Statistical Analysis Plan

Protocol No.	CPH-301-201417
Short Name	Volido
Title	A randomized, subject- and evaluator-blinded, controlled, non-inferiority multicenter, parallel group comparison study to evaluate effectiveness and safety of saypha® VOLUME Lidocaine for midface augmentation in order to correct volume deficit
IDE No.	G210347
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SAP Version and Date	**Final Version 2.0** **07-Feb-2025**

Dates & Signatures

By signature we declare our approval to the statistical analyses described in this SAP.
No additional changes will be made prior to database lock.

07-Feb-2025		[redacted]
[dd-mon-yyyy]		
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SAP Revision History

Version Number	Date	Purpose	Author	Reason for Change
0.1	05-Jan-2024	For internal review	[redacted]	-
0.2	12-Feb-2024	For external review	[redacted]	Incorporation from comments from internal Review
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1.0	27-Jun-2024	For signature	[redacted]	Final corrections and implementation of change requests
2.0	07-Feb-2025	For signature	[redacted]	Updated to add additional AE summary tables for repeat-treatment phase. Sections related to the analysis of initial treatment phase (and therefore of the primary endpoint) are unchanged.

Table of Contents

0. List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRO	Clinical Research Organization
DB-Lock	Database-Lock
DMP	Data Management Plan
DRM	Data Review Meeting
eCRF	Electronic Case Report Form
ES	Enrolled Set
FAS	Full Analysis Set
GAIS	Global Aesthetic Improvement Scale
IA	Interim Analysis
ICH	International Conference on Harmonization
IDRM	Interim Data Review Meeting
IMD	Investigational Medical Device
IMDRF	International Medical Device Regulators Forum
ISR	Injection Site Reaction
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
mSAF	Modified Safety Analysis Set
MVDSS	Midface Volume Deficit Severity Scale
NLF-SRS	Nasolabial Folds Severity Rating Scale
NPRS	Numerical Pain Rating Scale
PPS	Per Protocol Set
PT	Preferred Term
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
WHO	World Health Organization

1. Introduction

This Statistical Analysis Plan (SAP) is based on the clinical investigation protocol version 7.0, dated 15-May-2024, for the study CPH-301-201417, conducted by the sponsor CROMA-PHARMA GmbH, and its corresponding electronic Case report form (eCRF) built upon the CRF mock-up version 4.5 dated 14-May-2024.
Aim of this SAP is to prospectively determine the analysis strategy of this clinical investigation and to describe the methods to be used for the analysis. The statistical evaluation of all eCRF parameters will be performed by the CRO according to this SAP.

2. Changes from Protocol including Amendments

Two additional analysis populations are introduced in this SAP (see section 4.1): The modified Safety Analysis Set, and the modified Full Analysis Set. Both modify the original analysis sets by restricting the analysis population to subjects who received the repeat-treatment. Hence, the rationale is to exclude subjects from the analyses of the repeat treatment phase who have not received any treatment during that phase.

3. Study Overview

3.1. Study Objective(s)

Primary objective:

To demonstrate non-inferiority in the effectiveness of saypha® VOLUME Lidocaine for midface augmentation in order to correct moderate to severe volume deficit versus [redacted] based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase and compared to baseline assessments.

Secondary objectives:

Midface volume deficit and nasolabial fold improvement

- To further assess effectiveness of saypha® VOLUME Lidocaine for correction of moderate to severe midface volume deficit based on the blinded evaluator´s live assessment (except Week 24 after last injection of initial treatment phase for responder rate)
- To assess the effectiveness of saypha® VOLUME Lidocaine for correction of moderate to severe midface volume deficit based on the independent blinded photographic reviewer´s assessment (initial treatment phase only)
- To assess the mean change in midface volume deficit as measured by volumetric change measurement by using 3D digital photographic images (initial treatment phase only)
- To assess the effect of midface treatment with saypha® VOLUME Lidocaine on the nasolabial folds based on the blinded evaluator´s live assessment

Global aesthetic improvement

- To evaluate global aesthetic improvement based on subject's assessments (initial treatment phase only)
- To evaluate global aesthetic improvement based on the blinded evaluator's assessments (initial treatment phase only)

Subject's satisfaction with outcome and appearance appraisal

- To assess subject´s satisfaction with overall treatment outcome
- To assess subject´s appearance appraisal after treatment

Subject's pain assessment and injection volume

- To evaluate subject's perception of pain after each treatment
- To assess total injection volume needed for optimal correction

Safety objectives:

- To assess safety of saypha® VOLUME Lidocaine during the entire study period including subject complaints as recorded in the subject diaries
- To evaluate long term safety of saypha® VOLUME Lidocaine after repeat-treatment
- To assess safety of saypha® VOLUME Lidocaine when used in cross over treatment referring to initial and repeat treatment [redacted] in initial treatment phase switched to saypha® VOLUME Lidocaine in repeat-treatment phase)

3.2. Study Design

The clinical investigation is a randomized, subject- and evaluator-blinded, active treatment controlled, multicenter, clinical investigation, which comprises two treatment groups as follows:

- **Test device:** saypha® VOLUME Lidocaine
- **Comparator device:** [redacted]

Further specifications of the investigational products can be found in the study protocol.

At Visit 2, eligible subjects were randomized and underwent bilateral midface augmentation treatment with either saypha® VOLUME Lidocaine or [redacted] (baseline treatment), with the possibility of a touch-up treatment (TUP) at Week 2 (Visit 3, TUP 1) if an optimal aesthetic correction has not been achieved, as evaluated by the treating investigator.

At Week 48 (Visit 9 (SV1)) after last treatment of the initial treatment phase, subjects of both treatment groups may qualify for a repeat-treatment, which will be done with saypha® VOLUME Lidocaine only. At Visit RT1, subjects eligible for repeat-treatment phase underwent bilateral midface augmentation treatment with saypha® VOLUME Lidocaine (repeat-treatment), with the possibility of a TUP at Visit RT2 (TUP 2) if an optimal aesthetic correction has not been achieved, as evaluated by the treating investigator.

Follow-up visits on-site occur at:

- **Initial treatment phase:** Week 2 after baseline treatment, and 2, 4, 8, 16, 24, 36, 48 weeks after last treatment (Visits 3 to 9 (SV1))
- **Screening phase for repeat-treatment:** Week 4, 8 and 12 after Visit 9 (SV1) - (Visits SV2 to SV4)
- **Repeat-treatment phase:** Week 2 after repeat-treatment, and 2, 4, 12 and 24 weeks after last treatment (Visit RT2 to RT5)

Besides baseline characteristics, medical and aesthetic history and prior and concomitant treatments, assessments comprise midface volume deficit and nasolabial fold improvement, global aesthetic improvement, subject's satisfaction, subject's pain assessment and injection volume.

Safety is continuously monitored throughout the clinical investigation.

See table 1, table 2 and table 3 for a flow chart of visits and procedures.

Table 1: Schedule of procedures and assessments for the initial treatment phase

			Follow-up for initial treatment (baseline and touch-up treatment) (initial treatment phase)									
Visit	**Visit 1 Screening [0]**	**Visit 2 Baseline [0]**	**Visit 2a Phone contact**	**Visit 3 TUP1**	**Visit 3a Phone contact [13]**	**Visit 3b Safety Follow-up [13]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9 (SV1) [21, 24]**
Day / week	Day-14 to Day 0	Day 0	24 – 48 hours after Day 0	2 weeks after BL injection	24 – 48 hours after Visit 3	2 weeks after TUP1 injection	4 weeks after last injection [22]	8 weeks after last injection [22]	16 weeks after last injection [22]	24 weeks after last injection [22]	36 weeks after last injection [22]	48 weeks after last injection [22]
Visit window			± 4 hours	± 3 days	±4 hours	±3 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days
Procedure												
Informed consent	X*											
Medical History [10]	X	X*										
Aesthetic History	X	X*										
Prior and concomitant treatments [1]	X	X*	X	X	X	X	X	X	X	X	X	X
Demographics [2]	X*											
Fitzpatrick skin type	X*											
Body weight	X*						X	X	X	X	X	X
Urine pregnancy test [3]	X	X*		X*		X	X	X	X	X	X	X
Visual examinations [11]		X [11]		X [11]		X	X	X	X	X	X	X
Neurological examinations [17]		X		X		X	X	X	X	X	X	X
Clinical photography	X* [25]						X	X	X	X	X	X
MVDSS – blinded evaluator at site	X* [4]			X*			X	X	X	X	X	X [4]
MVDSS – central blinded photographic reviewer [5]	X						X	X	X	X	X	X
NLF-SRS –blinded evaluator at site [18]	X*			X*			X	X	X	X	X	X

			Follow-up for initial treatment (baseline and touch-up treatment) (initial treatment phase)									
Visit	**Visit 1 Screening [0]**	**Visit 2 Baseline [0]**	**Visit 2a Phone contact**	**Visit 3 TUP1**	**Visit 3a Phone contact [13]**	**Visit 3b Safety Follow-up[13]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9 (SV1) [21, 24]**
Day / week	Day-14 to Day 0	Day 0	24 – 48 hours after Day 0	2 weeks after BL injection	24 – 48 hours after Visit 3	2 weeks after TUP1 injection	4 weeks after last injection [22]	8 weeks after last injection [22]	16 weeks after last injection [22]	24 weeks after last injection [22]	36 weeks after last injection [22]	48 weeks after last injection [22]
Visit window			± 4 hours	±3 days	±4 hours	±3 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days
Procedure												
Volumetric Change Measurements [12]	X						X	X	X	X	X	X
Assessment of eligibility	X	X*		X*[13]								X[15]
Randomization		X*										
Treatment		X		X [16]								
Modified GAIS [6] – blinded evaluator at site							X	X	X	X	X	X
Modified GAIS [6] – subject							X	X	X	X	X	X
FACE-Q™ "Satisfaction with Outcome" – subject [7]							X	X	X	X	X	X
FACE-Q™ "Satisfaction with Cheeks" – subject [8]		X*					X	X	X	X	X	X
Evaluation of pain – subject (NPRS) [9]		X		X[13]								
Injection volume [23]		X		X[13]								
Initiate / Explain subject diary [19]		X		X[13]								
Review subject diary [20]				X		X	X					
Adverse events [14]	X	X	X	X	X	X	X	X	X	X	X	X
Device deficiencies		X		X[13]								

* Prior to injection (i.e., either at baseline or touch-up treatment (TUP1))

0 Screening and Baseline visits may be performed as one visit

1 Includes information on prior treatments, defined as all medications and non-drug therapies taken/received within the previous ten days prior to Screening up to end of study

2 Includes date of birth, sex, race and ethnicity

3 In women of childbearing potential only, including those who are postmenopausal for less than 12 months

4 Evaluation and grading of midface volume deficit by the blinded evaluator at the site (live assessment) using the 5-point MVDSS. The score does not have to be the same on both sides but must be 2 or 3.

5 Evaluation and grading of midface volume deficit severity by the central independent blinded photographic reviewer using the 5-point MVDSS and based on photographs

6 Evaluation of global aesthetic improvement using the modified GAIS against subject's photographs obtained at the Visit 1

7 Subject satisfaction will be determined using the FACE-Q^{TM} questionnaire "Satisfaction with Outcome"

8 Evaluation of subject appearance appraisal using the FACE-Q^{TM} questionnaire "Satisfaction with Cheeks"

9 NPRS starting immediately and every 15 min after last injection for 60 min post-treatment. Separate pain assessments will be performed for the right and left midface area treated.

10 Relevant medical history includes prior and ongoing concomitant diseases and possibly recurring conditions

11 Visual exams (including Snellen visual acuity, confrontational visual fields and ocular motility). The subject should wear the same corrective eyewear (i.e., glasses/contact lenses) at each assessment, if appropriate. At treatment visits: Examination will be performed both before and 30 min after the injection.

12 Volumetric change measurement on photographs will be done centrally by the photography provider once the photography images are received at the photography provider after all subjects have finalized Visit 9 (SV1). The left and right midface will be evaluated separately.

13 Concerning only subjects who receive touch-up treatment

14 All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection

15 Repeat-treatment is possible for all subjects who fulfill the eligibility criteria, irrespective of the treatment (either test device or comparator device) they received in the initial treatment (baseline plus touch-up). The subject does NOT have to return to his/her baseline severity to be permitted to receive a repeat-treatment, but the present condition of midface volume deficit has to meet the initial inclusion level of severity scores of 2 or 3 on the 5-point MVDSS (see section 6.3.5 CIPI). The score does not have to be the same on both sides but must be 2 or 3. In case the subject is eligible in MVDSS score at Visit 9 (SV1), a full eligibility assessment for repeat-treatment will be performed (see Table 3).

16 Touch-up treatment for optimal correction if deemed necessary in the discretion of treating investigator

17 A basic neurological examination (F.A.S.T) will be performed for all subjects who show signs of ophthalmic complications due to filler injection in visual exams

18 Evaluation and grading of nasolabial folds severity by the blinded evaluator at the site (live assessment) using the 5-point NLF-SRS

19 Explain diary use incl. documentation of injection site reactions / other symptoms of interest to the subject.

20 Review subject diary regarding injection site reactions / other symptoms of interest; confirm review. Note: Subjects will record injection site reactions, and symptoms of interest (i.e., changes in vision or symptoms of stroke) over the first four weeks (28 days) after each treatment (i.e., 4 weeks after baseline treatment, and 6 weeks in case of touch-up treatment).

21 In case of Early Termination attempts should be made to perform the assessments described for Visit 9 (SV1).

22 Last injection always either refers to initial treatment (BL) or touch-up treatment (TUP1)

23 Injection volume will be documented by site of the midface (left/right) and for each of the 3 anatomical areas of midface treatment (anteromedial cheek, submalar, and zygomaticomalar)

24 Visit 9 (SV1) will be the end of study visit, in case an inclusion criterion is not met / an exclusion criterion is met for repeat-treatment (see section 6.3.5 CIP) and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment.

