STATISTICAL ANALYSIS PLAN

CLINICAL TRIAL NUMBER: 43USC1633

A Multicenter, Open-Label, Prospective Study of Cannula Injection of Restylane® Lyft with Lidocaine for Cheek Augmentation and the Correction of Age Related Midface Contour Deficiencies.

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1 Study Information

1.1 Background

1.1.1 Study design

This is a multicenter, open-label, 16-week prospective study of Restylane® Lyft with Lidocaine [redacted] for cheek augmentation and the correction of age related midface contour deficiency.

Eligible subjects will be injected by the Treating Investigator at Day 1. Subjects' midface will be treated to optimal augmentation. After treatment on Day1, a 72 hour phone call and follow-up visits at 2, 4, 8 and 16 weeks are scheduled. At the 16-week visit after all study procedures for the visit are completed, subjects can receive an optional additional treatment if optimal aesthetic improvement is not maintained.

1.1.2 Number of subjects and randomization

Approximately 60 subjects [redacted] will be enrolled. The study is not randomized; all subjects will be treated with Restylane® Lyft with Lidocaine [redacted].

1.2 Study Objective

The primary objective of the study is to assess the adverse events of Restylane® Lyft with Lidocaine [redacted] for cheek augmentation and the correction of age related midface contour deficiency.

1.3 Efficacy Assessments

For all assessments, baseline will be defined as the observation that is closest to but prior to study treatment on Day 1. Likewise, change from baseline will be calculated as the value at a given time point minus the baseline value.

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1.4 Efficacy endpoints

The efficacy endpoints that will be used for analysis are given below. Responder rates will be calculated as the number of responders divided by the number of subjects with a non-missing value for the specified assessment and time point in the intention-to-treat (ITT) population.

[redacted]

1.5 Safety Assessments

1.5.1 Adverse events

The methods for collecting safety data are described in Section 8 of the Clinical Study Protocol (CSP) and include assessments of Injection site reactions in Subject Diary, Adverse Events (AE), Serious Adverse Events (SAE), and Device Deficiency.

A two-point scale ("Yes" or "No" response) will be used for the causality assessments. The 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 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. In the case of a disagreement, the AE will be classified as "Related".

1.5.2 Evaluation of midface sensation

[redacted]

Midface sensation will be assessed at screening/baseline and at all physical visits.

[redacted]

1.6 Safety Endpoints

Safety endpoints include:

(v) **Incidence, intensity, onset, and duration of all adverse events (AEs) as collected throughout the study**

(vi) **Incidence, intensity and duration of pre-defined, expected, post-treatment events reported during the first 2 weeks after treatment as recorded in the subject diary**

(vii) **Incidence of abnormal midface sensation** [redacted]

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2 Statistical Methods

2.1 General Methods

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9.4 or later).

[redacted]

Any change made to the finalized statistical analysis plan (SAP) will be documented in the Clinical Study Report (CSR).

2.2 Analysis Populations

The following population will be defined:

- Safety — Includes all subjects who were injected at least once.
- Intention-to-treat (ITT) — [redacted]

Safety population will be the basis for all safety evaluations. When performing effectiveness analysis, the ITT population will be used. In case these two populations are identical, all analyses will be performed using the safety population.

2.3 Study Subjects

2.3.1 Accountability and subject disposition

The number of subjects in each study population will be summarized by site [redacted] Study population variables will also be presented in a data listing.

The disposition and subject accountability will be presented as shown in [redacted] and [redacted]

2.3.2 Withdrawals and protocol deviations

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

Subjects with CSP deviations will be summarized ([redacted]

Deviations from the SAP will be documented in the CSR.

2.3.3 Demographic characteristics

Subject demographic data will be summarized for the safety population as shown in [redacted].

2.3.4 Medical and surgical history, concomitant medication/procedures

All summaries will be done based on the safety population. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Medical History will be coded according to MedDRA.

The number and percent of subjects reporting medical history will be summarized as shown in [redacted] and [redacted].

Reasons for concomitant procedures/treatments will be summarized as shown in [redacted].

Data on concomitant medications will be summarized as shown in [redacted] to [redacted].

