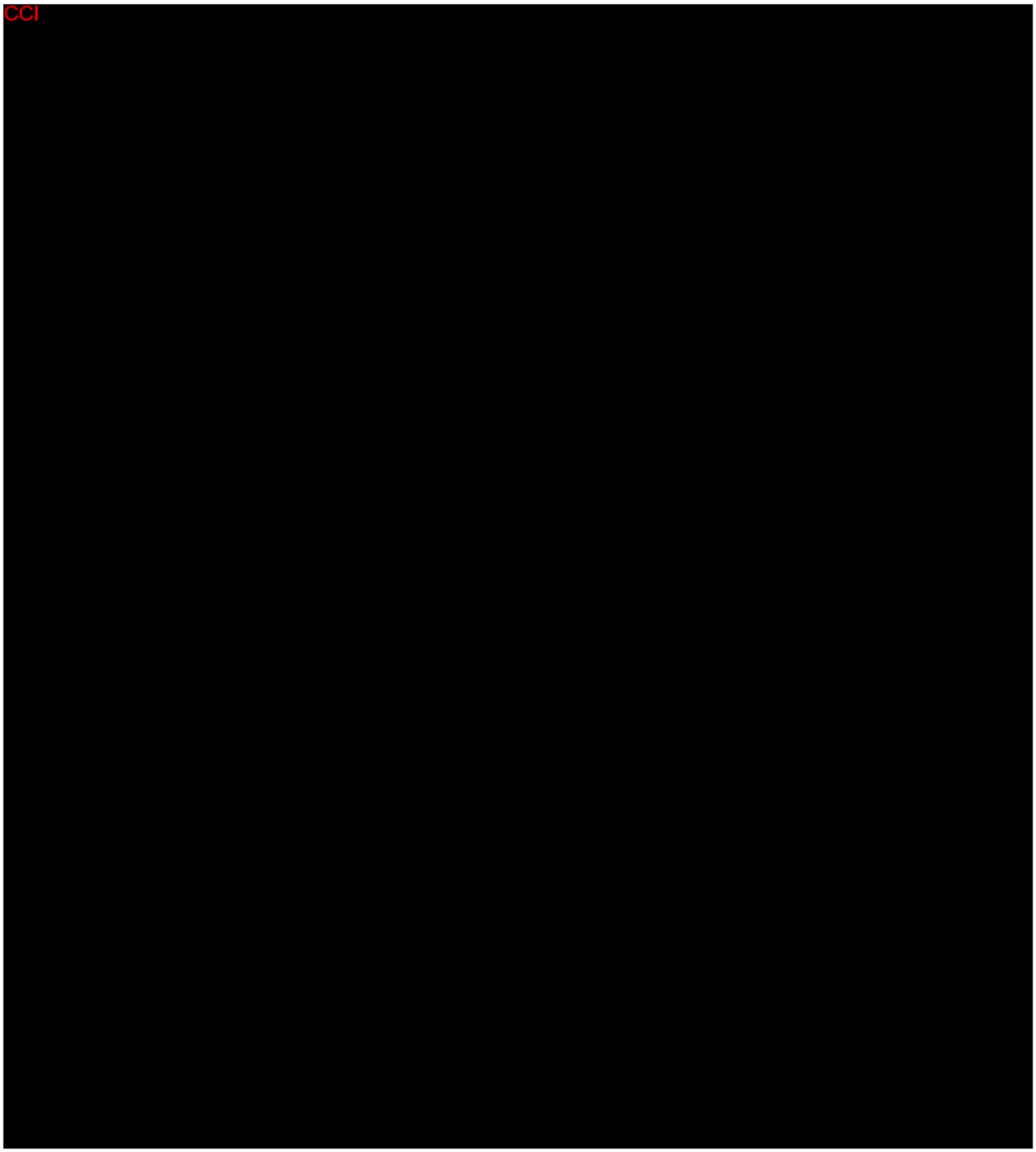

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GALDERMA	Title 43USTT1904 Statistical analysis plan - Tear Trough	Doc id MA-42205