25 In addition to clinical photography (3D photos), another baseline photo (2D) should be taken on-site at Visit 1.

Abbreviations: CIP: Clinical Investigation Protocol; MVDSS: Midface Volume Deficit Severity Scale; NLF-SRS: Nasolabial Folds Severity Rating Scale; GAIS: Global Aesthetic Improvement Scale; NPRS: Numerical Pain Rating Scale; SV: Screening Visit; TUP1: Touch-up treatment after baseline treatment

Table 2: Schedule of procedures and assessments for screening phase for repeat-treatment (Visit SV2 to SV4)

	Screening phase for repeat-treatment		
Visit	**Visit SV2** [3] (optional)*	**Visit SV3** [3] (optional)*	**Visit SV4** [3] (optional)*
Day / week	4 weeks after Visit 9 (SV1)	8 weeks after Visit 9 (SV1)	12 weeks after Visit 9 (SV1)
Visit window	±7 days	±7 days	±7 days
MVDSS [1]– blinded evaluator at site [2]	X	X	X
Concomitant treatments [4]	X	X	X
Adverse events [5]	X	X	X

* Visits SV2 to SV4 are optional. As soon as the subject is eligible in MVDSS score, a full eligibility assessment for repeat-treatment will be done and Visit RT1 will be performed (see Table 3).

1 Subjects do not have to return to their baseline severity of midface volume deficit to be eligible and receive a repeat-treatment, but the present condition of midface volume deficit has to meet the initial inclusion level of severity scores of 2 or 3 on the 5-point MVDSS (see section 6.3.5 CIP). The score does not have to be the same on both sides but must be 2 or 3.

2 Midface volume deficit severity is determined by the blinded evaluator. Note: The blinded evaluator at the site is not blinded for treatment allocation during the repeat-treatment phase. However, he/she will be still blinded for the treatment a subject received during the initial treatment phase

3 Visit SV4 will be the end of study visit for subjects who do not qualify for repeat-treatment. In case an inclusion criterion is not met / an exclusion criterion is met during the screening phase for repeat-treatment (see section 6.3.5 CIP) and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment, SV 2 or SV 3 will be the end of study visit for the respective subject.

4 All medications taken and non-pharmacological procedures applied by a subject during the course of a clinical study.

5 All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection

A**bbreviations**: MVDSS: Midface Volume Deficit Scale; SV: Screening Visit; RT: Repeat Treatment

Table 3: Schedule of procedures and assessments for repeat-treatment phase (Visits RT1 to RT5)

	Repeat-treatment and Follow-up for repeat-treatment (repeat-treatment phase)							
Visit	**Visit RT1** [0]	**Visit RT1a** **Phone contact**	**Visit RT2** **TUP2**	**Visit RT2a** [13] **Phone contact**	**Visit RT2b**[13] **Safety Follow-up**	**Visit RT3**	**Visit RT4**	**Visit RT5** **(EOS)**[21]
Day / week	Up to 14 days after Screening Visit †	24 – 48 hours after RT1	2 weeks after RT1 injection	24 – 48 hours after RT2	2 weeks after TUP2 injection	4 weeks after last injection [22]	12 weeks after last injection [22]	24 weeks after last injection [22]
Visit window		± 4 hours	± 3 days	± 4 hours	±3 days	± 5 days	± 7 days	± 7 days
Procedure								
Assessment of eligibility	X*		X*[13]					
Concomitant treatments [1]	X*	X	X	X	X	X	X	X
Body weight	X*		X			X	X	X
Urine pregnancy test [2]	X*		X*		X	X	X	X
Visual examinations [8]	X		X		X	X	X	X
Neurological examinations [17]	X		X		X	X	X	X
MVDSS – blinded evaluator at site [3]	X*		X*			X	X	X
NLF-SRS – blinded evaluator at site [4]	X*		X*			X	X	X
Treatment	X		X [16]					
FACE-Q™ "Satisfaction with Outcome" – subject [6]	X*		X*			X	X	X
FACE-Q™ "Satisfaction with Cheeks" – subject [7]	X*		X*			X	X	X
Evaluation of pain – subject (NPRS) [9]	X		X[13]					
Injection volume [23]	X		X[13]					
Initiate / Explain subject diary [19]	X		X[13]					
Review subject diary [20]			X		X	X		
Adverse events [10]	X	X	X	X	X	X	X	X
Device deficiencies	X		X[13]					

* Prior to injection (i.e., either at repeat-treatment or touch-up treatment (TUP2))

† Visit RT1 may be performed up to 14 days after Screening Visit case the subject qualifies for repeat-treatment at one of these Visits. Screening Visit are Visit 9 (SV1) to SV4.

0 Screening Visits (i.e., Visit 9 (SV1) to SV4) and Visit RT1 may be performed as one visit in case the subject qualifies for repeat-treatment at one of these visits. In case of only one visit, the following assessments do not need to be done twice

- Visit 9 (SV1) = RT1: * pre-treatment assessments at Visit RT1
- Visits SV2 to SV4 = RT1: MVDSS by blinded evaluator, concomitant treatments, adverse events

1 Defined as all medications and non-drug therapies taken/received within the previous ten days prior to initial Screening up to end of study

2 In women of childbearing potential only, including those who are postmenopausal for less than 12 months

3 Evaluation and grading of midface volume deficit by the blinded evaluator at the site (live assessment) using the 5-point MVDSS. Note: The blinded evaluator at the site is *not* blinded for treatment allocation during the repeat-treatment phase. However, he/she will be still blinded for the treatment a subject received during the initial treatment phase.

4 Evaluation and grading of nasolabial folds severity by the blinded evaluator at the site (live assessment) using the 5-point NLF-SRS.

6 Subject satisfaction will be determined using the FACE-Q^{TM} questionnaire “Satisfaction with Outcome”

7 Evaluation of subject appearance appraisal using the FACE-Q^{TM} questionnaire “Satisfaction with Cheeks”

8 Visual exams (including Snellen visual acuity, confrontational visual fields and ocular motility). The subject should wear the same corrective eyewear (i.e., glasses/contact lenses) at each assessment, if appropriate. At treatment visits: Examination will be performed both before and 30 min after the injection.

9 NPRS starting immediately and every 15 min after last injection for 60 min post-treatment

10 All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection

13 Concerning only subjects who receive touch-up treatment.

16 Touch-up treatment for optimal correction if deemed necessary in the discretion of treating investigator

17 A basic neurological examination (F.A.S.T) will be performed for all subjects who show signs of ophthalmic complications due to filler injection in visual exams

19 Explain diary use incl. documentation of injection site reactions / other symptoms of interest to the subject.

20 Review subject diary regarding injection site reactions / other symptoms of interest; confirm review. Note: Subjects will record injection site reactions, and symptoms of interest (i.e., changes in vision or symptoms of stroke) over the first four weeks (28 days) after each treatment (i.e., 4 weeks after repeat-treatment, and 6 weeks in case of touch-up treatment.

21 In case of Early Termination attempts should be made to perform the assessments described for Visit RT5.

22 Last injection in repeat treatment phase always either refers to repeat-treatment (RT1) or touch-up treatment (TUP2)

23 Injection volume will be documented by site of the midface (left/right) and for each of the 3 anatomical areas of midface treatment (anteromedial cheek, submalar, and zygomaticomalar)

Abbreviations: MVDSS: Midface Volume Deficit Severity Scale; NLF-SRS: Nasolabial Folds Severity Rating Scale; GAIS: Global Aesthetic Improvement Scale, NPRS: Numerical Pain Rating Scale; SV: Screening Visit; RT: Repeat Treatment; TUP2: Touch-up treatment after repeat-treatment

3.2.1. Target Population

Desired study subjects for enrolment were subjects aged between 22 to 75 years (inclusive) at the time of Screening who correspond to score of 2 or 3 on the 5-point Midface Volume Deficit Severity Scale (MVDSS), assessed by the blinded evaluating investigator at the site. For more information on in- and exclusion criteria refer to section 6.3.3 of the study protocol.

For information on in- and exclusion criteria for touch up treatment as well as repeated-treatment, also refer to section 6.3.4 and 6.3.5 of the study protocol.

3.2.2. Blinding

The blinded evaluator at the site, who performs live assessments of treatment effectiveness, as well as the central independent blinded photographic reviewer are blinded to the treatment administered.

Subjects are also blinded to the treatments they received until completion of Visit 9 (SV1).

3.2.3. Randomization

The randomization was performed at the Baseline visit (Visit 2), after final confirmation of subject's eligibility. Treatment assignment was pre-planned according to a computer-generated randomization schedule in a 2:1 ratio (test device : comparator device). The schedule contains the following treatment assignments, which were randomly allocated to sequential randomization scheme:

- **Test device:** saypha® VOLUME Lidocaine
- **Comparator device:** [redacted]

The randomization information assigned the subject to one of the treatment groups. In addition, a minimum of 100 subjects randomized to the test device were treated with either needle or cannula.

3.3. Study Conduct

The duration of investigation per subject is up to 92 weeks from the beginning to the end of the investigation. The actual investigation duration per subject may vary.

The total anticipated duration of the investigation, from the first-subject-first visit to the last-subject-last-visit, is around 114 weeks, based on expected recruitment period of about 22 weeks.

3.4. Study Data

Regarding handling of data from external sources, volumetric data of 3-D photos, ratings of the independent blinded photographic reviewer, flags for identification of non-allowed medication, assignment of Adverse Events (AEs) to treatment phases, assignment of eCRF entries to medical history incl. aesthetic facial procedures and non-pharmacological procedures, and protocol deviations (PDs) will be converted to SAS datasets. Randomization data will be uploaded to the eCRF. All other study data are manually entered into the eCRF by the study team. The complete study data will finally be exported from the database as SAS datasets.

3.5. Study Endpoints

3.5.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 24 (Visit 7) after last injection of initial treatment phase compared to the pre-treatment score at Baseline visit.

3.5.2. Secondary Effectiveness Endpoints (Initial Treatment Phase)

The effectiveness of the investigational device during initial treatment phase will be further evaluated using the following secondary effectiveness endpoints:

MVDSS, NLF-SRS and Volumetric Change measurement

- The percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 4, 8, 16, 36, and 48 after last injection of initial treatment phase compared to the score at Baseline visit.
- The percentage of responders on the 5-point MVDSS, based on the independent blinded photographic reviewer´s assessment by using Baseline photographs at Week 4, 8, 16, 24, 36 and 48 after last injection of initial treatment phase compared to the score at Baseline visit
- Mean change in midface volume deficit measured on the 5-point MVDSS and based on the blinded evaluator´s live assessment at Week 4, 8, 16, 24, 36 and 48 after last injection of initial treatment phase compared to the score at Baseline visit
- Mean change in midface volume deficit as measured by volumetric change measurement by using 3D digital photographic images at Week 4, 8, 16, 24, 36 and 48 after last injection of initial treatment phase compared to Baseline visit
- Shift from baseline (Baseline visit) in nasolabial folds measured by NLF-SRS based on the blinded evaluator´s live assessment at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase

Global aesthetic improvement based on modified GAIS

- The percentage of subjects with a global aesthetic improvement over baseline (at Baseline visit) (subjects who have been rated as “much improved” or “improved”), based on subject´s assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment phase using the 5-point modified GAIS.
- The percentage of subjects with a global aesthetic improvement over baseline (at Baseline visit) (subjects who have been rated as “much improved” or “improved”), based on the blinded evaluator`s assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment phase using the 5-point modified GAIS.

Subject’s satisfaction with outcome and appearance appraisal based on FACE-Q™ assessments

- The extent of subject´s satisfaction with overall treatment outcome at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase as assessed by the subject using the Face-Q™ Questionnaire “Satisfaction with Outcome”.
- The extent of subject´s appearance appraisal at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase as assessed by the FACE-Q™ questionnaire “Satisfaction with Cheeks” compared to Baseline visit.

Subject´s pain assessment and injection volume

- Subject evaluation of pain after each treatment (baseline and TUP) on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable

- Injection volume required to achieve optimal aesthetic result at each treatment (baseline- and TUP together)

3.5.3. Other Endpoints (Repeated Treatment Phase)

The investigational device during repeat-treatment phase (saypha® VOLUME Lidocaine) will be evaluated using the following other effectiveness endpoints:

MVDSS and NLF-SRS

- The percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 4, 12 and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1
- Mean change in midface volume deficit measured on the 5-point MVDSS and based on the blinded evaluator´s live assessment at Week 4, 12, and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1
- Shift from baseline (Visit RT1) in NLF-SRS based on the blinded evaluator´s live assessment at Week 4, 12 and 24 after last injection during repeat-treatment phase

Subject's satisfaction with outcome and appearance appraisal based on FACE-Q™ assessments

- The extent of subject´s satisfaction with overall treatment outcome at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome"
- The extent of subject´s appearance appraisal at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the FACE-Q™ questionnaire "Satisfaction with Cheeks" compared to the score at Visit RT1

Subject´s pain assessment and injection volume

- Subject evaluation of pain after each treatment (repeat and TUP) on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable
- Injection volume required to achieve optimal aesthetic result at each treatment (repeat and TUP together)

3.5.4. Safety Endpoints

- Occurrence and frequency of adverse events during the entire study period including repeat-treatment phase (long-term safety).
- Injection site reactions as recorded in the subject diaries during the first 4 weeks (28 days) after each treatment (i.e., either 4 weeks after baseline and repeat-treatment, respectively, and 6 weeks in case of TUP).

