STATISTICAL ANALYSIS PLAN

Study Number:	43CH2305
Study Title:	A Randomized, Split-Hand, Subject-Blinded Study Comparing Pain, Safety and Effectiveness of Restylane Skinboosters Vital Lidocaine and Restylane Vital without Lidocaine for Improved Appearance of the Dorsal Hand in Chinese Subjects
Study Short Name:	Vital Lido SmartClick Hand
Protocol Version and Date of Issue:	Final, version 3.0, date 13MAR2024
Sponsor:	Galderma SA Zählerweg 10 6300 Zug Switzerland
Author:	PPD Principal Biostatistician
Version and Date of Issue:	Final, version 1.0, date 24APR2024

This study is conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

DOCUMENT HISTORY

Version	Date of Issue	Reason for Change
Final 1.0	24APR2024	Initial version

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
CCI	[redacted]
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed Case
PPS	Per Protocol Analysis Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SAF	Safety Analysis Set
T0	At the end of the injection timepoint
T10	At 10 minutes after injection timepoint
T20	At 20 minutes after injection timepoint
T30	At 30 minutes after injection timepoint
VAS	Visual Analogue Scale
WHO	World Health Organization

1 INTRODUCTION

The Statistical Analysis Plan (SAP) describes the planned analysis and reporting required for the Clinical Study Report (CSR) for study protocol 43CH2305 entitled A Randomized, Split-Hand, Subject-Blinded Study Comparing Pain, Safety and Effectiveness of Restylane Skinboosters Vital Lidocaine and Restylane Vital without Lidocaine for Improved Appearance of the Dorsal Hand in Chinese Subjects, version 3.0, dated 13MAR2024. The SAP should be read in conjunction with the current protocol. Any changes from the analyses described within this SAP will be detailed in the CSR, together with the reason for such changes.
Post hoc exploratory analyses not necessarily identified in this SAP, may be performed to further examine the study data. Any post hoc, or unplanned, exploratory analyses performed, if included, will be clearly identified as such in the final CSR.

2 CHANGES FROM THE PROTOCOL ANALYSIS PLAN

There are no changes from the protocol analysis plan.

3 STUDY OBJECTIVES, ENDPOINTS AND STATISTICAL HYPOTHESES

3.1 Study Objectives

Primary Effectiveness Objective
To demonstrate that Restylane Skinboosters Vital Lidocaine is associated with less pain than Restylane Vital when injected in the dorsal hand for improvement of appearance.

Safety Objective
To evaluate the safety of Restylane Skinboosters Vital Lidocaine and Restylane Vital throughout the study.

3.2 Study Endpoints

3.2.1 Primary Endpoint

- The within-subject difference in Visual Analogue Scale (VAS) score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at end of injection (T0).

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3.2.3 Exploratory Endpoints

Not applicable.

CCI [redacted]

CCI [redacted]

3.3 Statistical Hypotheses

3.3.1 Primary Statistical Hypotheses

The hypothesis test for the primary endpoint can be formally defined as follows:

$$\begin{cases} H_0: \Delta \geq 0\ mm \\ H_1: \Delta < 0\ mm \end{cases}$$

where Δ is the within-subject difference in VAS score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at the end of injection.

The hypothesis test for the primary endpoint will be evaluated on the FAS at the one-sided significance level $\alpha = 0.025$. Effectiveness will be claimed if the within-subject difference on the primary endpoint is statistically significantly less than 0 mm, with a p-value ≤ 0.025.

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4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, multi-center, split-hand, subject-blinded study comparing pain, safety and effectiveness of Restylane Skinboosters Vital Lidocaine and Restylane Vital without lidocaine for improving appearance of the dorsal hands in Chinese subjects.
Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to study randomization on Day 1. The Screening Visit and Baseline Visit can be performed on the same day.

Each subject will receive treatment on Day 1 with Restylane Skinboosters Vital Lidocaine® in one hand and Restylane Vital in the opposite hand, as randomly assigned. Study treatment will be unblinded for the Treating Investigator. The first injection will always start in the right hand. No topical or local anesthetic or other pain-relieving medication should be used before all VAS assessments are completed. Ice for pain relief is allowed and should be applied equally on both hands before treatment, and an approximately two-minute ice application time per hand is recommended. Ice may also be used after all VAS evaluations have been completed. The second treatment, that is the injections in the left hand, will be performed after the treatment of the first (right) hand and the VAS assessment at T0 of the right hand is completed.

The subject will assess pain experienced directly after treatment on a 100 mm VAS at the end of each treatment (before massaging the treatment area). The time should be recorded in the electronic Case Report Form (eCRF) and the pain will thereafter be assessed by the subject at 10±3, 20±3, and 30±3 minutes on the VAS after the treatment on the right and left hand, respectively.

