Statistical Analysis Plan

Clinical Trial Number: 43CH1504

Title: A randomized, multi-center, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane with and without addition of 0.3% lidocaine hydrochloride

Table of Contents

1 Study Information

1.1 Introduction

This is a randomized, multi-center, subject-blinded and evaluator-blinded study in China to evaluate the pain and the safety profile associated with correction of moderate to severe nasolabial folds (NLFs) using Restylane Lidocaine compared to Restylane. Approximately 70 subjects will be randomized to be treated with Restylane Lidocaine in one NLF and Restylane in the other, thus it is a split-face design. The study subjects will be treated at the baseline visit and thereafter followed for 2 weeks.

For more information regarding the study, please refer to the study protocol.

1.2 Study Objectives

1.2.1 Primary Objective

The primary objective is to evaluate the pain associated with injections of Restylane Lidocaine compared to Restylane using a visual analogue scale (VAS).

The proportion of subjects that have a within-subject difference in VAS score (Restylane-Restylane Lidocaine) of at least 10 mm at injection will be calculated together with a two-sided 95% confidence interval. The objective is to show that the confidence interval lies above 50%.

1.2.2 Secondary Objectives

The secondary objectives and endpoints are:

- To evaluate the pain associated with injections of Restylane Lidocaine compared to Restylane by assessment of
  - Proportion of subjects that have a within-subject difference in VAS score (Restylane-Restylane Lidocaine) of at least 10 mm (at 15, 30, 45 and 60 minutes after injection).

CCI

CCI

1.2.3 Safety objectives

The safety objectives and endpoints are:

- To evaluate the safety of Restylane Lidocaine and Restylane during the whole study by collecting AEs.

CCI [redacted]

1.3 Efficacy Endpoints

1.3.1 Visual Analogue Scale (VAS)

The VAS is a subjective scale to measure pain intensity. The subject shall be instructed to put a vertical mark, approximating the pain experienced during the procedure, on a 100 mm horizontal line labeled “No pain” at the left end and “The worst pain you can imagine” at the right end. The distance in mm from the left end (no pain) to the subject’s VAS mark shall be measured with a standard ruler. Each NLF will be evaluated independently. Subjects will evaluate injection site pain for each side of the face at the time of injection (before massaging) and at 15, 30, 45, and 60 minutes post-treatment by completing a VAS.

Visual Analogue Scale (VAS)

No pain _____The worst pain you can imagine.