3.6. Determination of Sample Size

The primary outcome measures for effectiveness will be evaluated by means of a one-sided two-group Farrington-Manning score test for the difference between proportions with the following hypotheses:

- H0: $pA - pB \leq -10\%$
- H1: $pA - pB > -10\%$

At this, pA is the percent response rate for saypha® VOLUME Lidocaine based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase, while pB is the corresponding response rate for [redacted] Thus, a negative value for this difference means that the response rate of saypha® VOLUME Lidocaine is lower than the response rate for [redacted]

The non-inferiority margin is -10%.

Further assumptions for sample size calculation:

- Response rate at Week 24 after last injection of initial treatment phase for saypha® VOLUME Lidocaine is 85.6%
- Response rate at Week 24 after last injection of initial treatment phase for [redacted] is 85.6%
- Randomization ratio 2:1

Based on these assumptions, 437 subjects (saypha® VOLUME Lidocaine: n=291, [redacted] n=146) will be necessary in order to achieve power exceeding 83% with a one-sided α of 2.5%. Assuming 10% exclusion from PPS results in 486 subjects to be randomized. Adding 6% screen failures yields approximately 516 subjects to be enrolled.

Concerning FAS, it is expected that only very few subjects will be regarded as non-responder due to missing data for the primary effectiveness endpoint. Response rates at Week 24 after last injection of the initial treatment phase may be slightly smaller than assumed above. Due to the increased sample size in the FAS (more than 10% compared to the PPS) it is expected that the power will be adhered as specified above.

Sample size calculation was done using SAS® version 9.4.

Approximately 300 subjects are estimated to receive repeat treatment.

4. Data Analysis Considerations

4.1. Analysis Populations

Enrolled Set (ES)

All subjects who have signed an Informed Consent Form and provided any data on the eCRF.

Safety Analysis Set (SAF)

The SAF comprises all subjects who were randomized and received at least one treatment with device (test device or the comparator device). Subjects in the SAF will contribute to the evaluation "as treated" i.e., the subjects' assignment to the treatment group will be based on the device administered in initial treatment phase.

Modified Safety Analysis Set (mSAF)

The mSAF comprises all subjects received at least one treatment with device (test device or the comparator device) during the repeat treatment phase. Subjects in the mSAF will contribute to the evaluation "as treated" i.e., the subjects' assignment to the treatment group will be based on the device administered in initial treatment phase.

Full Analysis Set (FAS)

The FAS consists of all randomized subjects who received at least one administration of the test device or the comparator device. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomized".

Modified Full Analysis Set (mFAS)

The mFAS consists of all subjects who received at least one treatment with device (test device or the comparator device) during the repeat treatment phase. The statistical evaluation of the mFAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomized".

Per-Protocol Set (PPS):

The PPS is defined as a subset of the subjects in the FAS without major PD(s) affecting the primary effectiveness endpoint and assessed as 'major excluding from PPS'.

The relevance of PDs will be assessed at the interim and final Data Review Meetings (DRMs). PDs will be assessed as either "minor" or "major". Major PDs that could directly interfere with analysis of the primary effectiveness endpoint will be further assessed as either 'major *excluding* from PPS´ or `major *not* excluding from PPS´. Randomization errors will be considered 'major excluding from PPS'.

The criteria for this assessment will be defined before analysis in the PD Manual. Listings will be prepared to assess the eligibility of all subjects during the (i)DRM.

All effectiveness analyses for the initial treatment phase will be conducted using the PPS and the FAS. The effectiveness analysis for the repeat treatment phase will be conducted using the mFAS only. Safety analyses will be based on the SAF and the mSAF in case an analysis comprises repeat-treatment only.

4.2. Definition of Subgroups

The primary analysis will be based on the total trial population. Besides the total study population, the following subgroups are defined:

- Injection equipment: Needle versus cannula (baseline treatment)
- Gender: Female versus male
- Fitzpatrick skin type
- Race
- Ethnicity
- Age groups (22-45 years, 46-65 years and 66-75 years, boundaries included)
- Baseline MVDSS value
- Study site
- Injection volume (sum of baseline treatment and TUP 1), categorized as follows:
    - Group 1: ≤ 3 ml
    - Group 2: > 3 ml and < 7 ml
    - Group 3: ≥ 7 ml
- Combined race and ethnicity: White & hispanic or latino vs. white & not hispanic or latino

4.3. Definition of Derived Variables

In this clinical investigation, baseline is defined as follows:

Concerning the follow-up for *initial treatment*, the last measurement / assessment before first treatment (Visit 2) is defined as baseline.

Concerning the time after *repeat-treatment*, the last measurement / assessment before first repeat-treatment (Visit RT1) is defined as baseline.

Treatment phases are defined (on a subject level) as follows:

Initial treatment phase comprises Visit 1 to Visit 9 (SV1), both visits included.

Repeat-treatment phase comprises Visit RT1 to Visit RT5, both visits included.

If an analysis is conducted by treatment phase, only those subjects who entered the respective treatment phase will be analyzed. As subjects receive saypha® VOLUME Lidocaine only during repeat-treatment phase, analysis by treatment group refers to the allocation after randomization (dependent on the analysis set). This will be indicated by the phrase ‘former treatment group’.

For the allocation of AEs to treatment phases, only the start date will be considered.

If Visit 9 and Visit RT1 happen to be on the same day, assignment will be as follows:

- AEs: Assignment will be performed by medical experts. A flag variable will be created to be able to assign the AE to treatment phases. Identification and flagging will be performed before interim DB-Lock.
- MVDSS / NLF-SRS / FACE-Q questionnaires / NPRS: Assessments are assigned to both treatment phases.

A duration in time will be computed for the applicable variables as follows:

- Stop date – start date + 1.

The relative days to an event from treatment are defined as

- Date of event – date of treatment + 1 if the date of event >= date of treatment Date of event – date of treatment if date of event < date of treatment.

Subjects are defined as responder on the MVDSS scale if they are showing an ≥1 point improvement on the 5-point MVDSS, based on the respective score at a given visit relative to the respective baseline score. Assessments will be evaluated by either the blinded evaluator at the site or by 3 central independent blinded photographic reviewers. For analysis of central independent blinded photographic reviewer assessments, the median of the 3 assessments will be used.

The items of FACE-Q™ satisfaction with outcome will be coded as follows:

1 = Definitely disagree
2 = Somewhat disagree
3 = Somewhat agree
4 = Definitely agree

The items of FACE-Q™ satisfaction with cheeks will be coded as follows:

1 = Very dissatisfied
2 = Somewhat dissatisfied
3 = Somewhat satisfied
4 = Very satisfied

NLF-SRS grade will be coded as follows:

0 = none/minimal
1 = mild
2 = moderate
3 = severe
4 = extreme.

The modified GAIS based on subject´s assessment as well as the modified GAIS based on the blinded evaluator`s assessment will be coded as follows:

-2 = much worse
-1 = worse
0 = no change
1 = improved
2 = much improved.

4.4. Coding Dictionaries

Medical terms are coded with the following dictionaries:

CRF Module	Dictionary
Adverse Events	MedDRA
User / Other Person Adverse Events	MedDRA
Medical and Aesthetic History	MedDRA

CRF Module	Dictionary
Prior and Concomitant Non-Pharmacological Procedures	MedDRA
Prior and Concomitant Medication	WHO Drug Global
Device Deficiency	IMDRF Annex A

4.5. Final Data Review and Protocol Deviations

After finishing the data cleaning process, the final data review will be performed. The conduct details of the final data review, participants, and required data listings to be reviewed (and their suppliers) will be detailed in a separate (interim) Data Review Plan.

A (interim) Data Review Meeting ((i)DRM) will be arranged prior to locking the database. The primary purposes of the (i)DRM are:

- to define possible consequences due to irresolvable queries,
- to discuss any other data issues with respect to statistical analysis,
- to review the PDs detected among the randomized subjects. The relevance of PDs will be assessed at the interim and final DRMs. For this purpose, PDs that could directly interfere with analysis of the primary effectiveness endpoint or could affect subject´s safety and rights will be assessed as either 'minor' or 'major *excluding* from PPS´ or `major *not* excluding from PPS´. Randomization errors will be considered 'major excluding from PPS'.
- The criteria for this assessment will be defined before the analysis in the PD Manual. Listings will be prepared to assess the eligibility of all subjects during the (i)DRM.Taking the rating of PDs into consideration, each subject is assigned to the corresponding analysis population (see section 4.1),

Detailed meeting minutes that summarize all decisions taken at the (i)DRM will be written and signed.

4.6. General Presentation of Summaries and Analysis

All relevant data will be presented in (subject) data listings. Data will be sorted by treatment group, subject number and Visit (if applicable).
Unless otherwise specified, all measurements will be summarized descriptively at each visit by (former) treatment group.

Descriptive statistics will be computed in general as follows:

- Continuous variables will be described using the number of non-missing values, arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile and maximum value ('summary statistics')
- Categorical variables will be presented by the absolute frequency (n) and the relative percentage (%) for each observed modality, whereas missing values will be displayed as own category ('frequency table'). The basis for percentages (= 100%) will be the number of subjects in the corresponding analysis set and treatment group / other strata (if applicable).

In addition, estimated treatment differences will be presented together with two-sided 95%-level confidence intervals (CIs). Main and sensitivity analyses with respect to the primary endpoint will utilize 97.5 % one-sided CIs and corresponding one sided p-values.

For continuous data, the minimum and maximum value will be displayed with the precision available in the data; mean, standard deviation, median and quartiles will be given with one additional decimal.

Further specifications regarding the layout of end-of-text tables and listing are given in Appendix 12.3 of this SAP. A list of all statistical tables and listings to be produced can be found in Appendices 12.1 and 12.2. These overviews also indicate the analysis population(s) for which a respective parameter will be evaluated. Any figures/graphics produced must be legible after been copied in black even if the original version is colored.

4.7. Statistical Software

All statistical analyses will be performed using SAS® Version 9.4 or higher (STATISTICAL ANALYSIS SYSTEM, SAS Institute, Cary, NC, USA).

5. Statistical/Analytical Issues

5.1. General Considerations

Based on the raw database containing the eCRF and external data SDTM datasets following CDISC standards will be created. ADaM datasets following CDISC standards will be programmed based on the SDTMs which will be used for the generation of tables, figures and listings (TFLs).

To meet highest quality control requirements in programming the TFLs, the following parameters will be double-programmed at CRO by a second biostatistician:

- Primary effectiveness endpoint

All other summary tables, listings and graphics will be checked for consistency visually, and a code review of SAS programs will be conducted. All SAS programs used for the evaluation will be stored in a study-specific directory on CRO file server together with the corresponding 'list' and 'log' files.

If the FAS and SAF are identical in terms of subject IDs and treatment allocation, then only results for the FAS will be reported, with the exception of analysis of safety data. Analysis of safety data will be reported with respect to the SAF. The same will be done if mFAS and mSAF are identical as described above.

Only the result of the primary endpoint will be interpreted in a confirmatory sense. All other analyses performed on secondary and other endpoints and all other variables will have purely explorative character.

An observed-cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit).

5.2. Adjustments for Covariates

There will be no adjustment for covariates.

5.3. Handling of Dropouts and Missing Data

Subjects with missing baseline MVDSS score and / or missing MVDSS score at Week 24 after last injection of the initial treatment phase will be considered as non-responders for the primary analysis on the FAS. Different imputation methods for the primary analysis on the FAS are defined

as sensitivity analyses in section 9.2. With respect to all other effectiveness analyses, no values will be imputed.

Partial dates needed to classify medical and aesthetic history and concomitant disease, medications and non-drug therapies as well as AEs will be imputed using the following rules:

- Missing day: date of baseline treatment if treated in the same month. If subject has not been treated in the same month, use first day of the month if baseline treatment was performed before recorded month, and last day of month if baseline treatment was performed after recorded month.
- Missing day and month: date and month of baseline treatment if treated in the same year. If subject has not been treated in the same year, use first day of the year if baseline treatment was performed before recorded year, and last day of year if baseline treatment was performed after recorded year.

If no date is recorded, the most conservative assumption will be done, i.e. diseases, medications and non-drug therapies will be defined as concomitant. AEs will be defined as treatment emergent.

If the intensity of an AE is missing, it will be considered as 'severe'. AEs with missing relationship to device and/or procedure will be counted as related AEs (ADEs).

In addition, there will be no imputation of missing values. All data will be analyzed as they appear in the data base.

5.4. Interim Analysis and Data Monitoring

An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit 48 weeks after their last injection during the initial treatment phase (Visit 9 (SV1)) or dropped out from the study before Visit 9 (SV1). For each subject, statistical evaluation of IA will comprise all data up to and including date of Visit 9 (SV1). Data that cannot be assigned to a visit will be filtered by the individual date of Visit 9 (SV1) of each subject, that is:

Visit/Form	Comment	Relevant Data
Subject Diary	First Treatment and, if applicable, TUP1	All Data
Medical and Aesthetic History		All Events which started prior Visit 9
Prior and Concomitant Non-Drug Procedures		All Events which started prior or at day of Visit 9
Prior and concomitant medication		All Events which started prior or at day of Visit 9
Adverse Events		All Events with start date at Visit 9 (except those assigned to repeat-treatment phase in case Visit 9 and Visit RT1 were performed on the same day, see section 4.3) or earlier
User / Other Person Adverse Events		All Events with start date at Visit 9 or earlier
Device deficiency Log		All Events with start date at Visit 9 or earlier

Unscheduled Visit		All Events until Date of Visit 9
End of Investigation		All Forms where the subject does not attend the Repeat Treatment Phase (Completed Initial Treatment Phase. Dropout)

Data of unscheduled visits before Visit 9 (SV1) will be listed.

