Q-Med AB, a Galderma Affiliate

Clinical Trial No. 43USK1701 [redacted]

STATISTICAL ANALYSIS PLAN

A Randomized, Controlled, Evaluator-Blinded, Multi-Center Study To Evaluate The Effectiveness And Safety of *Restylane*® *Kysse* Versus A Control In The Augmentation of Soft Tissue Fullness of The Lip

[redacted]

October 25, 2018

Version 1.0
Revision History:
October 25, 2018 Amendment 1.0

[redacted]

[redacted]

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1 Study Information

1.1 Background

1.1.1 Study design

This is a randomized, controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Kysse* for lip augmentation and correction of perioral rhytids.

Approximately 280 subjects will be randomized in a 2:1 ratio of treatment to control and treated. Approximately 187 subjects will be treated with *Restylane® Kysse* and 93 subjects will receive the control in the lips and perioral rhytids and will be followed for 48-weeks. [redacted]

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

Safety assessments will be performed by non-blinded personnel. Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1.

1.1.2 Number of subjects and randomization

Approximately 280 subjects will be randomized to treatment or to control in a 2:1 ratio (treatment: control) stratified by FST (I-III, IV or V-VI) to achieve a total sample size of 234 evaluable subjects [redacted]

Before starting the study, a randomization list will be prepared under the supervision of a designated statistician. Randomization will be performed using an Interactive Response System by assigning each subject to *Restylane® Kysse* or the control according to the randomization list.

1.2 Study objectives

1.2.1 Primary efficacy objective

The primary objective of the study is to demonstrate non-inferiority of *Restylane® Kysse* versus a control in lip fullness augmentation by comparing change from baseline [redacted] in the upper and lower lip separately, at 8 weeks after last injection.

1.2.2 Secondary efficacy objectives

- To evaluate the effectiveness of *Restylane® Kysse* in lip fullness augmentation [redacted]

- To evaluate the aesthetic improvement of the upper perioral rhytids and oral commissures after treatment with Restylane® Kysse, [redacted]
- To evaluate the aesthetic improvement (overall appearance) after treatment *Restylane® Kysse*, [redacted]
- Subjects' satisfaction after treatment with *Restylane® Kysse* [redacted]
- Lip fullness compared to baseline, [redacted]

1.2.3 Safety objectives

- To evaluate all AEs at all visits and pre-defined, expected, post-treatment events reported during the first 4 weeks after treatment as recorded in the subject diary.
- To evaluate the safety assessment at all visits, as assessed by a qualified staff member:
  - [redacted]

1.2.4 Exploratory objectives

- To evaluate the consistency of the primary analysis results across different subgroups, specifically:
  - Study site
  - Fitzpatrick skin types (I-III and IV-VI)
  - Race
- To evaluate the consistency of AE data across different subgroups, specifically:
  - Study site
  - Injection volume
  - Fitzpatrick skin types (I-III and IV-VI)
- [redacted]

1.3 Efficacy assessments

Day 1 is defined as the date of initial treatment.

For all assessments, baseline is defined as the last observation before initial treatment takes place at the baseline visit on Day 1. Change from baseline is defined as the post-baseline value minus the baseline value.

1.3.1 [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

1.3.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.3.5 [redacted]

[redacted]

[redacted]

1.4 Efficacy endpoints

1.4.1 Primary efficacy endpoint

The primary end point is change from baseline [redacted] at 8 weeks after last injection of *Restylane® Kysse* or control treatment.

1.4.2 Secondary efficacy endpoints

The secondary efficacy endpoints will include the following:

(i) [redacted]

(iv) [redacted]

[redacted]

[redacted]

1.5 Safety assessments

The methods for collecting safety data are described in Section 8 of the Clinical Study Protocol (CSP) and includes the following: assessment of adverse events (AEs) by direct question to subject and evaluation of subject, as well as pre-defined, expected, post-treatment events reported in the subject diaries; [redacted] laboratory assessments (urine pregnancy test only); and device deficiencies.

Each AE, serious as well as non-serious, shall be assessed by the Investigator for causal relationship with the study product and its use (the injection procedure) and for seriousness (Yes or No) of the event.

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall 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?", and
- "Do you consider that there is a reasonable possibility that the event may have been caused by the device injection procedure?"