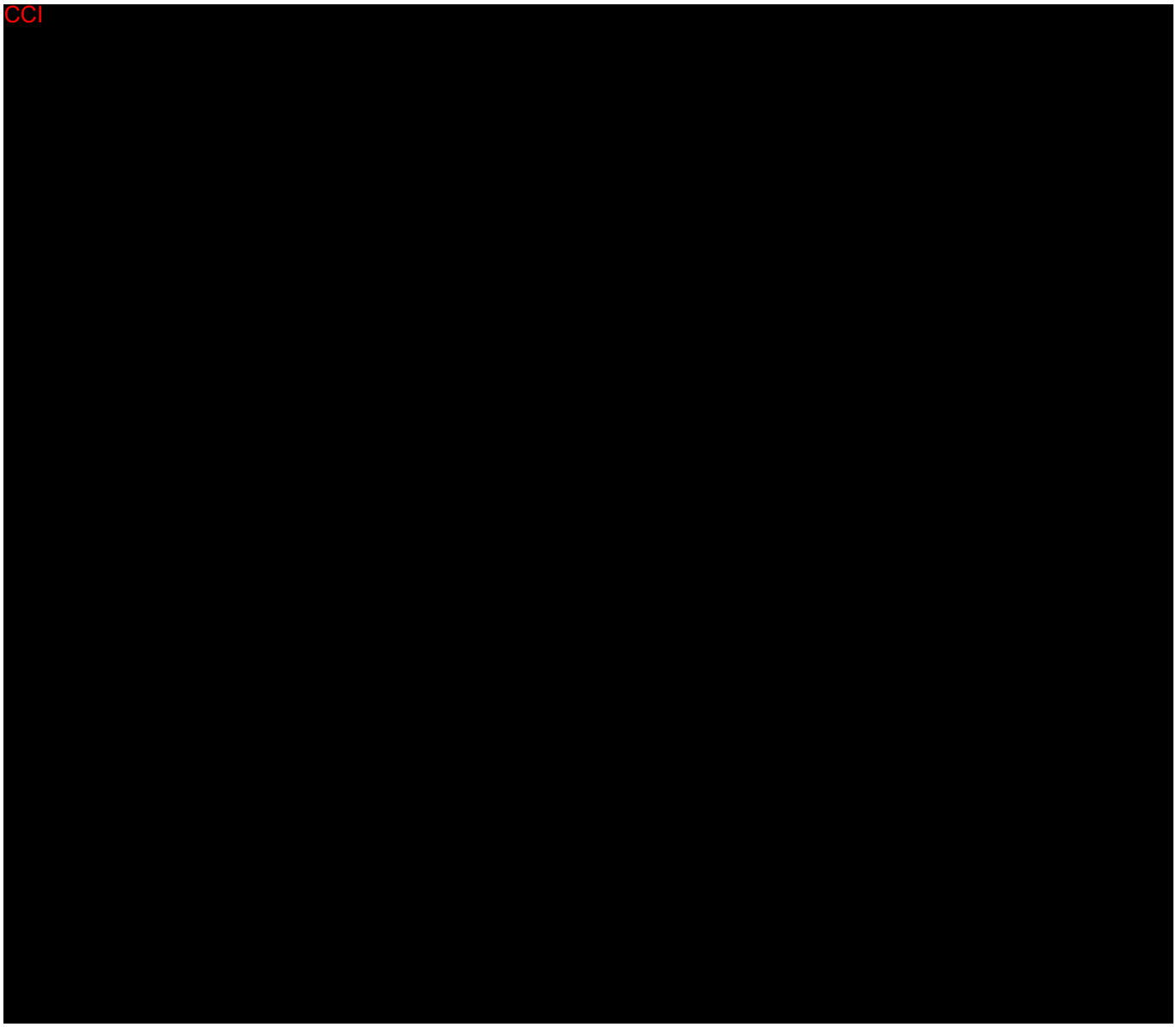
Derived endpoints:

At each time point, the following variables will be derived:

- The within-subject difference in VAS scores, calculated as Restylane-Restylane Lidocaine.
- A dichotomous variable taking the value 1 if the within-subject difference in VAS scores is at least 10 mm, and 0 otherwise.

CCI [redacted]

CCI



1.4 Safety Assessments

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 CCI , Adverse Events (AE), Serious Adverse Events (SAE), and Device Deficiency. Laboratory assessments and ECG will also be assessed, but at screening only.

Derived variables

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 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".

Time to onset of an AE will be derived as the start date minus Day 1. If the start date is missing, it will be assumed that the AE started on Day 1.

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 Day 1. 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.

2 Statistical Methods

2.1 General

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9).
Confidence intervals will be 2-sided and made at the 95% confidence level. CCI [redacted].
Continuous or semi-continuous variables will be summarized using descriptive statistics, e.g. mean, median and standard deviation. Categorical variables will be presented in frequency tables with number (n) and percent of observations for each level. All study data will be listed in subject listings.

Baseline value is defined as the latest measurement taken prior to treatment on Day 1.

2.2 Disposition of subjects

The disposition of subjects will be presented by the treatment group, and in total, including numbers of subjects that were:

- Screened
- Randomized
- Treated
- Completed
- Withdrawn

These numbers may also be presented by center. The number of completed and withdrawn subjects will also be presented by visit. Reasons for screening failures, if applicable, will be summarized.

In addition, the number of subjects in each analysis population set (see Section 2.6) will be presented by center and in total.

2.3 Withdrawals and Protocol Deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed. Subjects with CSP deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the

deviation, subject might be excluded from the Per Protocol (PP) population, which shall be documented prior to database lock. For this study, the following protocol deviations that will exclude subjects from PP are identified (but not limited to):

- VAS assessment at injection missing for at least one side
- Study products not administered according to randomization

CCI [redacted]

Deviations from the Statistical Analysis Plan (SAP) will be documented in the protocol deviation log.

2.4 Treatment procedure

Data related to study treatment will be summarized by means of descriptive statistics and/or subject listings as appropriate using the Intention-To-Treat (ITT) analysis set, as defined in Section 2.6.