All data of subjects who terminated prior to Visit 9 (SV1) will be included. In case no date for Visit 9 (SV1) but a later visit is available, all data until the theoretical date of Visit 9 (SV1) (48 weeks after last treatment) will be included.
For the IA the database will be cleaned and a data base lock prior to export for data analysis will be done. For more information, refer to the Data Cut Off Plan version 1.0, dated 09-Feb-2024.

A list of tables to be produced for IA is given in Appendix 12.1.

5.5. Multicenter Studies

This study will take place in approximately 16 investigation sites. Inclusion of subjects is planned to be as equally distributed as possible between the sites.

Possible geographical cluster and study site effects will not be included in the primary analysis, but will be evaluated on an exploratory level by tabulation of the primary endpoint by study site (subgroup analysis, see sections 4.2 and 5.7).

5.6. Multiple Comparisons/Multiplicity

Since confirmatory testing will only be performed for the primary effectiveness endpoint, a multiplicity issue does not arise.

The IA will be conducted in an informal way without affecting further study conduct, so there are no multiplicity issues involved.

Adjustment for multiplicity is thus not necessary in this study.

5.7. Examination of Subgroups

Subgroups will be analyzed by descriptive statistical methods for the primary and the following main secondary effectiveness endpoints:

- proportion of subjects with response on the MVDSS as assessed by the blinded evaluator at the site
- proportion of subjects with response on the MVDSS as assessed by the independent blinded photographic reviewer
- mean change in midface volume deficit measured on the 5-point MVDSS and based on the blinded evaluator´s live assessment
- proportion of subjects with global aesthetic improvement (in modified GAIS) as assessed by the subject
- proportion of subjects with global aesthetic improvement (in modified GAIS) as assessed by the blinded evaluator

For the main secondary effectiveness endpoints, 95% CIs for the differences between treatment groups in means (CIs derived from 2-sample t-test) or proportions (Miettinen-Nurminen CIs) will be calculated for each subgroup and presented in a forest plot. This will be done for each time of assessment during follow-up for initial treatment.

In order to gather information on potential heterogeneity of treatment effects between the different subgroups, for the primary analysis of the primary effectiveness endpoint an exploratory analysis will be performed using separate binary regression models using the identity link (aiming at the calculation of risk differences) with the respective subgroup as covariate and a treatment by subgroup interaction. No regression Model will be calculated for the subgroup parameters “Study site” and ‘Combined race and ethnicity’. Predicted probabilities >1 will be rounded to 1, and predicted probabilities <0 will be rounded to 0. For each model, a joint hypothesis F-test testing the null hypothesis that all interaction effects are zero will be performed (in case of 3 or more subgroups). 95% CIs based on the profile log-likelihood for the differences of the treatment effect (= risk difference, represented by interaction effects) between subgroups will be calculated and presented in a table and in a forest plot. The forest plot will additionally contain information about the p-value of the F-test (if applicable), as well as a reference to the respective table.

For differences between treatment effects between subgroups, the following reference categories will be used:

- Injection equipment: Needle
- Gender: Female
- Fitzpatrick skin type: Type III
- Race: White
- Ethnicity: Not Hispanic or Latino
- Age groups: 46-65 years
- Baseline MVDSS: mild
- Injection Volume: Group 2: > 3 ml and < 7 ml

In addition, incidence of the following AE types will be summarized within all subgroups:

- AEs
- Treatment Emergent Adverse Events (TEAEs)
- Dermatological TEAEs
- TEAEs of special interest
- Adverse Device Effects (ADEs) related to Investigational Medical Device (IMD)
- ADEs related to procedure
- TEAEs leading to withdrawal of subjects from investigation
- TEAEs leading to premature discontinuations of injection
- Serious Adverse Device Effects (SADEs) related to IMD
- SADEs related to procedure
- AEs due to persisting Injection Site Reactions (ISRs)
- AEs of User/other Persons

Furthermore, all TEAEs will be summarized by preferred term (PT) and system organ class (SOC) within all subgroups.

Additionally, maximum intensity of ISRs from diary will be summarized within all subgroups, including number and frequencies of at least one ISR and each specific type of ISR.

6. Study Population Characteristics

6.1. Population Overview

For IA:

For describing the subject disposition, the following populations will be summarized in frequency tables:

- Subjects screened
- Subjects screened but not randomized

For subjects screened but not randomized the percentage denominator will be the number of screened subjects.

In addition, the following frequencies will be derived (by treatment group and overall):

- Subjects randomized
- Subject randomized by site
- Subjects randomized and received at least one administration of device
- Subjects completed Week 48 after last injection of initial treatment phase
- Subjects in each analysis set defined in section 4.1.
- Number of subjects at each visit (subjects at site and subjects continued up to the visit)
- Number of subjects withdrawn from the study and the reason for withdrawal (percentages for reason will be based on the number of withdrawn subjects)

Percentages will be derived based on the number of randomized subjects, except where indicated otherwise.

Moreover, the following information will be presented in a table:

- The date of the first subject in (date of informed consent),
- The date of the last Week 48 after last injection of initial treatment phase

For final analysis:

For describing the subject disposition, the following populations will be summarized in frequency tables:

- Subjects screened
- Subjects screened but not randomized

For subjects screened but not randomized the percentage denominator will be the number of screened subjects.

In addition, the following frequencies will be derived (by (former) treatment group and overall):

- Subjects randomized

- Subject randomized by site
- Subjects randomized and received at least one administration of device
- Subjects eligible for repeat treatment
- Subjects eligible for repeat treatment and received at least one administration of device
- Subjects completed week 48 (Visit 9) after last injection of initial treatment phase
- Subjects completed week 24 (Visit RT 5) after last injection of the repeat-treatment phase
- Subjects in each analysis set defined in section 4.1 (initial treatment phase)
- Subjects in each analysis set defined in section 4.1 (repeat-treatment phase)
- Number of subjects at each visit (subjects at site and subjects continued up to the visit)
- Number of eligible subjects withdrawn from the study and the reason for withdrawal (percentages for reason will be based on the number of withdrawn subjects)
- Number of eligible subjects withdrawn from the study by sponsors decision and the reason for withdrawal (percentages for reason will be based on the number of withdrawn subjects)

Percentages will be derived based on the number of randomized subjects, except where indicated otherwise.

Moreover, the following information will be presented in a table:

- The date of the first subject in (date of informed consent),
- The date of the last subject out (date of last documented visit),

6.2. Protocol Deviations

For all randomized subjects, a frequency table will give the number and percentage of subjects by (former) treatment group and overall with

- at least one deviation from the study protocol,
- at least one major deviation,
- at least one minor deviation but no major deviation.

In addition, the number and percentage of all subjects with major deviations will be summarized by type of deviation and separately for major deviations that occurred before or at Week 24 (Visit 7) after last injection of initial treatment phase and after Week 24 (Visit 7) after last injection of initial treatment phase. Furthermore, the number and percentage of all subjects with major deviations that occurred before or at Week 24 (Visit 7) after last injection of initial treatment phase will be summarized by type of deviation, separately for major deviations excluding from PPS and major deviations not excluding from PPS. The number and percentage of all subjects with minor deviations will be summarized by type of deviation.

A subject data listing will be prepared displaying for each subject the PDs.

6.3. Subjects Excluded from Analysis Sets

The number and percentage of excluded subjects from the analysis sets per each exclusion reason will be displayed by treatment phase and by (former) treatment group and overall.

A by-subject listing will be prepared displaying the subjects excluded from analysis set(s) and the reason(s) for exclusion.

7. Demographics and Other Baseline Characteristics

Computations will be done on the SAF, FAS and PPS, except where stated otherwise.

7.1. Demographic Data

Summary statistics or frequency tables will be computlocked for baseline variables for initial treatment and repeat-treatment (at Visit 1 / RT1, using mSAF and mFAS instead if SAF and FAS). Variables included will be age, sex, race, ethnicity, body weight and Fitzpatrick Skin Type. Fitzpatrick Skin Type will additional be categorized as

- Types I – III
- Types IV – VI
- Types V and VI

Women of childbearing potential (only Visit 1) will be displayed in a frequency table. Data will be summarized by (former) treatment group, by study site (only for initial treatment) and overall.

7.2. Disease Characteristics

The analysis at baseline of the variable MVDSS (as assessed by blinded evaluator at site) will be computed through summary statistics by treatment group and overall.

For baseline at repeat-treatment phase, analysis will be repeated. Data will be summarized by the treatment group subjects originally belonged to.

Other disease characteristics at baseline will be displayed together with the post baseline visits (see section 9.3).

7.3. Medical and Aesthetic History

Medical History is defined as clinically relevant medical findings which are resolved prior to start of the clinical investigation (prior diseases) or are persisting (concomitant diseases) at start of the clinical investigation (Screening/Visit 1).

Relevant medical history findings include all existing concomitant diseases obtained at Screening (Visit 1). Moreover, the aesthetic history, defined as aesthetic findings limited to procedures on the face of at least the last 24 months, is included in the medical history. A flag variable will be created to be able to assign eCRF entries to medical history incl. aesthetic facial procedures and non-pharmacological procedures when performing statistical analysis. Flagging will be performed once before interim DB-Lock and will be updated before final DB-Lock if necessary.

Medical or aesthetic histories with a stop date prior to screening are defined as ‘prior’, otherwise as ‘concomitant’. If the stop date of a medical or aesthetic history is missing, then it will be defined as concomitant.

If at least the year of the stop date is specified, the imputation rules in section 5.3 will be applied.

The number and percentage of subjects with at least one reported disease / aesthetic facial procedure will be presented by treatment group and overall. In addition, the number and percentage of subjects with at least one dermatological disease / aesthetic facial procedure will be provided by treatment group, overall and by location. For location of dermatological diseases / aesthetic facial procedures, the percentage denominator will be the number of subjects with dermatological diseases / aesthetic facial procedures.

Medical diseases / aesthetic findings will be summarized by System Organ Class (SOC) and PT, by treatment group and overall. Summary tables will be generated on a subject level: Subjects are counted only once for each PT when they have more than one disease / aesthetic finding with the same PT. Subjects with more than one disease / aesthetic procedure within a SOC will be counted for each corresponding PT within the SOC, but are counted only once for the SOC. All tabulations will be sorted alphabetically by SOC and by frequency of PTs within each SOC.

Analyses will be performed separately for prior and concomitant medical diseases / aesthetic facial procedures.

7.4. Prior and Concomitant Medication

All medications (prescription and over-the-counter products) taken from 10 days prior to Screening (screening) up to End of Investigation Visit are documented.

Medications started prior to screening (Visit 1) of initial treatment phase and stopped before the date of baseline treatment are defined as ‘prior’, otherwise as ‘concomitant’. If the stop date of a medication is missing, then it will be defined as concomitant.

If at least the year of the start or stop date is specified, the imputation rules in section 5.3 will be applied.

Prior and concomitant medications will be summarized by ATC Level 1 and 2 and PT, by treatment group and overall. Summary tables will be generated on a subject level: Subjects are counted only once for each PT when they have more than one medication with the same PT. Subjects with more than one medication within ATC Level 1 or 2 will be counted for each corresponding PT within the ATC Level, but are counted only once for each ATC Level. All tabulations will be sorted alphabetically by ATC Level 1 and 2 and by frequency of PTs within each ATC.

Prior and concomitant medications will be presented separately in subject data listings using Level 1 and Level 2 of the ATC code and the PT. Specific details of prior or concomitant medication findings (e.g., dose, route of administration, etc.) will also be presented in the subject data listings.

7.5. Non-Pharmacological Procedures

All non-pharmacological procedures performed from 10 days prior to Screening (screening) up to End of Investigation Visit are documented. A flag variable will be created to be able to assign eCRF entries to medical history incl. aesthetic facial procedures and non-pharmacological procedures when performing statistical analysis. Flagging will be performed once before interim DB-Lock and will be updated before final DB-Lock if necessary.

Non pharmacological procedures started prior to screening and stopped before the date of baseline treatment are defined as ‘prior’, otherwise as ‘concomitant’. If the stop date of a non-pharmacological procedure is missing, then it will be defined as concomitant.

If at least the year of the start or stop date is specified, the rules in section 5.3 will be applied.

The number and percentage of subjects with at least one reported non-pharmacological procedure will be given by treatment group and overall. This table will also contain number and percentage of subjects with at least one dermatological non-pharmacological procedure by treatment group and overall as well as by location. For location of dermatological non-pharmacological procedures, the percentage denominator will be the number of subjects with dermatological non-pharmacological procedures.

Non-pharmacological procedures will be summarized by SOC and PT, by (former) treatment group and overall. Summary tables will be generated on a subject level: Subjects are counted only once for each PT when they have more than one non-pharmacological procedure with the same PT. Subjects with more than one non-pharmacological procedure within a SOC will be counted for each corresponding PT within the SOC, but are counted only once for the SOC. All tabulations will be sorted alphabetically by SOC and by frequency of PTs within each SOC.

Analyses will be performed separately for prior and concomitant non-pharmacological procedures.

7.6. Other Baseline Characteristics

7.6.1. Visual Examinations

Frequencies of test results for snellen acuity test, confrontational visual field test and ocular motility will be computed at baseline (prior to injection). Tabulations will be done by treatment group and overall and be displayed together with the post baseline visits (see section 10.6).

This applies to both treatment phases.

7.6.2. Neurological Examinations

Neurological examination at baseline will be displayed together with the post baseline visits (see Section 10.7). Tabulations will be done by treatment group and overall.

This applies to both treatment phases.

8. Study Treatments

Data will be analyzed for the FAS, PPS and SAF.

8.1. Exposure to Study Treatment

The number of subjects who received treatment will be displayed by treatment group and side of the face and overall.

Frequency tables and summary statistics for the following parameters will be derived by (former) treatment group and overall:

- Duration of treatment (by left, right side and overall)
- Injection equipment used (needle, cannula)
- Occurrence of safety event (AE, Device Deficiencies, Other) during treatment visit.

