05DF2004: A Study Comparing Hyaluronic Acid Effectiveness & Evaluating Cheek Results with Restylane (CHEEKY Study)

NCT04638816

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GALDERMA

Galderma Research and Development, LLC

Protocol Number: *CTN 05DF2004*

Statistical Analysis Plan

Version 1.0

[redacted]

Advanced Clinical

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1.0 PURPOSE

This SAP describes the methods to be used in the analysis of trial data from clinical protocol CTN 05DF2004 titled "A Study Comparing Hyaluronic Acid Effectiveness & Evaluating Cheek Results with Restylane" in order to answer the trial objective(s) and is based on v1.0 of the trial protocol, dated 03NOV2020.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the CSR for this trial. The SAP outlines any differences in data analysis methods relative to those planned in the trial protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

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2.0 ACRONYMS

Below is the list of acronyms that will be used throughout this document.

Abbreviation	Definition
AE	Adverse Event
ATC-4	Anatomical Therapeutic Chemical 4th level
BMI	Body Mass Index
CSP	Clinical study protocol
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
FST	Fitzpatrick Skin Type
[redacted]	[redacted]
IPR	Independent Photographic Reviewer
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TC	Telephone Call
WHO	World Health Organization

3.0 OVERALL STUDY DESIGN AND OBJECTIVE

3.1 Trial Objectives

3.1.1 Primary Objective

To evaluate the aesthetic improvement (cheek appearance) with Restylane® Volyme and Restylane® Lyft Lidocaine compared to pre-treatment.

The primary endpoint:

- Improvement assessed by the Treating Investigator week 4 after last treatment, [redacted]

3.1.2 Secondary Objectives

[redacted]

3.1.3 Safety Objective

To evaluate the safety of Restylane® Volyme and Restylane® Lyft Lidocaine by assessment of adverse events (AEs) by the Treating Investigator throughout the study period.

[redacted]

3.2 Trial Design and Trial Procedures

This is an 8-week, multi-center, phase IV, post-marketing study [redacted]

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[redacted]

Approximately 60 female subjects will be treated at 3 sites in Canada. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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3.3 Treatments and Assignment to Treatments

Approximately 60 subjects will be enrolled at 3 sites in Canada. [redacted]

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4.0 GENERAL STATISTICAL METHODS

4.1 Determination of Sample Size

The sample size of approximately 60 subjects [redacted] is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of effectiveness and safety of the two products for cheek augmentation/volumization [redacted]

4.2 General Methods

All tables, listings, and figures will be programmed using SAS Version 9.4 or higher. Data collected in this study will be documented using summary tables and subject data listings created by using the SAS® system. 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.

All efficacy, safety and baseline characteristics variables will be presented using descriptive statistics within each treatment group, and graphs as appropriate. Continuous variables will be summarized using descriptive statistics (number of observations, mean, standard deviation [SD], median, minimum, and maximum). Categorical variables will be presented in frequency tables with number and percentage 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 injection of study drug. Day 1 will be the day of study drug administration. Baseline will be the last assessment prior to the injection of study drug unless otherwise indicated. The Screening Visit 1 (Day -30 to Day 0) will be considered the visit prior to injection of study drug. 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, prior dermatological procedures or implant history events, medical history events, and concomitant treatments/procedures will be coded using MedDRA, Version 23.0. Prior/concomitant medications and procedural anesthetics will be coded using the World Health Organization (WHO) Drug Dictionary Global, 1 March 2020 or higher.

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In general, efficacy and safety analyses will be performed and summarized by treatment group, unless otherwise stated.

4.3 Trial Periods

The total duration of the study is expected to 16 weeks [redacted]

[redacted]

4.4 Visit Windows

Study visits are expected to occur according to the protocol schedule. 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 of all dates will be presented.

4.5 Handling of Missing Data

Study data will be presented based on observed cases, i.e. no imputation of missing values will be performed.

4.6 Site Pooling

There will be no pooling of centers.

4.7 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made. P-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of the results.

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[redacted]

4.8 Interim Analysis and Data Monitoring

No interim analysis is planned for this study.

5.0 ANALYSIS POPULATIONS

The Analysis Populations to be used for the analyses in this study are described below.

5.1 Full Analysis Set (FAS)

Includes all subjects who were injected in both cheeks. FAS is the primary population for all effectiveness analyses.

5.2 Per-Protocol Population

If there are any clinical study protocol (CSP) deviations considered to have substantial impact on the effectiveness outcome, a per protocol (PP) population excluding those subjects may be defined.

5.3 Safety Population

The Safety Population includes subjects who were injected in at least one cheek. Safety analysis is performed based on the safety population set.

6.0 SUBJECT STATUS

6.1 Subject Disposition

Subject disposition will be summarized by treatment group and overall. The number of subjects screened, randomized, and treated will be presented as well as the number of subjects in each analysis population (FAS, Safety, and PP). The number and percentage of subjects in the FAS population who complete the study will be summarized, along with the number and percentage of subjects who did not complete the study for each discontinuation reason as specified on the eCRFs.

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

Inclusion/exclusion data also will be presented by subject in a data listing.