After the treatment of each hand is finished, and after the T0 pain assessment is complete, massage can be performed on the treated area of that hand. It is recommended not to exceed five minutes of massage to avoid affecting subsequent VAS assessments. It is not necessary to massage both hands simultaneously.

A safety follow-up telephone call should be made 72 hours after treatment.

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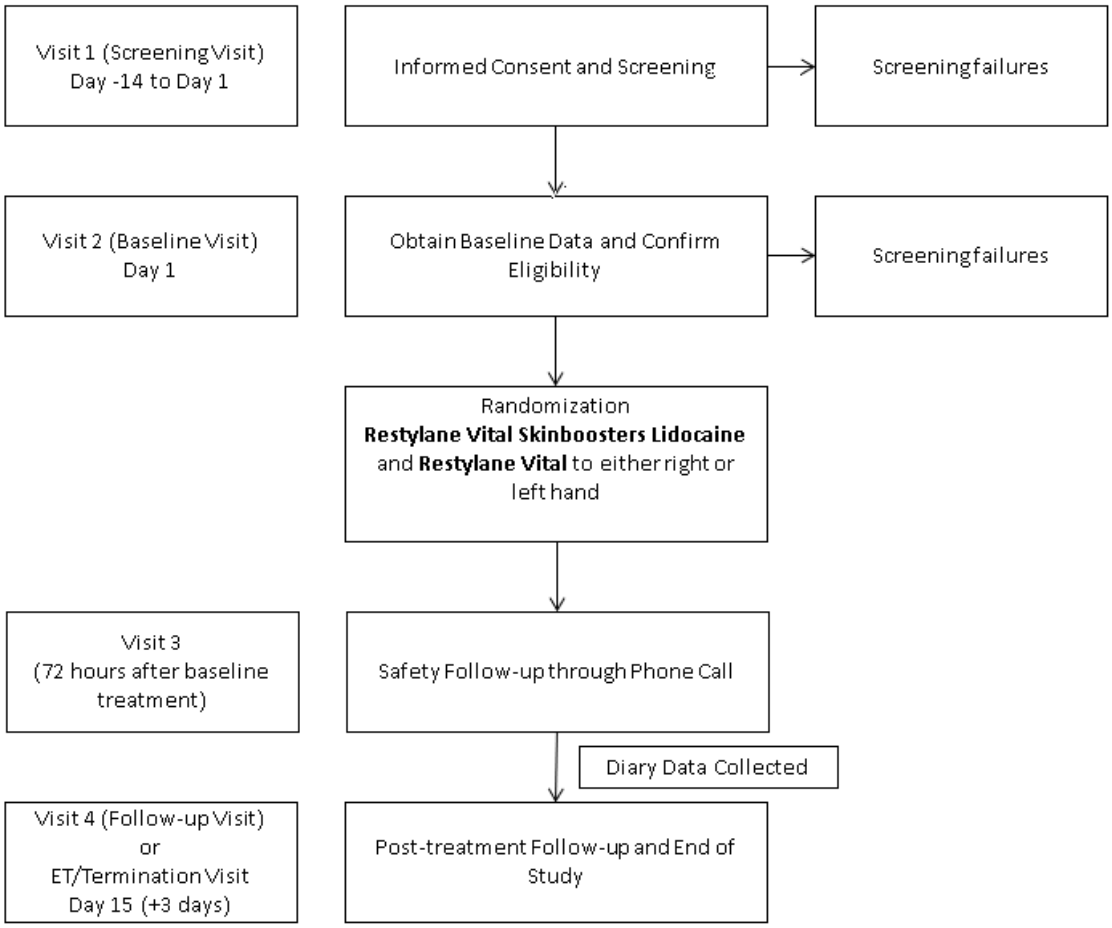
4.1.1 Study Schema

Figure 1 Study Schema



4.1.2 Schedule of Assessments

Table 1 Schedule of Assessments

Assessment/Event Visit windows are calculated from Visit 2.	**Visit 1** Screening[1] Day -14 to 1	**Visit 2** Baseline Treatment Day 1	**Visit 3** 72 hours after Baseline (Phone Call) (±24 hours)	**Visit 4** End of Study/Early Termination Day 15 (+3 days)
Informed Consent	X			
Demographic Data[2] including, medical history & concurrent diseases, previous hand treatments/procedures	X	X		
Demographic Data of Height and Weight		X		
Eligibility criteria	X	X		
Urine Pregnancy Test[3]		X		