Regarding TUP, numbers and percentages of TUP performed and TUP side will be computed.

All numbers will be computed by treatment phase (i.e., baseline (Visit 2), touch-up 1 (Visit 3), repeat-treatment (Visit RT1), touch-up 2 (Visit RT2)).

The analysis of injection volume as a secondary endpoint is described in section 9.3.

The overall duration of treatment will be derived by adding up the duration of the left and the right side. In case the times overlap, the overlap is deducted once.

Furthermore, the total injected volume over the investigation will be displayed by left and right side and both sides combined, separately for each treatment (initial- and TUP in each treatment phase).

9. Effectiveness Analysis

The subjects pain assessment and nasolabial folds will be assessed and analyzed for the left and right side of the face separately, as well as Volumetric change measurement.

All other endpoints will be assessed and analyzed globally, with the exception of injection volume, which is assessed by side and will be analyzed globally by taking the sum of both sides.

9.1. Primary Effectiveness Endpoint

The PPS and the FAS will be both considered equally important for the primary analysis, meaning that non-inferiority will only be demonstrated if the results are consistent for both analysis populations.

Hence, the analysis of the primary endpoint will be performed on the PPS and FAS. Confirmatory testing will be performed in a hierarchical ordering: First analysis will be performed on the PPS, and if the corresponding p-value is below 0.025, the analysis will be performed on the FAS.

Subjects with missing baseline MVDSS score and / or missing MVDSS score at Week 24 after last injection of the initial treatment phase will be defined as non-responders for the primary analysis on the FAS. No values will be imputed on the PPS.

To calculate the primary outcome measure, the improvement over baseline in the MVDSS score assessed live by the blinded evaluator at the site at Week 24 after last injection of the initial treatment phase will be calculated by subtracting the MVDSS Score obtained at Baseline from the MVDSS Score at Week 24. The proportion of subjects with MVDSS score improvement of ≥1 point will be then calculated for each treatment group.

The primary outcome measure for effectiveness will be evaluated by means of a one-sided two-group large-sample normal approximation test of proportions with the following hypotheses:

- H_0: $p_A - p_B \leq -10\%$
- H_1: $p_A - p_B > -10\%$

At this, p_A is the response rate for saypha® VOLUME Lidocaine and p_B is the response rate for [redacted]. Thus, a negative value for this difference means that the response rate of saypha® VOLUME Lidocaine is lower than the response rate for [redacted] Here, the non-inferiority margin is defined as $\delta_0 = -10\%$.

The study decision will be based on a Farrington-Manning-statistics with a one-sided type I error rate level of 0.025. The one-sided 97.5% CI (exact unconditional CI limit based on the score statistic as computed by *proc freq*) for the difference $p_A - p_B$ will also be displayed.

In addition to this, the response rates for both treatment groups along with their Clopper-Pearson exact 95% CIs will be tabulated.

9.2. Sensitivity Analyses

The following sensitivity analyses of the primary effectiveness endpoint will be performed on the FAS:

A complete case analysis for the primary endpoint will be performed, meaning that the primary analysis will be repeated, but subjects with missing MVDSS at either baseline or week 24 after last injection of initial treatment phase will be excluded from the analysis, irrespective of treatment group.

The primary analysis will be repeated but subjects with non-allowed concomitant medication / treatments before Week 24 after last injection of the initial treatment phase will be regarded as non-responder, irrespective of treatment group. Non-allowed medication will be identified by medical experts and a flag variable will be created to be able to filter these medications when performing statistical analysis. Identification and flagging will be performed before interim DB-Lock.

Finally, a multiple Imputation under the MNAR assumption for imputing missing MVDSS at week 24 after last injection of initial treatment phase as assessed live by the blinded evaluator will be performed.

In a first step, a monotone missing data pattern will be created via joint modelling and a Markov Chain Monte Carlo Algorithm. The number of imputations will be set to 100. In a second step, the remaining missing data will be imputed, which is accomplished by using a pattern mixture model for deriving imputations. Unidentified parameters of patterns with missing data will be specified using the complete case missing values method (Little, 1993).

The steps using multiple imputation will be as follows:

1. The multiple imputation algorithm will make use of the MVDSS values recorded at each time point up to and including week 24 after last injection of initial treatment phase, separately for each treatment.
2. For MVDSS, the number of missing values and the missing patterns among those will be examined.
3. Multiple imputation will be performed incorporating the variables from 1. as auxiliary variables (MVDSS measured before Week 24 after last injection of initial treatment phase). Joint modelling (assuming multivariate normality) with a Markov Chain Monte Carlo Algorithm will be used to create a monotone missing pattern, and the number of imputed datasets will be set to 100. Imputation will be performed for each treatment group separately.
4. A pattern mixture model applying the complete case missing values method (Little, 1993) will be used to impute the remaining missing data. This model works under the Missing not at Random assumption by relating unidentified parameters to the complete cases. Imputation will be performed for each treatment separately.
5. Each of the 100 separate imputed datasets for the two treatments are merged (pairwise).
6. Responder status is obtained by dichotomizing according to the responder definition stated above.
7. For each of the merged multiply imputed data sets, the proportion of responders in each treatment group as well as the difference in proportion of responders and its standard error will be calculated. Results will be combined by applying Rubins Rules to derive a single point estimate as well as a 95% CI (this will be a Wald-type CI, based on the normal distribution). The degrees of freedom used in this calculation are calculated as given below.

Degrees of freedom will be calculated as follows:

Defining

$$FMI = \frac{V_B + V_B/m}{V_W + V_B + V_B/m},$$

where V_B is the between-imputation variance, V_W is the within sampling variance and m is the number of multiple imputations, and

$$v = (m-1)\frac{1}{FMI^2},$$

the degrees of freedom will be calculated as

$$df = \left(\frac{1}{v} + \frac{1}{v^*}\right)^{-1},$$

with v^* defined as

$$v^* = (1 - FMI)\left(\frac{df^*+1}{df^*+3}\right)df^*.$$

Here, df^* denotes the degrees of freedom that would have resulted had the data been complete.

9.3. Secondary Effectiveness Endpoints (Initial Treatment Phase)

All secondary effectiveness endpoints will be analyzed in an exploratory manner by means of descriptive statistics. In this section, only visits from initial treatment phase are considered. Analysis will be carried out both in the PPS and in the FAS for the initial treatment phase. Analysis will be done by treatment group, but not overall.

The percentage of responders on the MVDSS (for both the blinded evaluator at site as well as the central blinded photographic reviewer) will be displayed in frequency tables for Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase.

Summary statistics will be computed for MVDSS (for both the blinded evaluator at site as well as the central blinded photographic reviewer, using values of 0 for 'none/minimal' to 4 for 'very severe') for baseline, Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase, including change from baseline. Assessments on the MVDSS (for both the blinded evaluator at site as well as the central blinded photographic reviewer) will be presented additionally by categories in frequency tables for each time of assessment.

In addition, shift tables from baseline will be provided for the assessments on the MVDSS (for both the blinded evaluator at site as well as the central blinded photographic reviewer) for Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase.

Midface volume deficit as measured by volumetric change measurement by using 3D digital photographic images will be presented for each of the specified areas of interest (anteromedial cheek, submalar, zygomaticomalar) as well as side of the face (left side, right side, and total) at Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase, including change from baseline.

Concerning nasolabial folds measured by NLF-SRS based on the blinded evaluator's live assessment, shift tables from baseline will be presented for Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase. In addition, summary statistics (using values of 0 for 'none/minimal' to 4 for 'extreme') of the NLF-SRS will be displayed for baseline, Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase. Tabulations will be presented for each of the specified areas of interest (left side and right side).

The percentage of subjects with a global aesthetic improvement over baseline (subjects who have been rated as “much improved” or “improved”), based on the blinded evaluator`s assessment at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase will be displayed in frequency tables, using the 5-point modified GAIS. This will be repeated using the 5-point modified GAIS based on the subjects assessments at Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase.

Categories as well as summary statistics of the modified GAIS assessed by the subject as well as the blinded evaluator will be displayed in tables for Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase

The subject’s satisfaction with overall treatment outcome as evaluated by FACE-Q™ Questionnaire “Satisfaction with Outcome” will be computed for Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase using the Rasch transformed scale (given in Appendix 12.5).

Correspondingly, the subject’s satisfaction with overall midface augmentation will be tabulated using the FACE-Q™ Questionnaire “Satisfaction with Cheeks”, for baseline, Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase. The Rasch transformed scale will be used. Changes from baseline will also be derived.

Concerning each injection, the subject’s assessment of pain intensity on the Numeric Pain Rating Scale will be displayed by means of summary statistics at each time of assessment (for each injection: immediately after the injection, 15, 30, 45 and 60 minutes after injection). Tabulations will be presented for each of the specified areas of interest (left side and right side). Subjects receiving Lidocaine (PD-Category 04-02, topical treatment) before the assessment will be excluded from the analysis for a respective visit.

Injection volume required to achieve optimal aesthetic result at each treatment (initial and TUP together) will be analysed by means of summary statistics.

In addition, for each time of assessment after initial treatment during initial treatment period, the following secondary effectiveness endpoints will be compared between the treatment groups by means of 95% CIs for the differences in means (CIs derived from 2-sample t-test) or proportions (Miettinen-Nurminen CIs), respectively:

- proportion of subjects with response on the MVDSS as assessed by the blinded evaluator at the site
- proportion of subjects with response on the MVDSS as assessed by the independent blinded photographic reviewer
- mean change in midface volume deficit measured on the 5-point MVDSS and based on the blinded evaluator´s live assessment
- proportion of subjects with global aesthetic improvement (in modified GAIS) as assessed by the subject
- proportion of subjects with global aesthetic improvement (in modified GAIS) as assessed by the blinded evaluator

The resulting 95% CIs will be presented in forest plots.

Mean MVDSS, mean modified GAIS as assessed by the subject and the investigator as well as mean overall nasolabial folds measurements (by taking the arithmetic mean of both sides) will be

displayed in plots by visit and treatment group, using scatterplots. For each timepoint and treatment group, the plots will also contain the 95 % CIs from a 1-sample t-test.

9.4. Other Endpoints (Repeat-treatment Phase)

The investigational device during repeat-treatment phase (saypha® VOLUME Lidocaine) will be analyzed in an exploratory manner by means of descriptive statistics. Analysis will be carried out on the mFAS. Changes from baseline will only be computed with respect to baseline of repeat-treatment phase. Analysis will be done by treatment group and overall.

The percentage of responders on the MVDSS based on the blinded evaluator´s live assessment will be displayed in frequency tables at Week 4, 12 and 24 after last injection of repeat-treatment phase.

Summary statistics will be computed for MVDSS based on the blinded evaluator´s live assessment for baseline, Week 4, 12 and 24 after last injection of repeat-treatment phase, including change from baseline of repeat treatment phase.

Concerning nasolabial folds measured by NLF-SRS based on the blinded evaluator's live assessment, change from baseline of repeat treatment phase will be displayed in a shift table. Tabulations will be presented for each of the specified areas of interest (left side and right side).

The subject's satisfaction with overall treatment outcome as evaluated by FACE-Q™ Questionnaire "Satisfaction with Outcome" will be computed for baseline, Week 4, 12 and 24 after last injection of repeat-treatment phase using the Rasch transformed scale.

The subject's satisfaction with overall midface augmentation will be tabulated using the FACE-Q™ Questionnaire "Satisfaction with Cheeks", for baseline, Week 4, 12 and 24 after last injection of repeat-treatment phase using the Rasch transformed scale. Changes from baseline of repeat treatment phase will also be displayed.

Concerning each injection, the subject's assessment of pain intensity on the Numeric Pain Rating Scale will be displayed by means of summary statistics at each time of assessment (for each injection: immediately after the injection, 15, 30, 45 and 60 minutes after injection). Tabulations will be presented for each of the specified areas of interest (left side and right side). Subjects receiving Lidocaine before the assessment (PD-Category 04-02, topical treatment) will be excluded from the analysis for a respective visit.

Injection volume required to achieve optimal aesthetic result at each treatment (initial and TUP together) will be analysed by means of summary statistics. Injection volume required to achieve optimal aesthetic result at each treatment for overall study (for initial treatment phase and repeat treatment phase together) will be analysed by means of summary statistics.

Mean MVDSS will be displayed in scatter plots by visit and treatment group. For each timepoint and treatment group, the plots will also contain the 95 % CIs from a 1-sample t-test.

9.5. Unplanned Analyses

Not applicable.

10. Safety and Tolerability Analyses

All safety parameters will be evaluated for the SAF, except where indicated otherwise. Safety parameters will be evaluated on an exploratory level by means of descriptive statistics.

10.1. Adverse Events

AEs initially observed during or after baseline treatment are defined as treatment-emergent AEs. (TEAEs). Pre-existing AEs which worsened in intensity after baseline treatment are defined as treatment-emergent AEs. If an existing AE worsened in intensity during or after baseline treatment, a new AE was recorded in the eCRF with start date being the day the intensity worsened. AEs occurring after informed consent but before baseline treatment are defined as non-TEAEs.

An AE is defined as related to study treatment if the assessment of the relationship to IMD and/or the relationship to study procedure is other than 'not related'.

The following analysis (AE overview) will be carried out overall and by treatment phase. For analysis by treatment phase, only those events will be counted with onset in the respective phase, see section 4.3. For repeat treatment phase, the mSAF will be used.

An overview will be generated tabulating the number and proportion of subjects (and the total number of events) with at least one:

- AE
- TEAE
- Dermatological TEAE
- TEAE of special interest
- ADE
- TEAE leading to withdrawal of subjects from investigation
- TEAE leading to discontinuations of injection
- SAE
- SADE
- AE due to persisting ISRs
- AE of User/other Persons
- All TEAEs by outcome and action taken

by (former) treatment group and overall.