Injection technique or procedure applied, administered volume, and any technical problems (Device Deficiencies) will be summarized by treatment.

2.5 Baseline Values and Subject Characteristics

Subject characteristics variables, such as demographic data, will be presented by descriptive statistics. Other measures taken at baseline, including medical history, and concomitant medication/procedures, will also be presented as appropriate using the ITT analysis set.

2.6 Analysis Populations

The following analysis sets will be defined:

- Safety analysis set — Includes all subjects who were injected in at least one NLF, based on the as treated principle.
- Intention To Treat (ITT) — Includes all subjects who were injected in both NLFs. Subjects are analyzed according to the randomization assignment.
- Per Protocol (PP) — Includes all ITT subjects who completed the VAS assessment at injection without any deviations considered to have substantial impact on the primary efficacy outcome.

The ITT population is the primary population for all efficacy analyses. All safety analyses will be based on the Safety population.

2.7 Handling of Missing Data

As the design is intra-individual, in which the outcome of both treatments to be compared is available on each subject, it is expected that when a data is missing, it will be missing for both NLFs in most of the cases. A majority of the deviations to the protocol can be expected to affect both NLFs and evaluations of the same subject the same way.
ITT analysis of VAS at the time of injection will impute a difference (Restylane-Restylane Lidocaine) of 0 mm as the primary method of imputation. This corresponds to assuming no pain relief using Restylane Lidocaine compared to Restylane and is considered as a worst case approach.
All other endpoints will be analyzed on available data, i.e. no imputations will be done.

2.8 Efficacy Analysis

2.8.1 Primary analysis

The proportion of subjects that have a within-subject difference in VAS (Restylane-Restylane Lidocaine) of at least 10 mm at the time of injection will be calculated together with a two-sided 95% confidence interval. The objective is to show that the confidence interval lies above 50% based on the ITT analysis set. To assess the robustness of the results, the same analysis will be re-run using the PP analysis set.
The calculation of this proportion utilizes the split-face design of the study since it is based on within-subject difference in pain. The limit of 50% is chosen in order to show that the majority of subjects have at least 10 mm less pain when treated with Restylane Lidocaine as compared to Restylane.

2.8.2 Secondary analyses

The secondary analyses will be carried out using the ITT analysis set, and will be descriptive in nature.

VAS assessments
The proportion of subjects that have a within-subject difference in VAS of at least 10 mm at post injection time points (15, 30, 45 and 60 minutes after injection) will be calculated together with a two-sided 95% confidence interval.

CCI

2.9 Safety Analysis

All safety evaluations will be performed based on the safety analysis set.
AEs will be summarized in frequency tables by group, presenting number of subjects with no AEs and subjects with at least one AE subdivided by related/unrelated, and serious/non-serious. All AEs will be summarized and listed by SOC and PT assigned using MedDRA. Furthermore, AEs will be summarized by causality and maximum intensity. For related AEs the number of days to onset and the duration of the event will be summarized by PT.

All AEs will be included in the data listings. Any serious adverse events and/or AEs that led to withdrawal will be listed separately.

CCI

[redacted]

2.10 Interim Analysis

Not applicable.

2.11 Determination of Sample Size

CCI

[redacted]

2.12 Changes in the Analysis planned in the Clinical Study Protocol

In CSP it was stated that all statistical analyses will be performed using the SAS® system, version 9.0. This is an old SAS® version, and a newer one will be used.

CSP text: "All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9.0)."

New text in this SAP: "All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9)."

3 References

1. Clinical Study Report MA-1100-01: A Randomized, Double-Blind Study Comparing Safety and Tolerability of Restylane® With and Without Addition of 0.3% Lidocaine HCL During Correction of Nasolabial Folds. 2009.

GALDERMA	Title **43CH1504 Restylane Lido Statistical Analysis Plan**	Doc id **MA-28883**

SIGNATURES PAGE

Date	Signed by
2016-04-18 08:53	PPD
Justification	Approved by Owner

2016-04-18 09:24	PPD
Justification	Approved by Technical Expert

2016-04-18 16:49	PPD
Justification	Approved by Technical Expert

2016-05-04 09:07	PPD
Justification	Approved by Project Manager