Photography		X[4]		X
Randomization		X		
Treatment		X[5]		
VAS pain assessment		X[6]		
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Device deficiencies		X		
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Concomitant Meds/Procedures	X	X	X	X
Adverse Events		X	X	X
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1. Screening and baseline/treatment may be performed on the same day.
2. Includes date of birth, gender, and ethnicity.
3. Only for women with childbearing potential. Should be done before randomization and must be negative for subject to be enrolled. U-HCG should be analyzed at the local hospital laboratory.
4. Should be done before injection and after injection, also be done once AE occurs after injection.
5. Right and left hand will be assigned treatment with either Restylane Vital Skinboosters Lidocaine or Restylane Vital. The right hand should be treated first, and the injections in the left hand will be performed after the treatment of the first (right) hand and the VAS assessment at T0 of the right hand is completed.
6. Subjects will evaluate injection site pain for each hand using the VAS at the end of treatment and 10±3, 20±3, and 30±3 minutes post-treatment.

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4.2 Selection of Study Population

4.2.1 Number of Planned Subjects

Approximately 90 subjects are planned to be randomized to receive treatment with Restylane Skinboosters Vital Lidocaine in the right hand, and Restylane Vital in the left hand, or vice versa. Refer to Section 7 for the statistical considerations on which the sample size is based.

4.2.2 Inclusion Criteria

Refer to Section 5.2.1 of the study protocol.

4.2.3 Exclusion Criteria

Refer to Section 5.2.2 of the study protocol.

4.2.4 Method of Assigning Subjects to Treatment Groups

Upon signature of the Informed Consent Form (ICF), each subject will be assigned a screening number consisting of "S" and the site number followed by a consecutive number starting with 01 at each site, e.g., S101, S102. The screening number shall be listed on a subject screening and inclusion log.

Each subject will be assigned a subject number as they arrive for the treatment visit. Randomization will be assigned via the eCRF system. The subject number is also the randomization number and will ensure the assignment of Restylane Skinboosters Vital Lidocaine in the right hand, and Restylane Vital in the left hand, or vice versa, is random. The treatment information will be kept by the Treating Investigator during the study not to be disclosed to the subjects. Refer to Section 4.1.1 for an illustration of the study design and treatment allocation.

4.2.5 Allocation Concealment and Blinding

Only the subject will be blinded. Treating Investigator will not be blinded to the treatment assignment.
The Treating Investigator is not allowed to discuss treatment assignment per hand with the subjects.
All documents with information on study products shall be kept in a separate binder not available to the subjects.
To ensure the subject is kept treatment-blind the following measures are to be employed at the study site when injecting: the same injection techniques, volume per injection point and similar total volume should be used for both hands.
At the discretion of the investigator, the subject can listen to white noise/music in headphones during the treatment to cancel out the click sounds from the syringe when injecting Restylane Vital Skinboosters Lidocaine.
The injection will be performed behind a screen to prevent the subject from seeing the type of syringe used.

5 PLANNED ANALYSES

5.1 Interim Analyses

Not applicable.

5.2 Final Analyses

The final analyses, including all data collected in the study, will be performed after database lock.

6 ANALYSIS SETS

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were treated with Restylane Skinboosters Vital Lidocaine in one hand and Restylane Vital in the other hand. Subjects are analyzed according to the randomization assignment.
The FAS is the primary set for all effectiveness analyses.

6.2 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPS) includes all subjects in FAS that comply to the protocol procedures with no deviations considered to have a substantial impact on the evaluation of the primary endpoint.
For this study, the following protocol deviations that will exclude subjects from PPS are identified (but not limited to):

- VAS assessment at end of injection missing for at least one side,
- Study products not administered according to randomization,
- Any topical or local anesthetic or other pain-relieving medication used before all VAS assessments are completed,
- Significantly different injection volumes in left and right hand.

6.3 Safety Analysis Set

The Safety Analysis Set (SAF) includes all subjects who were injected in at least one hand. Subjects are analyzed based on the as treated principle.
All safety analyses will be based on the SAF.

7 SAMPLE SIZE CONSIDERATION

Several studies have been performed comparing the same HA-filler product with and without the addition of lidocaine or other analgesics. In the study 43CH1504[1], comparing Restylane for treatment of nasolabial folds with and without Lidocaine in subjects with Chinese ethnicity, the observed within-subject difference in VAS score during injection was 33.0 mm with a standard deviation of 24.4 mm. In another study, in subjects with Chinese ethnicity, 43TW1628[2], comparing Restylane Perlane with and without Lidocaine, the mean within-subject difference in VAS score at injection was 32.0 mm with a standard deviation of 19.5 mm.
However, due to the many injection points in the treatment of the hands, it is believed that the within-subject difference in VAS score will be considerably less in this study than what was seen in the NLFs in the previous two studies referred to. Thus, assuming a true mean within-subject difference of -10 mm and a standard deviation of 25 mm, a significance level of 2.5% and using a one-sided one-sample t-test, inclusion of 68 subjects will give a power of 90% to reject the null hypothesis of > 0 mm within-subject difference. To ensure sufficient power in the event of the need of a non-parametric test for the primary analysis, approximately 15% more subjects will be added

to the 68 needed for the t-test. Hence, approximately 80 subjects will be needed for the primary analysis. In addition, a drop-out rate of 10% is assumed. Thus, approximately 90 subjects will need to be randomized in order to have at least 80 evaluable subjects for the statistical analysis.