A second overview table will be programmed displaying TEAEs by outcome and by action taken. Analysis will be done for the initial treatment phase and overall.

The following summaries for AEs will be provided broken down by System Organ Class (SOC) and PT within SOC. Tabulations will be done by (former) treatment group and overall, separately for initial treatment phase, repeat treatment phase and overall:

- All AEs
- All TEAEs
- All TEAEs by maximum intensity (mild, moderate, severe)
- All dermatological TEAEs by location (within treatment area, outside treatment area, both)
- All TEAEs leading to withdrawal of subjects from investigation
- ALL TEAEs leading to discontinuation of injection
- All ADEs (related to IMD, related to procedure, overall)
- All ADEs by intensity (mild, moderate, severe)
- All AEs of special interest
- All AEs of special interest by maximum intensity (mild, moderate, severe)
- All AEs of special interest by maximum relationship to IMD
- All AEs of special interest by maximum relationship to procedure
- All SAEs by maximum relationship to IMD (related, not related, overall)

- All SAEs by maximum relationship to procedure (related, not related, overall)

The number and percentage of subjects with any AEs as well as the number of events will be summarized by SOC and PT within SOC on a subject level: Subjects are counted only once for each PT when they have more than one AE with the same PT. Subjects with more than one AE within a SOC will be counted for each corresponding PT within the SOC, but are counted only once for the SOC. All tabulations will be sorted alphabetically by SOC and by frequency of PTs within each SOC.

If a subject reported multiple AEs with different severities for the same PT or SOC, the maximum intensity is used. That means AEs with maximum intensity on Subject-Level are considered for the 'Overall' rows of tables, on Subject*SOC-Level for the SOC rows and on Subject*SOC*PT-Level for the PT rows.
If a subject reported multiple AEs with different relationship, the most related category is used, i.e. in order 'not related' -→ 'possible' → 'probable' → 'causal'.

TEAEs by SOC and PT, TEAEs by maximum intensity and by SOC and PT, ADEs by SOC and PT ADEs by maximum intensity and by SOC and PT, AEs of Special Interest by SOC and PT and AEs of Special Interest by maximum intensity and by SOC and PT will be programmed additionally for the repeat-treatment phase only.

All AEs and additionally separately AEs leading to discontinuation of injection, serious AEs and ADEs will be listed.

The detailed listings will provide an overview of the individual cases and include, the AE preferred and reported terms, the system organ class, causality and intensity of the AE, the action taken with the IMD and subject, AE outcome, start and stop date of AE, duration of AE, the relative days since baseline treatment, TUP 1, repeat-treatment and TUP 2, as well as relation to persisting ISRs and location of the AE.

10.2. Death

In addition to the general AE listing, a separate subject listing will be generated for death cases.

10.3. Adverse Events of Special Interest

AEs of special interest will be listed separately. Tabulations are described in section 10.1.

10.4. Device Deficiencies

Device deficiency items (number of events, nature of deficiency, individual affected, action taken with the IMD, could the device deficiency have led to SA(D)E, relationship to investigation intervention) will be presented in a listing and will be summarized in a frequency table by treatment group and overall.

The number and percentage of DDs will be summarized by IMDRF Level 1 and IMDRF Level 2 within IMDRF Level 1. All tabulations will be sorted alphabetically by IMDRF Level 1 and by frequency of IMDRF Level 2 within each IMDRF Level 1. Analyses will be carried out by actual device applied and overall. For the analysis the total number of kits used in the study which were reported in the eCRF modules 'Treatment' and/or 'Device Deficiency Log' will be considered.

In addition, the number of non-subjects device deficiencies will be summarized by IMDRF Level 1 and IMDRF Level 2. Analyses will be carried out by actual device applied and overall.

Tabulations by IMDRF Levels will be performed overall and additionally for the initial treatment phase and repeat treatment phase.

10.5. Injection Site Reactions

For the analysis described below, only those subjects with at least one entry in the diary will be considered.

Initial treatment phase:

Summaries of the number and percentage of subjects with ISRs (as documented by the subjects in the diary) will be presented by type of ISR and (former) treatment group. ISRs will be presented by midface side and overall (at least one side).

Summary statistics of the duration of ISRs by type and (former) treatment group will be presented, separately for each side of the midface and overall (both sides).

In addition, a frequency table of maximum intensity of ISRs by type and (former) treatment group will be computed. All tables will be presented by midface side and overall (both sides). If a subject reported multiple persisting ISRs with different intensities for the same PT or SOC, the maximum intensity is used. That means persisting ISRs with maximum intensity on Subject-Level are considered for the 'Overall' rows of tables, on Subject*SOC-Level for the SOC rows and on Subject*SOC*PT-Level for the PT rows. Only ISRs with intensity unequal none will be included.

Regarding the computations described above, for subjects who did not receive touch up treatment 1, all diary entries will be used. For subjects who did receive TUP 1, all diary entries up to (and including) the last day before TUP will be included.

Analysis will be repeated including only those subjects who did receive TUP 1. Here, only diary entries at and after TUP will be considered.

Repeat treatment phase:

Description of analysis for repeat-treatment phase is analogously to initial treatment phase, replacing baseline treatment by repeat-treatment and TUP 1 by TUP 2. That is, tables will be repeated for repeat-treatment phase, including subjects and diary entries as indicated above, but with respect to repeat-treatment and TUP 2.

For repeat-treatment phase, the mSAF will be used.

Furthermore, duration of ISRs will be presented by categories (1-3 days, 4-7 days, 8-14 days, >14 days) by type and (former) treatment group. Duration will be assessed by the first start date and last end date (e.g. the date of the last diary entry for 'bruising minus the date of the first diary entry for 'bruising' + 1). ISRs will be presented by midface side and overall (both sides). For the overall case, this definition comprises both sides of the midface.

The following tables will be generated for analysis of duration by categories:

Initial treatment phase:

- Considering all diary entries after baseline treatment for subject who did not receive TUP 1, and all diary entries up to (and including) the last day before TUP for subjects who did receive TUP 1

- Considering only those diary entries after baseline treatment up to (and including) the last day before TUP 1 (including only those subjects who did receive TUP 1)
- Considering all diary entries after baseline treatment (including only those subjects who did not receive TUP 1)
- Considering all diary entries after (and including) date of TUP 1 (including only those subjects who did receive TUP 1)

Repeat-treatment phase:

- Considering all diary entries after repeat-treatment for subject who did not receive TUP 2, and all diary entries up to (and including) the last day before TUP for subjects who did receive TUP 2
- Considering only those diary entries after repeat-treatment up to (and including) the last day before TUP 2 (including only those subjects who did receive TUP 1)
- Considering all diary entries after repeat-treatment (including only those subjects who did not receive TUP 2)
- Considering all diary entries after (and including) date of TUP 2 (including only those subjects who did receive TUP 2)

For repeat-treatment phase, the mSAF will be used.

All ISRs from the diary will be presented in by-subject listings.

ISRs lasting longer than 28 days will be captured as AEs and defined as “persisting ISR”. The number and percentage of subjects with persisting ISRs (including serious persisting ISRs) will be displayed in a frequency table by SOC, PT and maximum intensity, by (former) treatment group and overall.

10.6. Visual Examination

Frequencies of test results for snellen acuity test, confrontational visual field test and ocular motility will be computed at each relevant visit (at treatment visits, the test was performed both before and after injection).

A shift table will be produced showing the change in test results from baseline (with respect to initial treatment phase and repeat treatment phase) to each relevant subsequent visit.

For Snellen acuity test, an additional category will be introduced (‘performed adequately’), indicating if same corrective eyewear than at baseline was used as captured in eCRF module ‘Visual Examination’. A separate listing which lists only test results for subjects where snellen acuity test has not been performed adequately will be programmed.

Tabulations will be done by (former) treatment group and overall, separately for initial and repeat-treatment phase, using the SAF and the mSAF respectively.

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10.7. Neurological Examination

The results will be presented in data listing only.

10.8. Urine Pregnancy Test

Women of childbearing potential will do pregnancy tests. The results will be presented in a data listing only.

11. References

Clinical Investigation Protocol, Version 7.0, dated 15-May-2024.

Data Cut-Off Plan, Version 1.0, dated 09-Feb-2024.

Data Management Plan, Version 1.1, dated 13-Dec-2023.

ICH E3, Structure and Content of Clinical Study Reports,1996.

ICH E9, Statistical principles for clinical trials,1998.

ISO 14155:2020, Clinical investigation of medical devices for human subjects – Good clinical practice, 2020.

Little R. J. A. (1993). Pattern-Mixture Models for Multivariate Incomplete Data. Journal of the American Statistical Association, 88(421), 125–134. https://doi.org/10.2307/2290705

Miettinen, O. S., and Nurminen, M. M. (1985). Comparative Analysis of Two Rates. Statistics in Medicine 4(2), 213–226. https://doi.org/10.1002/sim.4780040211.

PD Manual, version 1.0, dated 14-Dec-2022.

SAS, SAS Institute, Cary, NC, USA.

12. Appendices

12.1. Table of 'End-of-Text' Tables / Figures

The numbering of statistical tables follows the ICH E3. Shown abbreviations denote the analysis populations for which a variable will be evaluated.

Please note that some tables may be split into subtables covering different aspects of the evaluation. Tables presented that are repeated for different analysis populations are numbered with the suffix '.1' for FAS, '.2' for PPS, and '.3' for SAF.
Tables computed additionally for subgroups are numbered as follows: First, an additional number is enhanced depending on the subgroup, i.e.:

1 = Injection equipment
2 = Gender
3 = Fitzpatrick Skin Type
4 = Race
5 = Ethnicity
6 = Age groups.
7 = Baseline MVDSS value
8 = Study Site
9 = Injection volume
10 = Combined race & ethnicity

Second, the table number is enhanced for the respective analysis population as described above.

Table / Figure	**Title**	**Analysis Population**	**Stratification / Subgroups**	**Compute for IA** Note: using data until cut-off as defined in section 5.4	**Compute for Final Analysis** Note: Using data from the whole study period
14.1.1.1	Subject Disposition	Randomized Subjects	Overall By treatment group	X	X
14.1.1.2	Number of Subjects by Site	Randomized Subjects	Overall By treatment group	X	X
14.1.2	Subjects at each Visit	SAF	Overall By treatment group	X	X
14.1.3	Summary of Protocol Deviations	SAF	Overall By treatment group	X	X
14.1.4	Subjects excluded from Analysis Populations	Randomized Subjects	Overall By treatment group	X	X
14.1.5.1	Demographic Data - Initial treatment Phase	SAF, FAS, PPS	Overall By treatment group By Site	X	
14.1.5.2	Demographic Data – Overall	SAF	Overall By treatment group		X
14.1.5.3	Demographic data – Repeat Treatment Phase	mSAF, mFAS	Overall By treatment group		X
14.1.6.1	Disease Characteristics: MVDSS by Blinded Evaluator at Site - Initial Treatment Phase	SAF, FAS, PPS	Overall By treatment group	X	
14.1.6.2	Disease Characteristics: MVDSS by Blinded Evaluator at Site - Repeat-treatment Phase	mSAF, mFAS	Overall By treatment group		X
14.1.7.1.1	Prior Medical Conditions / Aesthetic Facial Procedures by Location	SAF, FAS, PPS	Overall By treatment group	X	
14.1.7.1.2	Prior Medical Conditions / Aesthetic Facial Procedures by SOC and PT	SAF, FAS, PPS	Overall By treatment group	X	
14.1.7.2.1	Concomitant Conditions / Aesthetic Facial Procedures by Location	SAF, FAS, PPS	Overall By treatment group	X	X
14.1.7.2.2	Concomitant Conditions / Aesthetic Facial Procedures by SOC and PT	SAF, FAS, PPS	Overall By treatment group	X	X

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
14.1.8.1.1	Prior Non-Pharmacological Procedures by Location	SAF, FAS, PPS	Overall By treatment group	X	
14.1.8.1.2	Prior Non-Pharmacological Procedures by SOC and PT	SAF, FAS, PPS	Overall By treatment group	X	
14.1.8.2.1	Concomitant Non-Pharmacological Procedures by Location	SAF, FAS, PPS	Overall By treatment group	X	X
14.1.8.2.2	Concomitant Non-Pharmacological Procedures by SOC and PT	SAF, FAS, PPS	Overall By treatment group	X	X
14.1.9.1	Prior Medication	SAF, FAS, PPS	Overall By treatment group	X	
14.1.9.2	Concomitant Medication	SAF, FAS, PPS	Overall By treatment group	X	X
14.1.10.1.1	Exposure to Investigational Medical Device – Overview (Initial Treatment Phase)	SAF, FAS, PPS	Overall By treatment group By treatment administered (baseline and touch-up 1)	X	
14.1.10.1.2	Exposure to Investigational Medical Device – Overview (Repeat-treatment Phase)	mSAF, mFAS,	Overall By treatment group By treatment administered (repeat-treatment and touch-up 2)		X
14.1.10.2.1	Exposure to Investigational Medical Device – Injection Equipment Used (Initial Treatment Phase)	SAF, FAS, PPS	Overall By treatment group By treatment administered (baseline and touch-up 1)	X	
14.1.10.2.2	Exposure to Investigational Medical Device – Injection Equipment Used (Repeat-treatment Phase)	mSAF, mFAS,	Overall By treatment group By treatment administered (repeat-		X