2.4 Efficacy Analysis

2.4.1 Handling of missing data

All efficacy endpoints will be analyzed on available data, i.e. no imputations will be done.

2.4.2 Analysis of responder rates

[redacted]

2.5 Safety Analysis

2.5.1 Extent of exposure

Injection volume will be presented for initial treatment and optional re-treatment. [redacted]

2.5.2 Adverse events

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

The AE data will be presented as shown in [redacted] to [redacted].

[redacted]

[redacted]

2.7 Interim Analysis

Not applicable.

2.8 Determination of Sample Size

Sixty subjects were chosen to be enrolled in this study with the aim of fifty subjects completing the study. The sample size has been established based on the probability of detecting an AE given the true population rate of 5%. This 5% criterion has been selected based on this value representing the point-estimate cut-off AE rate for inclusion in product labelling.

[redacted]

2.9 Changes in the Analysis Planned in the Protocol

For the primary safety endpoints, onset of adverse events has been added.

Text in CSP (Section 3.1.1):

"… incidence, intensity, and duration of all adverse events (AEs) as collected throughout the study…"

Text in this SAP (Section 1.6):

"Incidence, intensity, onset, and duration of all adverse events (AEs) as collected throughout the study"

3 Reference List

4 Planned Tables and Figures

[redacted]

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Table of figures

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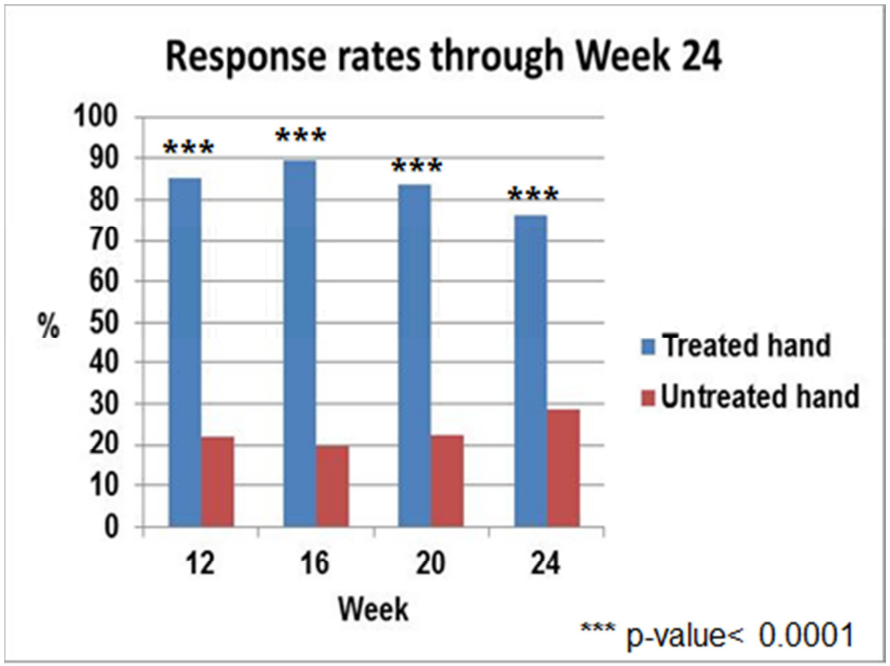

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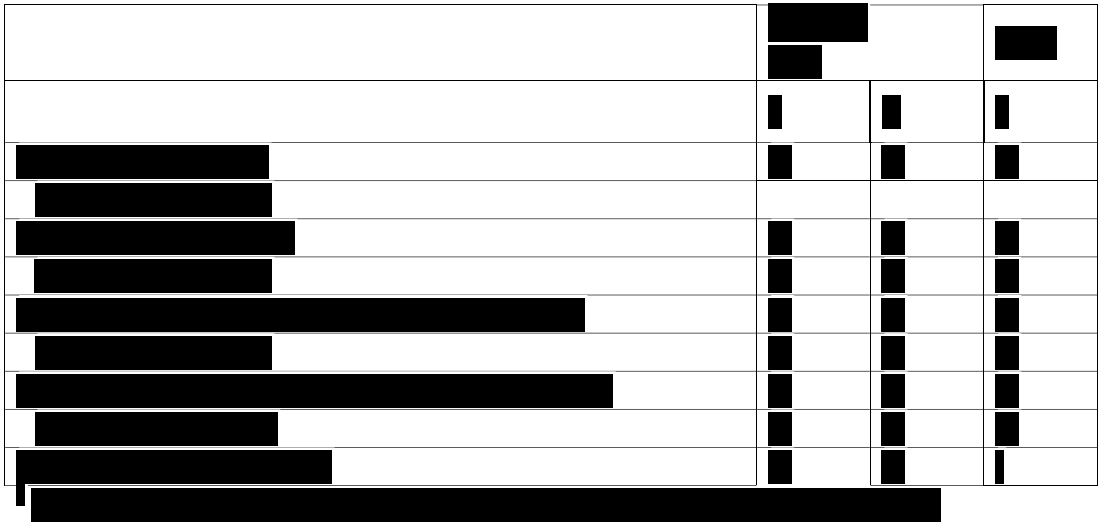