7.1 Sample Size Re-Estimation

Not applicable.

8 EFFECTIVENESS, SAFETY AND OTHER ASSESSMENTS

8.1 Effectiveness Assessments

8.1.1 Pain assessment by Visual Analogue Scale (VAS)

The VAS is a subjective scale to measure pain intensity (Appendix 12.1). The subject shall be instructed to put a vertical mark, approximating the pain experienced after the procedure, on a 100 mm horizontal line labelled “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 hand will be evaluated independently.
Subjects will evaluate injection site pain for each hand at the time of injection completion (before massaging) and at 10, 20, and 30 minutes post-treatment by completing a VAS.

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8.3 Safety Assessments

8.3.1 Adverse Events Assessment

AEs are to be monitored throughout the course of the clinical study from the time the ICF has been signed. All AEs are to be reported on the AE form in the eCRF with complete information as required.

If AEs occur, the main concern shall be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical study site personnel for reporting AEs and medical emergencies.

At each post-enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example, “Have you noticed any change in your health since the last visit?” Additional questioning and examination will then be performed as appropriate.

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8.3.2.1 *Vital Signs Assessment*

Not applicable.

8.3.2.2 *Physical Findings Assessment*

Not applicable.

8.4 Other Assessments

8.4.1 Photography

Photographs will be taken at baseline, prior to the first injection of the study product and at the follow-up visit at Day 15. The baseline photographs were used for the assessment CCI The photographs could also be used to document AEs in the treatment area.
Camera equipment will be provided by the Sponsor and standardized photographs will be obtained according to detailed instructions in a separate photography user manual. Each hand will be photographed separately. Each Investigator and other study site personnel designated to take photographs, if applicable, shall be thoroughly trained in the equipment and techniques, and how to upload photographs to the secured web portal, if applicable, before study start. For further details, please see the instruction in photography user manual.

9 DERIVATION OF EFFECTIVENESS, SAFETY AND OTHER ENDPOINTS

9.1 Effectiveness Endpoints

9.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the within-subject difference in VAS score at the end of injection (T0), and will be calculated as:

- Δ_{T0} = (VAS score at T0 for the Restylane Skinboosters Vital Lidocaine hand) – (VAS score at T0 for the Restylane Vital hand).

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9.1.3 Exploratory Effectiveness Endpoints

Not applicable.

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10 STATISTICAL METHODS AND DATA CONSIDERATIONS

10.1 General Considerations

10.1.1 Baseline

For statistical analyses purpose, baseline is defined as the last non-missing measurement prior to the first treatment.

Change from baseline will be calculated as follows:

Absolute Change from Baseline = PostBaseline – Baseline.

10.1.2 Missing and Partial Dates Management

10.1.2.1 *Missing and Partial Dates of Adverse Events*

While every effort will be made to obtain complete information on every reported AE, imputation will be made for any respective missing AE data for the purpose of calculating onset time and duration. Dates will be presented as is in the listings.

The following date imputation rules will used.

- Start Date
    - If start date is completely missing, it will be assumed that the AE started at the treatment date.
    - If the start date is missing the day, the treatment day will be used.
    - If the start date is missing the month, the treatment month will be used, provided it is on or after the subject's treatment date; otherwise, the subsequent month after the treatment date will be used (i.e., if treatment date is 15-DEC-2023, and AE start date is 01-UNK-2023 then start date becomes 01-JAN-2024).
    - If the start date is missing the year, the treatment year will be used provided it is on or after the subject's randomization date; otherwise, the subsequent year after randomization will be used.
- End Date
    - If end date is completely missing, it will be assumed that the AE is still ongoing and will not be imputed.
    - If the end date is missing the day, the last day of the month will be used (i.e., UNK-JAN-2024 becomes 31-JAN-2024)
    - If the end date is missing the month, the subsequent month after the start date will be used.
    - If the end date is missing the year, the year of treatment will be used (i.e., 01-JAN-UNK becomes 01-JAN-2024), provided it is after the start date; otherwise, the subsequent year after start date will be used.