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
			treatment and touch-up 2)		
14.1.10.3.1	Exposure to Investigational Medical Device – Duration (Initial Treatment Phase)	SAF, FAS, PPS	Overall By treatment group By side By treatment administered (baseline and touch-up 1)	X	
14.1.10.3.2	Exposure to Investigational Medical Device – Duration (Repeat-treatment Phase)	mSAF, mFAS,	Overall By treatment group By side By treatment administered (repeat-treatment and touch-up 2)		X
14.1.10.4.1	Exposure to Investigational Medical Device – Volume (Initial Treatment Phase)	SAF, FAS, PPS	Overall By treatment group By side By treatment administered (baseline and touch-up 1)	X	
14.1.10.4.2	Exposure to Investigational Medical Device – Volume (Repeat-treatment Phase)	mSAF, mFAS,	Overall By treatment group By side By treatment administered (repeat-treatment and touch-up 2)		X
14.1.10.4.3	Exposure to Investigational Medical Device – Volume (Overall)	SAF, FAS, PPS	Overall By treatment group By side By treatment administered		X
14.2.1.1	Initial Treatment Phase: Difference in Proportions of Responders in MVDSS Based on the Assessment of	FAS, PPS	By treatment group	X	

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
	the Blinded Evaluator at the Site, by Visit		By subgroups as defined in section 4.2		
Figure 14.2.1.2	Initial Treatment Phase: Forest Plot of Proportion of Responders in MVDSS Based on the Assessment of the Blinded Evaluator at the Site by Visit	FAS, PPS	By treatment group	X	
14.2.2.1	Initial Treatment Phase: Difference in Proportions of Responders in MVDSS at Week 24 After Last Injection of Initial Treatment Phase Based on the Assessment of the Blinded Evaluator at the Site	FAS, PPS	By treatment group By subgroups as defined in section 4.2	X	
14.2.2.2	Sensitivity analysis: Difference in Proportions of Responder in MVDSS at Week 24 After Last Injection of Initial Treatment Phase Based on the Assessment of the Blinded Evaluator at the Site (Complete Case Analysis)	FAS	By treatment group	X	
14.2.2.3	Sensitivity analysis: Difference in Proportions of Responder in MVDSS at Week 24 After Last Injection of Initial Treatment Phase Based on the Assessment of the Blinded Evaluator at the Site (Non-responder Imputation)	FAS	By treatment group	X	
14.2.2.4.1	Sensitivity analysis: Difference in Proportions of Responders in MVDSS at Week 24 After Last Injection of Initial Treatment Phase Based on the Assessment of the Blinded Evaluator at the Site (Multiple Imputation)	FAS	By treatment group	X	
14.2.2.4.2	Sensitivity analysis: Difference in Proportions of Responders in MVDSS at Week 24 After Last Injection of Initial Treatment Phase Based on the Assessment of the Blinded Evaluator at the Site (Multiple Imputation: Results of First 10 Imputed Datasets)	FAS	By treatment group	X	
14.2.2.4.3	Sensitivity Analysis: Missing Patterns for MVDSS Imputation (Multiple Imputation)	FAS	By treatment group	X	
14.2.3.1	Initial Treatment Phase: Descriptive Statistics on MVDSS Based on the	FAS, PPS	By treatment group	X	

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
	Assessment of the Blinded Evaluator at the Site, by Visit, Including Change From Baseline		By subgroups as defined in section 4.2		
Figure 14.2.3.2	Initial Treatment Phase: Forest Plot of Mean MVDSS Based on the Assessment of the Blinded Evaluator at the Site by Visit	FAS, PPS	By treatment group	X	
14.2.3.3	Initial Treatment Phase: Categories of MVDSS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group	X	
14.2.3.4	Initial Treatment Phase: Shift From Baseline in Categories of MVDSS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group	X	
14.2.4.1	Initial Treatment Phase: Proportion of Responders in MVDSS based on the Independent Blinded Photographic Reviewer by Visit	FAS, PPS	By treatment group By subgroups as defined in section 4.2	X	
Figure 14.2.4.2	Initial Treatment Phase: Forest Plot of Proportion of Responders in MVDSS Based on the Assessment of the Independent Blinded Photographic Reviewer by Visit	FAS, PPS	By treatment group	X	
14.2.4.3	Initial Treatment Phase: Descriptive Statistics on MVDSS based on the Independent Blinded Photographic Reviewer by Visit, Including Change From Baseline	FAS, PPS	By treatment group	X	
14.2.5	Initial Treatment Phase: Volume Change of the Midface Based on 3D Surface Imaging in Comparison to Baseline 3D Surface Image, by Visit	FAS, PPS	By treatment group By side and total	X	
14.2.6.1	Initial Treatment Phase: Descriptive Statistics on NLF-SRS Based on the Assessment of the Blinded Evaluator at the Site, by Visit, including Change From Baseline	FAS, PPS	By treatment group By side	X	
Figure 14.2.6.2	Initial Treatment Phase: Scatterplot of mean NLF-SRS Based on the Assessment of the Blinded Evaluator at the Site by Visit	FAS, PPS	By treatment group By side	X	

Table / Figure	**Title**	**Analysis Population**	**Stratification / Subgroups**	**Compute for IA** Note: using data until cut-off as defined in section 5.4	**Compute for Final Analysis** Note: Using data from the whole study period
14.2.6.3	Initial Treatment Phase: Shift From Baseline in Categories of NLF-SRS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group By side	X	
14.2.7.1	Initial Treatment Phase: Proportion of Responders in Modified GAIS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group By subgroups as defined in section 4.2	X	
Figure 14.2.7.2	Initial Treatment Phase: Forest Plot of Proportion of Responders in modified GAIS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group	X	
14.2.7.3	Initial Treatment Phase: Categories of Modified GAIS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group	X	
14.2.7.4	Initial Treatment Phase: Descriptive Statistics on Modified GAIS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group	X	
Figure 14.2.7.5	Initial Treatment Phase: Scatterplot of mean modified GAIS Based on the Assessment of the Blinded Evaluator at the Site, by Visit	FAS, PPS	By treatment group By side	X	
14.2.8.1	Initial Treatment Phase: Proportion of Responders in Modified GAIS Based on the Subject´s Assessment, by Visit	FAS, PPS	By treatment group By subgroups as defined in section 4.2	X	
Figure 14.2.8.2	Initial Treatment Phase: Forest Plot of Proportion of Responders in modified GAIS, Based on the Subject´s assessment, by Visit	FAS, PPS	By treatment group	X	
14.2.8.3	Initial Treatment Phase: Categories of Modified GAIS Based on the Subject´s Assessment, by Visit	FAS, PPS	By treatment group	X	
14.2.8.4	Initial Treatment Phase: Descriptive Statistics on Modified GAIS based on the Subject´s assessment, by Visit	FAS, PPS	By treatment group	X	
Figure 14.2.8.5	Initial Treatment Phase: Scatterplot of mean modified GAIS based on the Subject´s assessment, by Visit	FAS, PPS	By treatment group By side		

Table / Figure	**Title**	**Analysis Population**	**Stratification / Subgroups**	**Compute for IA** Note: using data until cut-off as defined in section 5.4	**Compute for Final Analysis** Note: Using data from the whole study period
14.2.9	Initial Treatment Phase: Descriptive Statistics on FACE-Q Questionnaire (Satisfaction with Outcome), by Visit	FAS, PPS	By treatment group	X	
14.2.10	Initial Treatment Phase: Descriptive Statistics on FACE-Q Questionnaire (Satisfaction with Cheeks) by Visit, including Change From Baseline	FAS, PPS	By treatment group	X	
14.2.11	Initial Treatment Phase: Descriptive Statistics on Numeric Pain Rating Scale, by Visit	FAS, PPS	By treatment group By side	X	
14.2.12	Initial Treatment Phase: Descriptive Statistics on total Injection volume	FAS, PPS	By treatment group By side and total	X	
14.2.13.1.1	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Injection Equipment	FAS, PPS	Not applicable	X	
14.2.13.1.2	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Gender	FAS, PPS	Not applicable	X	
14.2.13.1.3	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Fitzpatrick Skin Type	FAS, PPS	Not applicable	X	
14.2.13.1.4	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Race	FAS, PPS	Not applicable	X	
14.2.13.1.5	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Ethnicity	FAS, PPS	Not applicable	X	
14.2.13.1.6	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects	FAS, PPS	Not applicable	X	

Table / **Figure**	**Title**	**Analysis Population**	**Stratification** / **Subgroups**	**Compute for IA** Note: using data until cut-off as defined in section 5.4	**Compute for Final Analysis** Note: Using data from the whole study period
	Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Age Groups				
14.2.13.1.7	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Baseline MVDSS	FAS, PPS	Not applicable	X	
14.2.13.1.8	Initial Treatment Phase: Binary Regression Model for Assessing Heterogeneity of Treatment Effects Regarding Being a Responder in MVDSS at Week 24: Subgroup Analysis – Injection Volume	FAS, PPS	Not applicable	X	
Figure 14.2.13.2.1	Initial Treatment Phase: Forest Plot: CIs for Treatment Effect Differences in Proportion of Subjects with Response on the MVDSS at Week 24 Based on the Assessment of the Blinded Evaluator at the Site	FAS, PPS		X	
Figure 14.2.13.2.2	Initial Treatment Phase: Forest Plot: CIs for Difference in Proportion of Subjects With Response on the MVDSS Based on the Assessment of the Blinded Evaluator at the Site, by Subgroups and Visit	FAS, PPS		X	
Figure 14.2.13.2.3	Initial Treatment Phase: Forest Plot: CIs for Difference in Proportion of Subjects With Response on the MVDSS Based on the Assessment of the Independent Blinded Photographic Reviewer, by Subgroups and Visit	FAS, PPS		X	
Figure 14.2.13.2.4	Initial Treatment Phase: Forest Plot: CIs for Difference in MVDSS Based on the Assessment of the Blinded Evaluator at the Site, by subgroups and visit	FAS, PPS		X	
Figure 14.2.13.2.5	Initial Treatment Phase: Forest Plot: CIs for Difference in Proportion of Subjects with Global Aesthetic Improvement in Modified GAIS as Assessed by the Subject, by subgroups and Visit	FAS, PPS		X	
Figure 14.2.13.2.6	Initial Treatment Phase: Forest Plot: CIs for Difference in Proportion of	FAS, PPS		X	

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
	Subjects with Global Aesthetic Improvement (in Modified GAIS) Based on the Assessment of the Blinded Evaluator at the Site, by subgroups and visit				
14.2.14.1	Repeat-treatment Phase: Proportion of Responders in MVDSS Based on the Assessment of the Blinded Evaluator at the Site by Visit	mFAS	Overall By treatment group		X
14.2.14.2	Repeat-treatment Phase: Descriptive Statistics on MVDSS Based on the Assessment of the Blinded Evaluator at the Site by Visit, including Change From Baseline	mFAS	Overall By treatment group		X
Figure 14.2.14.3	Repeat-treatment Phase: Scatterplot of Mean MVDSS based on the Assessment of the Blinded Evaluator at the Site, by Visit	mFAS	Overall By treatment group		X
14.2.15	Repeat-treatment Phase: Shift from Baseline in Categories of NLF-SRS Based on the Assessment of the Blinded Evaluator at the Site by Visit	mFAS	Overall By treatment group By side and total		X
14.2.16	Repeat-treatment Phase: Descriptive Statistics on FACE-Q Questionnaire (Satisfaction with Outcome), by Visit	mFAS	Overall By treatment group		X
14.2.17	Repeat-treatment Phase: Descriptive Statistics on FACE-Q Questionnaire (Satisfaction with Cheeks) by Visit, including Change From Baseline	mFAS	Overall By treatment group		X
14.2.18	Repeat-treatment Phase: Descriptive Statistics on Numeric Pain Rating Scale, by Visit	mFAS	Overall By treatment group By side		X
14.2.19	Repeat-treatment Phase: Descriptive Statistics on total Injection volume (Initial and Touch-up Treatment together)	mFAS	Overall By treatment group By side and total		X
14.3.1.1.1.1	Overview of Adverse Events - Initial Treatment Phase	SAF	Overall By treatment group By subgroups as defined in section 4.2	X	

Table / Figure	**Title**	**Analysis Population**	**Stratification / Subgroups**	**Compute for IA** Note: using data until cut-off as defined in section 5.4	**Compute for Final Analysis** Note: Using data from the whole study period
14.3.1.1.1.2	Overview of Adverse Events – Overall	SAF	Overall By treatment group		X
14.3.1.1.1.3	Overview of Adverse Events – Repeat-treatment Phase	mSAF	Overall By treatment group		X
14.3.1.2.1	Adverse Events by SOC and PT	SAF	Overall By treatment group By SOC and PT	X	X
14.3.1.2.2.1	TEAEs by SOC and PT – Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT By subgroups as defined in section 4.2	X	
14.3.1.2.2.2	TEAEs by SOC and PT – Overall	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.2.3	TEAEs by SOC and PT – Repeat-treatment Phase	mSAF	Overall By treatment group By SOC and PT		X
14.3.1.2.3.1	TEAEs by Maximum Intensity and by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By intensity By SOC and PT	X	
14.3.1.2.3.2	TEAEs by Maximum Intensity and by SOC and PT – Overall	SAF	Overall By treatment group By intensity By SOC and PT		X
14.3.1.2.3.3	TEAEs by Maximum Intensity and by SOC and PT – Repeat-treatment Phase	mSAF	Overall By treatment group By intensity By SOC and PT		X
14.3.1.2.4.1	TEAEs (Dermatological) by Location and by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By location By SOC and PT	X	