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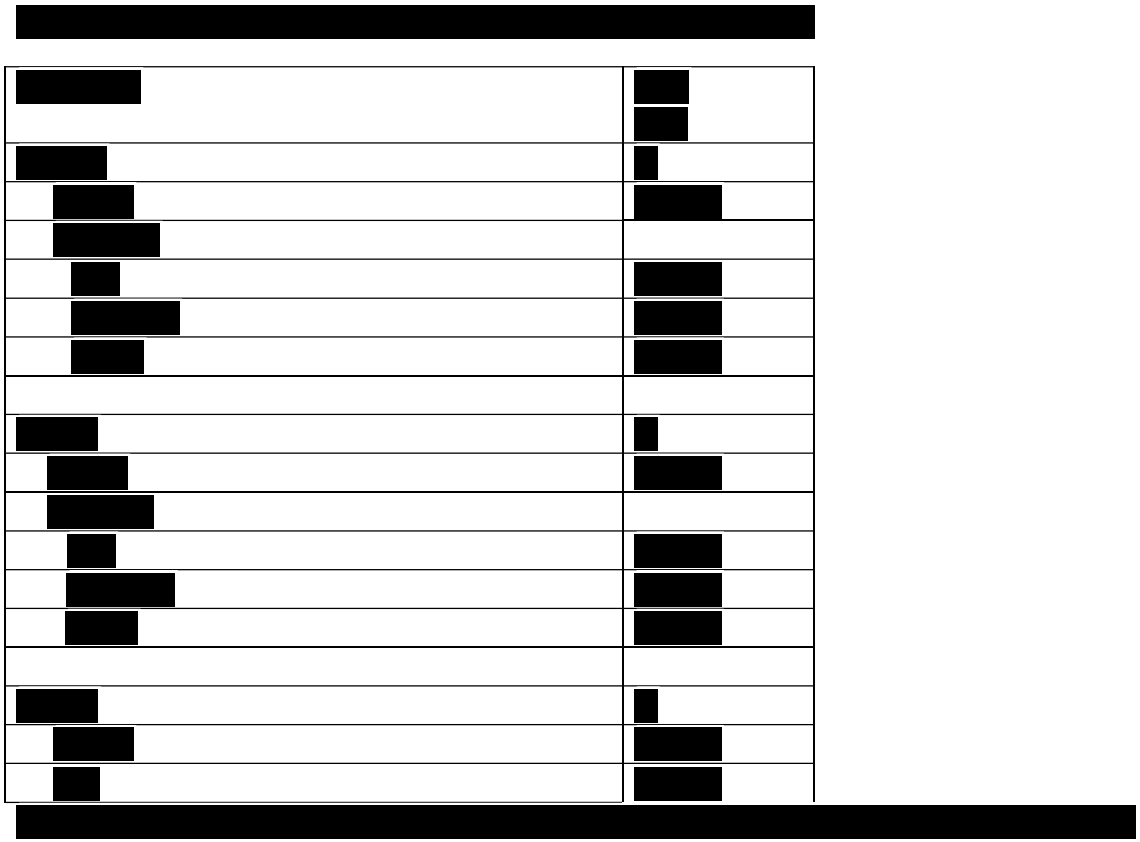

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