10.1.2.2 *Missing and Partial Dates of Prior/Concomitant Therapies and Prior Aesthetic Procedures or Implants*

As no calculations on start and stop dates will be done, no imputation of missing or partially missing dates will be performed.

10.1.2.3 *Missing and Partial Dates of Medical History Diseases*

As no calculations on start and stop dates will be done, no imputation of missing or partially missing dates will be performed. If the medical condition is ongoing at study start, this is indicated via the checkbox in the eCRF.

10.1.3 Reference Start Date and Analysis Day

The treatment date will be the reference start date.
Analysis day will be calculated from the reference start date and will be used to show start/end day of assessments, events, diseases, therapies, or procedures.

In the situation where the assessment/event/disease/therapy/procedure date is fully missing and cannot be imputed (i.e., when an adverse event, a disease, a therapy, or a procedure is reported as being ongoing), analysis day will be missing.

10.1.4 Descriptive Statistics

For the descriptive statistics, unless otherwise noted, the categorical endpoints will be summarized by frequencies and proportions expressed as percentages (n, %) of subjects for each classification category, and the continuous endpoints will be summarized using standard descriptive statistics (n, mean, standard deviation, median, min and max).

10.1.5 Statistical Tests and Confidence Intervals

A one-sided type I error $\alpha = 0.025$ will be used to declare statistical significance for the primary endpoint CCI [redacted]. Confidence intervals (CIs) will be two-sided with 95% coverage for the primary endpoint CCI [redacted].

10.1.6 Decimal Precision

Unless otherwise noted, the following rounding conventions will be applied:

- Means, medians, first and third quartiles will be rounded and presented to one more decimal digit than the source data.
- CIs of means will be rounded and presented to one more decimal digit than the source data.
- Standard deviations will be rounded and presented to two more decimal digits than the source data.
- Minima and maxima will be presented to the same number of decimal digits as the source data.
- Proportions will be reported as percentages (not as fraction of unit).

- Percentages will be rounded and presented to one decimal digit; percentages equal to 0 will be presented as '0'.
- CIs of percentages will be rounded and presented to one decimal digit.
- Standard errors of percentages will be rounded and presented to two decimal digits.
- P-values greater than or equal to 0.0001 and lower than or equal to 0.9999 will be rounded and presented to fourth decimal digits.
- P-values lower than 0.0001 will be presented as '< 0.0001'.
- P-values greater than 0.9999 will be presented as '>0.9999'.

10.1.7 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

10.2 Study Subjects

10.2.1 Disposition of Subjects

The disposition of subjects will be presented in total (based on all screened subjects), including frequencies and proportions (n, %) of subjects that were:

- Screened,
- Eligible,
- Randomized,
- Treated,
- Completed treatment,
- Completed study,
- Withdrawn.

These numbers will also be presented by study site. Reasons for withdrawal will be summarized.
Listing for subjects' disposition, screen failures, discontinued subjects, treatment completion status and withdrawal will be provided.

10.2.2 Accounting of Subjects

Frequencies and proportions (n, %) of subjects at each study visit will be summarized overall based on the FAS.
Listings for subject scheduled visits and subject unscheduled visits will be provided.

10.2.3 Protocol Deviations

Major protocol deviations and major protocol deviations leading to the exclusion from the PPS will be summarized using frequencies and proportions (n, %) of subjects in the FAS for each deviation coded term.
A listing of all protocol deviations will be provided.

10.2.4 Data Sets Analyzed

Frequencies and proportions (n, %) of subjects in each analysis set (FAS, PPS, and SAF) will be summarized by study site and in total based on all randomized subjects.

Listings for inclusion/exclusion criteria not met, and analysis set will be provided.

10.2.5 Demographic and Other Baseline Characteristics

Descriptive statistics (n, mean, standard deviation, median, min and max) or frequencies and proportions (n, %) of subjects for each classification category (as applicable) will be presented using the FAS for the following demographic data and baseline characteristics:

- Age (years)
- Sex
    - Male
    - Female
    - Female subjects of childbearing potential
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Ethnicity
    - Han Chinese
    - Other.

Listings for demographic data and baseline characteristics will be provided.

10.2.6 Medical History, Prior and Concomitant Therapies and Procedures

Prior and concomitant therapies/medications will be coded using WHO Drug Dictionary (version September 2023, or later). Medical history diseases and prior and concomitant medical/surgical procedures will be coded using MedDRA dictionary (version 26.1 or later).
Summaries will be presented using the FAS for the following:

- Frequencies and proportions (n, %) of subjects who had any medical history events by SOC and PT, as well as number of events
- Frequencies and proportions (n, %) of subjects who had medical history events that were ongoing at study start by SOC and PT, as well as number of events

- Frequencies and proportions (n, %) of subjects who had concomitant medications by ATC level 3 and Active Ingredient(s), as well as number of drugs
- Frequencies and proportions (n, %) of subjects who had prior aesthetic procedures or implants by SOC and PT, as well as number of events.
- Frequencies and proportions (n, %) of subjects who had concomitant procedures/non-pharmacological treatments by SOC and PT.