If any of these questions is answered with a 'Yes', the AE will be considered related. Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements. In case of disagreement, the AE will be classified as "Related".

1.6 Safety endpoints

Safety endpoints include:

(i) Incidence, intensity, duration, and onset of related Adverse Events (AEs) collected during the whole study

(ii) Incidence, intensity, and duration (defined as number of days with the event) of pre-defined, expected post-treatment events collected using a subject diary for 30 days after each treatment and for each treatment area

(iii) The safety assessment at all visits, as assessed by a qualified staff member:

- [redacted]

[redacted]

2 Statistical Methods

2.1 General methods

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (Version 9.3 or higher). Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. P values will be two-sided and performed at a significance level of 5%.

All study data including observed and derived variables (e.g., change from baseline, response status) used in the summaries of analyses will be presented in by-subject listings. In general, efficacy, safety, demography, subject characteristics, and treatment related variables will be presented using descriptive statistics. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of observations at that time point (i.e. observed cases). For continuous parameters, descriptive statistics will include number of observations, mean, standard deviation (SD), median, and range. Graphs will be used as appropriate.

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

For the primary analysis, non-inferiority will only be demonstrated if the CI is entirely below 0.5 for both co-primary endpoints in both the ITT and PP populations. Similarly, superiority will only be demonstrated if the lower confidence limit is entirely below 0 for both co-primary endpoints in both the ITT and PP populations. Therefore no multiplicity adjustment for Type I error is required.

2.2 Analysis Populations

The following populations will be defined for analysis:

- Safety population: Includes all subjects who received any of the investigational products, based on the as treated principle (i.e. according to the treatment actually received).
- Intention-to-treat (ITT) population: Includes all subjects who were randomized [redacted] All ITT analyses will be based on the as randomized principle (i.e. according to the treatment they were randomized to).
- Per protocol (PP) population: Includes all subjects in ITT who complete the Week 8 visit without any deviations considered to have substantial impact on the primary effectiveness outcome.

The primary efficacy analysis of non-inferiority will be performed both on the ITT and the PP analysis set. Secondary effectiveness and all safety evaluations will be performed based on the ITT and the safety population set, respectively.

2.3 Study subjects

2.3.1 Subject disposition

The number of subjects in each study population (i.e. Safety, ITT and PP) will be summarized. Study population variables will also be presented in a data listing.

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

- Screened
- Randomized
- Completed
- Withdrawn (overall and by reason for withdrawal)

All withdrawn subjects will be presented in a by-subject listing.

2.3.2 Protocol deviations

Protocol deviations will be presented in a by-subject listing. Major protocol deviations will be summarized by site and overall.

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

For this study, the protocol deviations that will exclude subjects from PP are identified (but not limited to) below:

- General
  - Treatment not given according to randomization scheme at initial or touch-up (if touch-up done) treatment
- Efficacy
  - Pre-treatment value missing for at least one lip
  - Any other deviation considered to have substantial impact on the primary effectiveness outcome
- Other
  - Any key inclusion/exclusion criteria not met ([redacted]
  - Use of any prohibited medications or procedures defined in study protocol between initial treatment and the Week 8 visit, that is considered to have a substantial impact on the primary effectiveness outcome

Deviations from the SAP will be documented in the CSR.

2.3.3 Demographic characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be summarized overall and by treatment for the ITT populations.

The following demographic and baseline variables will be included:

- Age (years)
- Sex
- Race
- Ethnicity

- Fitzpatrick skin types (FST)
- [redacted]

2.3.4 Medical and surgical history, prior and concomitant medication/procedures

All summaries will be done by treatment group based on the ITT population.

History of surgical events, medical conditions and any prior dermatological procedures or implants will be provided in a by-subject listing.

Prior (with stop dates prior to initial treatment) and concomitant medications (ongoing or with stop dates on or after initial treatment) for all randomized subjects will be provided in a by-subject listing. Prior and concomitant medications will be summarized using World Health Organization Drug Dictionary (WHO-DD) Anatomical-Therapeutic-Chemical (ATC) classification and preferred term (PT) for each treatment. The number and percent of subjects, and the number of drugs, will be summarized by ATC code. Concomitant medications that started due to an AE will be stated in indication.