6.2 Protocol Deviations

Protocol deviations will be presented by subject in a data listing. Subjects with protocol deviations will be listed individually, including subject number and observed deviation.

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Subjects may be excluded from the PP population based on the seriousness of the deviation, which shall be documented prior to database lock.

6.3 **Demographics and Baseline Characteristics**

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the FAS set using descriptive statistics by treatment, as appropriate. The variables to be summarized are described below:

- Continuous variables
  - Age (years)
  - Weight (kg)
  - Height (cm)
  - Body Mass Index (BMI) (kg/m2)

- Categorical variables

  - Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Fitzpatrick Skin Types (FST) (I, II, III, IV, V, VI)

If variables are collected at screening and baseline, the baseline value will be summarized. Demographic and baseline characteristics will be presented by treatment and subject in a data listing.

6.4 **Medical History**

History of relevant surgical events and medical conditions, including any prior dermatological procedures or implants, are collected.

Medical history will be summarized by individual treatment group and overall for the ITT population as given below:

i) Any Medical History
ii) Prior Dermatological Procedures or Implants

Each summary will separate events by system organ class (SOC) and preferred term (PT). Each subject will only be counted once per SOC and PT.

Medical history and Prior Dermatological Procedures/Implants history will be reported by treatment and subject in separate data listings.

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7.0 EFFICACY ANALYSIS

7.1 Primary Efficacy

7.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is [redacted] assessed by the Treating Investigator week 4 after last treatment compared to pre-treatment.

[redacted]

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Very much worse	Obvious worsening in appearance from the initial condition.

7.1.2 Primary Efficacy Analysis

[redacted]

7.2 Secondary Efficacy

7.2.1 Secondary Efficacy Endpoints

[redacted]

7.2.2 Secondary Efficacy Analysis

All secondary analysis will be done using the FAS population.

[redacted]

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[redacted]

[redacted]

[redacted]

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SAFETY ANALYSIS

7.3 Drug Exposure and Compliance

Data for injection characteristics will be summarized for initial treatment and optional touch-up for the safety population. The following parameters will be summarized for extent of exposure:

- Injection Volume and Total Injection Volume (initial plus touch up)
- Injection Depth
- Injection Method
- Needle Size

The extent of exposure data will also be presented by subject in a data listing.

7.4 Adverse Events

Adverse events (AEs) will be summarized for the safety population. All AEs will be coded using MedDRA and presented by MedDRA system organ class (SOC), preferred term (PT), and treatment.

Only AEs occurring after first injection will be included in analysis. AEs occurring before, if any, will only be listed in subject data listings.

All AE endpoints will be summarized by treatment group - Restylane® Volyme and Restylane® Lyft.

A summary of AEs will be provided, which will include:

i) number of subjects with at least one AE and number of events (in total as well as serious AEs)
ii) number of subjects with at least one AE, related to study product or injection procedure, and number of events (in total as well as serious AEs)
iii) number of subjects with at least one AE, unrelated to both study product and injection procedure, and number of events (in total as well as serious AEs)
iv) number of subjects who did not have an AE

AEs will be summarized by SOC, PT, and severity.

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

In addition, for related AEs, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median.

Time to onset of an AE will be derived as the start date minus the date of most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment.

Duration of an AE will be derived as the stop date minus the start date + 1. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment. Missing stop 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.

If a subject has more than 1 AE of the same PT and there are different grades of severity, only the highest grade will be represented in the summary of severity. If the severity assessment is missing, the highest level of severity will be assumed.

[redacted]

Action taken for related AEs will also be summarized.

All reported AEs will be listed in data listings including time to onset, duration of AE and timing of the AE. Timing would be the variable indicating whether the AE occurred after no treatment, initial treatment, or optional retreatment.

By-subject listings also will be provided for all subjects (safety population) for the following: AEs related to study product or injection procedure, AEs resulting in discontinuation of study product, and serious AEs.

7.5 Clinical Laboratory Data

For all women of childbearing potential, a urine pregnancy test will be performed at screening and all injection visits prior to treatment.
The pregnancy test data will be presented by treatment and subject in data listing.

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[redacted]

[redacted]

7.6 Prior and Concomitant Medications

The number and percentage of subjects reporting concomitant medications will be summarized by treatment. In addition, the number and percent of subjects reporting concomitant medication, and the number of drugs (total number and the number of ongoing drugs), will be summarized by reason. The same summary will be done for concomitant procedures/treatments. Also, the number and percentage of the subjects who took each medication will be tabulated by WHO Drug Dictionary Anatomical Therapeutic Chemical 4th level (ATC-4) and preferred name for concomitant medications. If the 4th level term is not available, the next available level (e.g., ATC-3) will be used. A subject will only be counted once within each ATC-4 code and within each preferred name. Concomitant medications that started due to an AE will be summarized separately.
All concomitant medication and concomitant procedures/treatments data will be presented by treatment and subject in a data listing.

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8.0 REFERENCES

9.0 RECORD RETENTION

Records related to the activities listed in this plan will be retained according to AC SOP AD-005.

10.0 CHANGE HISTORY

Version	Date	Description of Changes
1.0	Current version is final as of the last approval signature	Original Document

Version: *1.0*

[redacted]

[redacted]

11.0 SIGNATURE PAGE

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