Concomitant medications and concomitant procedure/non-pharmacological treatments will also be presented by reason to why they were given.
Listings of all medical history diseases, prior and concomitant therapies/medications and aesthetic procedures or implants will be provided.

10.2.7 Measurements of Treatment Compliance

10.2.7.1 *Treatment Administration and Procedural Anesthetics*

Treatment administration endpoints that will be summarized by study product and overall include (but are not limited to): injection volume, injection technique, approximate number of injection sites, depth of injection, and needle size.
The number of subjects (n, %) with any post-treatment care will be summarized by study product and type of post-treatment care:

- None
- Massage
- Ice/cooling
- Other.

Listings of treatment administration and procedural anesthetics will be provided.

10.3 Estimands

No estimands are defined for this study.

10.4 Effectiveness Analysis

Primary inference for effectiveness analysis will be based on the FAS at the end of injection (T0). Subjects will be summarized and analyzed according to the treatment they were randomized to (Restylane Skinboosters Vital Lido in the left hand and Restylane Vital in the right, or vice versa). All effectiveness data (including effectiveness data of incomplete treatments) will be listed.

10.4.1 Effectiveness Data Summary

10.4.1.1 *VAS*

VAS scores will be summarized at each timepoint (T0, T10, T20, and T30) using descriptive statistics (n, mean, standard deviation, median, min and max) by study product based on the FAS.

The within-subject differences (Δ_{T0}, Δ_{T10}, Δ_{T20}, and Δ_{T30}) will be summarized at each post-treatment timepoint using descriptive statistics (n, mean, standard deviation, median, min and max) in the total group based on the FAS.
Frequencies and proportions (n, %) of subjects that have a within-subject difference of less than 0 mm on the VAS will be summarized at each post-treatment timepoint (T0, T10, T20, and T30) in the total group in the FAS.
Summaries will be presented overall.

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10.4.2 Analysis of Primary Endpoint

The primary endpoint in this study is defined as the within-subject difference in VAS score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at the end of injection. The null hypothesis that the within-subject difference in VAS score is greater than or equal to 0 mm will be tested against the alternative hypothesis that the within-subject difference in VAS score is less than 0 mm using a one-sample t-test. See Section 3.3.1 for a more formal description of the statistical hypotheses to be tested.
If the one-sided p-value of the test is <0.025 the pain at the end of injection will be considered statistically significantly lower after treatment with Restylane Skinboosters Vital Lidocaine than after treatment with Restylane Vital, and thus the primary objective will be considered met. Results will include mean VAS score by treatment, mean within-subject difference in VAS, and the p-value along with standard descriptive statistics and the two-sided 95% CI around the difference (based on the t distribution).
The results for the primary endpoint will also be presented by study site, descriptively only.

See Section 10.4.6.3 for handling of missing values.

10.4.3 Sensitivity Analysis of Primary Endpoints

To investigate the assumptions underlying the model, analysis of the distribution of the within-subject differences will be done. If the distribution of the differences seems to be deviating from normal, a Wilcoxon signed-rank test will be used as a sensitivity analysis. However, the statistical hypotheses to be tested will change from the one specified in Section 3.3.1 to the following:

$$\begin{cases} H_0: \tilde{\Delta} \geq 0\ mm \\ H_1: \tilde{\Delta} < 0\ mm, \end{cases}$$

where $\tilde{\Delta}$ denotes the median within-subject difference in VAS score (Restylane Skinboosters Vital Lidocaine - Restylane Vital) at the end of injection.

To assess the robustness of the primary effectiveness results, the following sensitivity analyses will be conducted:

1. Observed Case (OC) analysis of the within-subject difference in VAS score at T0 on the FAS under Missing Completely at Random assumption,
2. Analysis of the within-subject difference in VAS score at T0 will be repeated on the PPS.

The analyses in 1) and 2) will follow the outline in Section 10.4.2, however, no analyses by study site will be done. If the normality assumption is found to be questionable, 1) and 2) will also be performed using the Wilcoxon signed-rank test.

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10.4.5 Analysis of Exploratory Endpoints

Not applicable.

10.4.6 Statistical/Analytical Issues

10.4.6.1 *Adjustments for Covariates*

No adjustment for covariates is planned for the primary, and CCI [redacted] effectiveness analyses.

10.4.6.2 *Handling of Dropouts*

Available data for subjects that drop out will be used up until the time of dropout. Missing values for the primary endpoint will be imputed as described in Section 10.4.6.3.