2.4 Efficacy analysis

2.4.1 Datasets analyzed

The primary efficacy analysis of non-inferiority will be performed both on the ITT and the PP analysis set. Secondary efficacy will be performed based on the ITT population set.

2.4.2 Handling of missing data

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

[redacted]

Impact of missing data on the primary analysis for Week 8 endpoint will be evaluated by performing sensitivity analysis based on the observed cases in the ITT population.

All other endpoints will be evaluated based on the observed cases in ITT, i.e. no imputations will be done.

2.4.3 Primary efficacy analysis

[redacted]

[redacted]

Non-inferiority will be established if the CI is entirely below 0.5 for both co-primary endpoints in both the ITT and PP populations. Superiority will be declared if the CI is entirely below 0 for both co-primary endpoints in both the ITT and PP populations. This decision criteria is consistent with a gate-keeping strategy (testing for superiority following the test for non-inferiority) to maintain the overall type I error rate at 5%.

2.4.4 Secondary analysis

CIs for responders mentioned below will be calculated using normal approximation.

(i) [redacted]

(iii) [redacted]

(v) [redacted]

2.5 Safety Analysis

2.5.1 Extent of exposure

The number of subjects receiving initial treatment, touch-up treatment, and Week 48 retreatment respectively, will be presented by treatment group and treatment occasion (i.e. initial treatment or retreatment)as well as injection volume and other relevant injection characteristics, such as injection depth, injection method.

2.5.2 Adverse events

AE terms will be coded using MedDRA dictionary. A treatment-emergent AE (TEAE) is defined as an AE with a start date and time on or after the first study product injection. If relationship to treatment is missing, the event will be conservatively summarized as being related to study product. If intensity is missing, a separate category of missing intensity will be included in the summary table, and no imputation of intensity will be performed. Through the data cleaning process, all attempts will be made to avoid missing values for relationship and intensity.

All AEs will be presented in a by-treatment and by-subject listing, detailing the verbatim term given by the investigator, the preferred term (PT), system organ class (SOC), onset date, end date, intensity, outcome, relationship to study product, relationship to study product injection procedure, action taken with study drug, other action taken, affected treatment area, seriousness and criteria for seriousness. Serious AEs will be presented in a separate listing.

Time to onset of an AE will be derived as the start date minus 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.

An overall summary of AEs will be presented by treatment. The summary will include the total number of events, frequency counts and percentages of subjects with:

- Any TEAE

- Any AE related to product and/or injection procedure
- Unrelated TEAEs
- No TEAEs reported

Summaries of related AEs (including the total number of events, frequency counts and percentages of subjects) will be displayed by treatment and treatment occasion according to the following:

- All AEs by SOC and PT in descending order of frequency (the combined frequency of both treatments)
- All AEs by SOC, PT, and maximum intensity (mild, moderate, or severe)
- All AEs by SOC, PT, and action taken (none, medical treatment, non-pharmacological treatment, subject withdrawn)

For related AEs, the number of days to onset and duration of event will be summarized by SOC and PT, using mean, SD, minimum, maximum, and median statistics.

2.5.3 Pre-defined, expected, post-treatment symptoms

Frequency counts and percentages of subjects reporting each pre-defined, expected, post-treatment symptoms [redacted] will be presented in total and by maximum severity, for each treatment area separately.

Number of days with the event will also be summarized using mean, SD, min, max, and median.

2.5.4 Safety assessment

[redacted]

Urine pregnancy test results will be presented in a by-subject listing.

2.5.5 Exploratory safety endpoints

- Related AEs by SOC, PT and maximum intensity will be separately summarized for the following subgroups:
  - Study site
  - Injection volume
  - Fitzpatrick skin types (I-III, IV and V-VI)
- [redacted].

2.6 Interim Analysis

There is no interim analysis planned.

2.7 Determination of Sample Size

[redacted]. Accounting for approximately 15% drop-outs and non-evaluable subjects due to protocol deviations at week 8, a total of approximately 280 subjects will be randomized in the study. It is expected that the number of randomized subjects will be similar across the study sites.

[redacted]

3 Reference List

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

GALDERMA	Title **43USK1701 Statistical Analysis Plan**	Doc id

[redacted]

[redacted]

Effective

Version: 2.0