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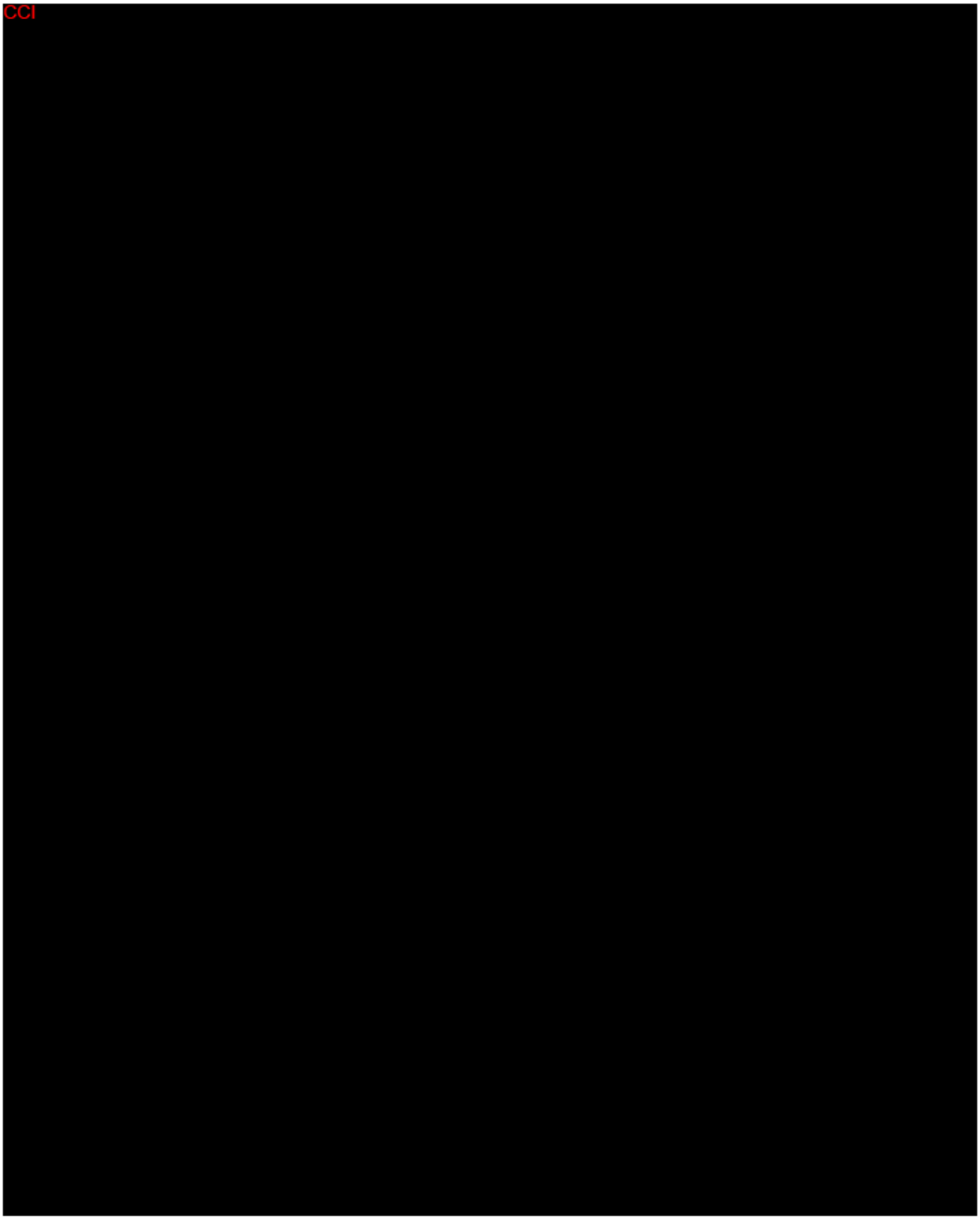

9 Appendix F. Effectiveness Estimands

Endpoints	Attributes				
	Population	Endpoints	Treatments	Intercurrent Events	Statistical Summary
Primary	mITT Population; includes all randomized subjects that did not have a remote month 3 GIHS assessment ITT Population; includes all randomized subjects PP Population	Responder rate based on the Blinded Evaluators' live assessment of the Galderma Infraorbital Hollows Scale (GIHS), at 3 months after baseline.	Restylane-L vs. Control	Subjects that don't have a Month 3 GIHS response, due to missed visit, missed procedure, or discontinuation prior to visit, Subject has a prohibited treatment/procedure performed prior to Month 3; Subject has an unstable medical history affecting the IOH area	Number and difference in proportion (n, %) of subjects
Secondary 1	ITT Population	Responder rate based on the Blinded Evaluators' live assessment of the GIHS, at 6, 9, and 12 months after baseline and at 3 and 6 months after optional treatment.	Restylane-L vs. Control	Subjects that don't have a GIHS response at a respective visit, due to missed visit, missed procedure, or discontinuation prior to visit	Number and difference in proportion (n, %) of subjects
Secondary 2	ITT Population	Proportion of subjects having at least "Improved" on the Global Aesthetic Improvement Scale (GAIS), as assessed live by the Subject and Treating Investigator separately at all follow-up visits after baseline.	Restylane-L vs. Control	Subjects that don't have a GAIS response at a respective visit, due to missed visit, missed procedure, or discontinuation prior to visit	Number and proportion (n, %) of subjects
CCI [redacted]					