10.4.6.3 *Handling of Missing Data*

The primary analysis is based on the FAS that includes only subjects that have received treatment in both hands, so the number of missing values for the primary endpoint is expected to be very low. However, any case of missing a primary endpoint value will be imputed by a within-subject difference of 0 mm. This corresponds to assuming no pain relief using Restylane Skinboosters Vital Lidocaine compared to Restylane Vital and is considered as a worst-case approach.
All other endpoints will be analyzed on available data, i.e., no imputations will be done.

10.4.6.4 *Interim Analyses and Data Monitoring*

Not applicable.

10.4.6.5 *Multicenter Study*

The primary endpoint will be presented descriptively for each of the study sites, including CIs. No other by-site subgroup analysis is planned for this study.

10.4.6.6 *Multiple Comparison/Multiplicity*

As there is only one primary endpoint defined for this study, no adjustment for multiplicity is needed for the primary analysis. For the CCI [redacted] no adjustments for multiplicity will be done. P-values obtained for any endpoint other than the primary will be considered descriptive and only provided for ease of interpretation.

10.4.6.7 *Active-Control Studies Intended to Show Equivalence*

Not applicable.

10.4.6.8 *Examination of Subgroups*

No subgroup analyses are planned for this study except for the study site subgroup analysis of the primary endpoint.

10.4.6.9 *Analysis Visits Definition*

Not applicable. All analyses will be performed using nominal visits.

10.5 Subject Reported Outcomes Analysis

Not applicable.

10.6 Safety Analysis

10.6.1 Adverse Events

All AEs will be coded according to MedDRA and summarized by System Organ Class (SOC), Preferred Term (PT), including number of subjects with at least one event (n, %) and number of events.
For subject counts, a subject will only be counted once per SOC and once per PT in cases where multiple events are reported for a subject within SOC or PT. For event counts, subjects with multiple events in a category will be counted for each event.
The number of subjects with AEs related to study product or study product injection procedure, as well as unrelated AEs, will be presented by SOC, PT, and maximum intensity also including the number of events. Action taken for related AEs will be summarized by SOC and PT using number of events. Serious AEs will be listed.
For AEs related to study product or study product injection procedure, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, standard deviation, median, minimum, and maximum.
In addition, a summary of all AEs will be provided, which will include (but is not limited to):

- frequency of subjects (n, %) with at least one AE and number of events (in total as well as serious AEs),
- frequency of subjects (n, %) with at least one related AE and number of events (in total as well as serious AEs),
- frequency of subjects (n, %) with at least one related AE in the hand treated with Restylane Skinboosters Vital Lidocaine, and number of events (in total as well as serious AEs),
- frequency of subjects (n, %) with at least one related AE in the hand treated with Restylane Vital, and number of events (in total as well as serious AEs),
- frequency of subjects (n, %) with at least one unrelated AE and number of events (in total as well as serious AEs),
- number of subjects who did not have an AE.

CCI [redacted]

[redacted]

11 SHELLS OF TABLES, FIGURES AND LISTINGS AND REPORTING OUTPUT (GENERAL FEATURES)

A Statistical Analysis Report shell will be produced including all planned TFL shells.