Endpoints	Attributes				
	Population	Endpoints	Treatments	Intercurrent Events	Statistical Summary
CCI					

10 Appendix G. Schedule of Events

Procedure	Visit 1a	Visit 1b	Visit 2[4]	Visit 3[4]	Visit 4	Visit 4a[4]	Visit 4b[4]	Visit 4c[4]	Visit 5 -7	Visit 8 or EOS/ET	Visit 8a[4]	Visit 8b[4]	Visit 8c[4]	Visit 8d[4]	Visit 8e[4] EOS for optional Tx
	Visits may be combined if subject meets eligibility criteria		72 hrs after Tx (±24 hrs)	14 days after Baseline (±3 days)	1 month[10] after Baseline (+7 days)	72 hrs after Optional touch-up (±24 hrs)	14 days after Optional touch-up (±3 days)	1 month[10] after Optional touch-up (+7 days)	3, 6, & 9 months[10] after Baseline (±7 days)	12 months[10] (±7 days) after Baseline	72 hrs after optional Tx (±24 hrs)	14 days after optional Tx (±3 days)	1 month after optional Tx (+7 days)	3 months[10] after optional Tx (±7 days)	6 months[10] after optional Tx (+7 days)
	Screening Day -30 to 1	**Baseline/ Tx Day 1**	**TC**	**Follow-up**	**Follow-up Optional TU**	**TC**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up Optional Tx**	**TC**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Informed Consent	X														
Med. Hx/prior therapies	X	X[1,2]													
Demographics	X														
Height/Weight[6]		X[1,3]		X[4]	X[4]		X[4]	X[4]	X[4]	X[4]		X[4]	X[4]	X[4]	X[4]
Inclusion/Exclusion Criteria	X	X[1,2]			X[1,3]					X[1,3]					
Urine pregnancy test[3]	X	X[1,2]			X[1,3]					X[1,3]					
Vision Function Assessments	X	X[2,8,9]		X	X[5,8,9]		X			X[5,8]		X			
Randomization		X													
Treatment with study product		X[9]			X[5,9]					X[5]					
Evaluate device deficiencies		X			X[5]					X[5]					
Dispense Subject Diary		X[9]			X[5]					X[5]					
Collect / Review Subject Diary			X[7]	X	X[5]	X[7]	X	X			X[7]	X	X		
2D Photography		X[4]		X	X[5]		X	X	X	X[5]		X	X	X	X
Concomitant Therapies	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treating Investigator Assessments															
GAIS					X[5]			X	X	X[5]			X	X	X
GlHS	X	X[1,2]			X[5]					X[5]					
Blinded Evaluator Assessments															
GlHS	X	X[1,2]							X	X[5]				X	X
Subject Assessments															
GAIS					X[5]			X	X	X[5]			X	X	X
CCI															

[1]Prior to any planned treatment
[2]Omitted if the screening and baseline visits occur on Day 1. Screening visit and baseline visit can be combined if no drug washout is needed
[3]For females of childbearing potential
[4]Visit is scheduled only if initial treatment, optional touch-up or optional treatment is performed
[5]Omitted if optional touch-up or optional treatment is not performed
[6]Subject self-reported. Height only needs to be collected at baseline
[7]Review diary with subject over the phone
[8]Performed prior and 30 minutes post injection of study product
[9]For subjects randomized to study treatment
[10]One month is defined as 4 weeks in the study

ET = Early Termination
EOS = End of Study
GlHS = Galderma Infraorbital Hollows Scale
GAIS = Global Aesthetic Improvement Scale
TC= Telephone call
TU = Touch up
Tx = Treatment

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SIGNATURES PAGE

Date	Signed by
2021-12-17 08:45	PPD
Justification	Approved by Owner

2021-12-17 09:01	PPD
Justification	Approved by Technical Expert

2021-12-17 13:25	PPD
Justification	Approved by Project Manager