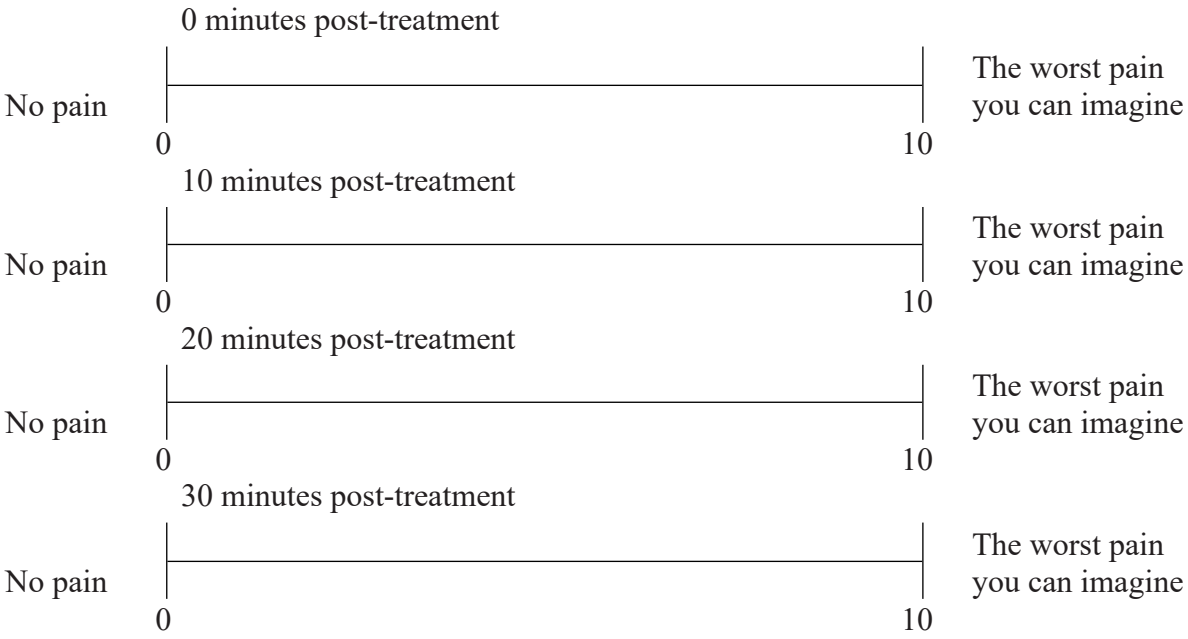
12 APPENDICES

12.1 Visual Analogue Scale (VAS)

Please mark, with a vertical line, how much pain you feel at the different timepoints.

VAS pain assessment RIGHT hand:

VAS pain assessment **LEFT** hand



CCI

[redacted]

CCI

[redacted]

12.3 Potentially Clinically Significant Values

Not applicable.

12.4 Model Checking and Diagnostic for Analyses

The histogram of the distribution of the primary endpoint Δ_{T0}, obtained from the t-test procedure as described in Section 12.5 below, will be used to check the normality assumption of the t-test.

12.5 Details of the SAS Code for Analysis

The primary and CCI [redacted] endpoints are to be analyzed using one-sample t-tests, or if deemed necessary, Wilcoxon signed-rank tests.
The analysis will be performed at T0, T10, T20, and T30.

The SAS (from the 9.4 version) syntax that will be used to obtain the one-sided p-values of the t-tests is:

```
proc ttest data=<dataset> h0=0 plots(showh0) sides=l alpha=0.025;
   var <ΔT variable>;
   ods output Ttests=work.Ttests;
run;
```

The SAS (from the 9.4 version) syntax that will be used to obtain the two-sided confidence intervals around the Δ_T estimates is:

```
proc ttest data=<dataset> h0=0 plots(showh0) sides=2 alpha=0.05;
   var <ΔT variable>;
   ods output ConfLimits=work.ConfLimits;
run;
```

The SAS (from the 9.4 version) syntax that will be used to obtain the p-values of the Wilcoxon signed-rank tests (in case needed) is:

```
proc univariate data=<dataset> mu0=0;
    var <ΔT variable >;
    ods output TestsForLocation=
      work.TestsForLocation(where=(Test='Signed Rank'));
run;
```

Note: the univariate procedure only gives two-sided p-values. Thus, the one-sided p-values for the Wilcoxon tests need to be calculated from the obtained two-sided p-values according to the following:

- If the Δ_T estimate is < 0 then the one-sided p-value is calculated as:
  - (two-sided p-value)/2.
- If the Δ_T estimate is ≥ 0 then the one-sided p-value is calculated as:
  - 1-(two-sided p-value)/2.

The SAS (from the 9.4 version) code that will be used to obtain the two-sided confidence intervals around the Δ_T medians (in case Wilcoxon test is used) by using Bootstrapping is:

```
* Define useful macros */
%macro ODSOff(); /* Call prior to BY-group processing */
ods graphics off;  ods exclude all;  ods noresults;
%mend;

%macro ODSOn(); /* Call after BY-group processing */
ods graphics on;  ods exclude none;  ods results;
%mend;

proc surveyselect data=<dataset> out=BootSamples noprint seed=59378
                  method=urs
                  OUTHITS
                  samprate=1 reps=10000;

run;


%ODSOff                           /* suppress output */

proc means data=BootSamples median;
 by Replicate;
 var <ΔT variable>;
 ods output summary=work.summary;
run;

%ODSOn                            /* enable output   */

proc univariate data=summary;
  var <ΔT variable>_median;
  output out=BootStats pctlpts =2.5  97.5  pctlname=P025 P975
```

```
                    pctlpre =Median_;
run;
```

13 REFERENCES

1. 43CH1504 Clinical Study Report, Internal Doc. No. MA-33230 version 2.0.
2. 43TW1628 Clinical Study Report, Internal Doc. Np. MA-37493 version 1.0

SIGNATURES PAGE

Date	Signed by
2024-04-24 14:30	PPD
Justification	Approved by Owner

2024-04-25 04:31	PPD
Justification	Approved by Technical Expert

2024-04-25 10:28	PPD
Justification	Approved by Technical Expert