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
14.3.1.2.4.2	TEAEs (Dermatological) by Location and by SOC and PT – Overall	SAF	Overall By treatment group By location By SOC and PT		X
14.3.1.2.4.3	TEAEs (Dermatological) by Location and by SOC and PT – Repeat-treatment Phase	SAF	Overall By treatment group By location By SOC and PT		X
14.3.1.2.5.1.1	TEAEs leading to Withdrawal of Subject by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT		
14.3.1.2.5.1.2	TEAEs leading to Withdrawal of Subject by SOC and PT – Overall	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.5.1.3	TEAEs leading to Withdrawal of Subject by SOC and PT – Repeat-treatment Phase	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.5.2.1	TEAEs leading to Discontinuation of Injection by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT	X	
14.3.1.2.5.2.2	TEAEs leading to Discontinuation of Injection by SOC and PT – Overall	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.5.2.3	TEAEs leading to Discontinuation of Injection by SOC and PT – Repeat-treatment Phase	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.6.1	Adverse Device Effects by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT	X	
14.3.1.2.6.2	Adverse Device Effects by SOC and PT - Overall	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.6.3	Adverse Device Effects by SOC and PT – Repeat-Treatment Phase	mSAF	Overall By treatment group By SOC and PT		X

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
14.3.1.2.7.1	Adverse Device Effects by Maximum Intensity and by SOC and PT- Initial Treatment Phase	SAF	Overall By treatment group By intensity By SOC and PT	X	
14.3.1.2.7.2	Adverse Device Effects by Maximum Intensity and by SOC and PT – Overall	SAF	Overall By treatment group By intensity By SOC and PT		X
14.3.1.2.7.3	Adverse Device Effects by Maximum Intensity and by SOC and PT – Repeat-treatment Phase	mSAF	Overall By treatment group By intensity By SOC and PT		X
14.3.1.2.8.1	Adverse Device Effects Related to Procedure by SOC and PT- Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT	X	
14.3.1.2.8.2	Adverse Device Effects Related to Procedure by SOC and PT- Overall	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.8.3	Adverse Device Effects Related to Procedure by SOC and PT- Repeat-treatment Phase	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.9.1	Adverse Device Effects Related to Investigational Device by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT	X	
14.3.1.2.9.2	Adverse Device Effects Related to Investigational Device by SOC and PT – Overall	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.9.3	Adverse Device Effects Related to Investigational Device by SOC and PT - Repeat-treatment Phase	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.10.1	Serious Adverse Events by Maximum Relationship to Procedure and by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT	X	
14.3.1.2.10.2	Serious Adverse Events by Maximum Relationship to Procedure and by SOC and PT – Overall	SAF	Overall By treatment group		X

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
			By SOC and PT		
14.3.1.2.10.3	Serious Adverse Events by Maximum Relationship to Procedure and by SOC and PT – Repeat-treatment Phase	SAF	Overall By treatment group By SOC and PT		
14.3.1.2.11.1	Serious Adverse Events by Maximum Relationship to Investigational Device and by SOC and PT – Initial Treatment Phase	SAF	Overall By treatment group By relationship By SOC and PT	X	
14.3.1.2.11.2	Serious Adverse Events by Maximum Relationship to Investigational Device and by SOC and PT – Overall	SAF	Overall By treatment group By relationship By SOC and PT		X
14.3.1.2.11.3	Serious Adverse Events by Maximum Relationship to Investigational Device and by SOC and PT – Repeat-treatment Phase	SAF	Overall By treatment group By relationship By SOC and PT		X
14.3.1.2.12.1	Adverse Events of Special Interest by SOC and PT – Initial Treatment Phase	SAF	Overall By treatment group By SOC and PT	X	
14.3.1.2.12.2	Adverse Events of Special Interest by SOC and PT – Overall	SAF	Overall By treatment group By SOC and PT		X
14.3.1.2.12.3	Adverse Events of Special Interest by SOC and PT – Repeat-treatment Phase	mSAF	Overall By treatment group By SOC and PT		X
14.3.1.2.13.1	Adverse Events of Special Interest by Maximum Intensity by SOC and PT – Initial Treatment Phase	SAF	Overall By treatment group By intensity By SOC and PT	X	
14.3.1.2.13.2	Adverse Events of Special Interest by Maximum Intensity by SOC and PT – Overall	SAF	Overall By treatment group By intensity By SOC and PT		X
14.3.1.2.13.3	Adverse Events of Special Interest by Maximum Intensity by SOC and PT – Repeat-treatment Phase	mSAF	Overall By treatment group By intensity		X

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
			By SOC and PT		
14.3.1.2.14.1	Adverse Events of Special Interest by Maximum Relationship to Procedure and by SOC and PT – Initial Treatment Phase	SAF	Overall By treatment group By relationship By SOC and PT	X	
14.3.1.2.14.2	Adverse Events of Special Interest by Maximum Relationship to Procedure and by SOC and PT – Overall	SAF	Overall By treatment group By relationship By SOC and PT		X
14.3.1.2.14.3	Adverse Events of Special Interest by Maximum Relationship to Procedure and by SOC and PT – Repeat-treatment Phase	SAF	Overall By treatment group By relationship By SOC and PT		X
14.3.1.2.15.1	Adverse Events of Special Interest by Maximum Relationship to Investigational Device and by SOC and PT - Initial Treatment Phase	SAF	Overall By treatment group By relationship By SOC and PT	X	
14.3.1.2.15.2	Adverse Events of Special Interest by Maximum Relationship to Investigational Device and by SOC and PT – Overall	SAF	Overall By treatment group By relationship By SOC and PT		X
14.3.1.2.15.3	Adverse Events of Special Interest by Maximum Relationship to Investigational Device and by SOC and PT – Repeat-treatment Phase	SAF	Overall By treatment group By relationship By SOC and PT		X
14.3.2.1.1	Device Deficiencies - Initial Treatment Phase	SAF	Overall By treatment group	X	
14.3.2.1.2	Device Deficiencies - Overall	SAF	Overall By treatment group		X
14.3.2.1.3	Device Deficiencies - Repeat-treatment Phase	SAF	Overall By treatment group		X
14.3.2.2.1	Device Deficiencies by IMDRF Level 1 and Level 2 - Initial Treatment Phase	SAF	Overall By treatment group By IMDRF Levels 1 and 2	X	

Table / Figure	**Title**	**Analysis Population**	**Stratification / Subgroups**	**Compute for IA** Note: using data until cut-off as defined in section 5.4	**Compute for Final Analysis** Note: Using data from the whole study period
14.3.2.2.2	Device Deficiencies by IMDRF Level 1 and Level 2 - Overall	SAF	Overall By treatment group By IMDRF Levels 1 and 2		X
14.3.2.2.3	Device Deficiencies by IMDRF Level 1 and Level 2 - Repeat-treatment Phase	SAF	Overall By treatment group By IMDRF Levels 1 and 2		X
14.3.3.1.1	Initial Treatment Phase: Overview of Injection Site Reactions from Diary after Baseline Treatment	SAF	By treatment group By side and overall	X	
14.3.3.1.2	Initial Treatment Phase: Overview of Injection Site Reactions from Diary after Touch-up Treatment 1	SAF	By treatment group By side and overall	X	
14.3.3.1.3	Repeat Treatment Phase: Overview of Injection Site Reactions from Diary after Repeat Treatment	mSAF	By treatment group By side and overall		X
14.3.3.1.4	Repeat Treatment Phase: Overview of Injection Site Reactions from Diary after Touch-up Treatment 2	mSAF	By treatment group By side and overall		X
14.3.3.2.1	Initial Treatment Phase: Injection Site Reactions from Diary after Baseline Treatment (Duration: Descriptive Statistics, up to Touch-up Treatment 1 if received)	SAF	By treatment group By side and overall	X	
14.3.3.2.2	Initial Treatment Phase: Injection Site Reactions from Diary after Touch-up Treatment 1 (Duration: Descriptive Statistics) – SAF Table	SAF	By treatment group By side and overall	X	
14.3.3.2.3	Repeat Treatment Phase: Injection Site Reactions from Diary after Repeat Treatment (Duration: Descriptive Statistics, up to Touch-up Treatment 2 if received)	mSAF	By treatment group By side and overall		X
14.3.3.2.4	Repeat Treatment Phase: Injection Site Reactions from Diary after Touch-up Treatment 2 (Duration: Descriptive Statistics)	mSAF	By treatment group By side and overall		X
14.3.3.3.1	Initial Treatment Phase: Injection Site Reactions from Diary after Baseline	SAF	By treatment group	X	

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
	Treatment (Duration Categories, up to Touch-up Treatment 1 if received)		By side and overall		
14.3.3.3.2	Initial Treatment Phase: Injection Site Reactions from Diary after Baseline Treatment (Duration Categories, up to Touch-up Treatment 1) for Subjects who received Touch-up Treatment 1	SAF	By treatment group By side and overall	X	
14.3.3.3.3	Initial Treatment Phase: Injection Site Reactions from Diary after Baseline Treatment (Duration Categories) for Subjects who did not receive Touch-up Treatment 1	SAF	By treatment group By side and overall	X	
14.3.3.3.4	Initial Treatment Phase: Injection Site Reactions from Diary after Touch-up Treatment 1 (Duration Categories)	SAF	By treatment group By side and overall	X	
14.3.3.3.5	Repeat Treatment Phase: Injection Site Reactions from Diary after Repeat Treatment (Duration Categories, up to Touch-up Treatment 2 if received)	mSAF	By treatment group By side and overall		X
14.3.3.3.6	Repeat Treatment Phase: Injection Site Reactions from Diary after Repeat Treatment (Duration Categories, up to Touch-up Treatment 2) for Subjects who received Touch-up Treatment 2	mSAF	By treatment group By side and overall		X
14.3.3.3.7	Repeat Treatment Phase: Injection Site Reactions from Diary after Repeat Treatment (Duration Categories) for Subjects who did not receive Touch-up Treatment 2	mSAF	By treatment group By side and overall		X
14.3.3.3.8	Repeat Treatment Phase: Injection Site Reactions from Diary after Touch-up Treatment 2 (Duration Categories)	mSAF	By treatment group By side and overall		X
14.3.3.4.1	Initial Treatment Phase: Injection Site Reactions from Dairy after Baseline Treatment (Maximum Intensity)	SAF	By treatment group By side and overall By subgroups as defined in section 4.2	X	

Table / Figure	**Title**	**Analysis Population**	**Stratification / Subgroups**	**Compute for IA** Note: using data until cut-off as defined in section 5.4	**Compute for Final Analysis** Note: Using data from the whole study period
14.3.3.4.2	Initial Treatment Phase: Injection Site Reactions from Dairy after Touch-up Treatment 1 (Maximum Intensity)	SAF	By treatment group By side and overall By subgroups as defined in section 4.2	X	
14.3.3.4.3	Repeat Treatment Phase: Injection Site Reactions from Dairy after Repeat Treatment (Maximum Intensity)	mSAF	By treatment group By side and overall		X
14.3.3.4.4	Repeat Treatment Phase: Injection Site Reactions from Dairy after Touch-up Treatment 2 (Maximum Intensity)	mSAF	By treatment group By side and overall		X
14.3.3.5.1	Persisting Injection Site Reactions (including Serious Injection Site Reactions) by Maximum Intensity and by SOC and PT – Initial Treatment Phase	SAF	Overall By treatment group By intensity By SOC and PT	X	X
14.3.3.5.2	Persisting Injection Site Reactions (including Serious Injection Site Reactions) by Maximum Intensity and by SOC and PT - Repeat Treatment Phase	SAF	Overall By treatment group By intensity By SOC and PT		X
14.3.4.1.1.1	Visual Examination at Each Visit – Initial Treatment Phase	SAF	Overall By treatment group	X	
14.3.4.1.1.2	Visual Examination at Each Visit – Initial Treatment Phase for Subjects who received Touch-up Treatment 1	SAF	Overall By treatment group	X	
14.3.4.1.2.1	Visual Examination at Each Visit – Repeat-treatment Phase	mSAF	Overall By treatment group		X
14.3.4.1.2.2	Visual Examination at Each Visit – Repeat-treatment Phase for Subjects who received Touch-up Treatment 2	mSAF	Overall By treatment group		X
14.3.4.2.1.1	Visual Examination (Shift from Baseline) – Initial Treatment Phase	SAF	Overall By treatment group	X	
14.3.4.2.1.2	Visual Examination (Shift from Baseline) for Subjects who received Touch-up Treatment 1 – Initial Treatment Phase	SAF	Overall By treatment group	X	

Table / Figure	Title	Analysis Population	Stratification / Subgroups	Compute for IA Note: using data until cut-off as defined in section 5.4	Compute for Final Analysis Note: Using data from the whole study period
14.3.4.2.1.3	Visual Examination (Shift from Baseline) for Subjects who received Touch-up Treatment 1 – with last assessment before Touch-up Treatment 1 as baseline	SAF	Overall By treatment group	X	
14.3.4.2.2.1	Visual Examination (Shift from Baseline) – Repeat-treatment Phase	mSAF	Overall By treatment group		X
14.3.4.2.2.2	Visual Examination (Shift from Baseline) – Repeat-treatment Phase for Subjects who received Touch-up Treatment 2	mSAF	Overall By treatment group		X
14.3.4.2.2.3	Visual Examination (Shift from Baseline) – Repeat-treatment Phase for Subjects who received Touch-up Treatment 2 - with last assessment before Touch-up Treatment 2 as baseline	mSAF	Overall By treatment group		X

12.2. Table of Subject Data Listings

The numbering of statistical tables follows the ISO 14155 guideline. Shown abbreviations denote the analysis populations for which a variable will be listed. Please note that some listings may be split into sublistings covering different aspects of the data.

Listing	Title	Analysis Population
16.1.6	Application of Investigational Medical Device: Batches Used	SAF
16.1.7	Randomization	Randomized Subjects
16.2.1.1.1	Subject Disposition	Screened Subjects
16.2.1.1.2	Inclusion/Exclusion Criteria	Screening Failures
16.2.1.2	Study Completion and Withdrawal	ES
16.2.1.3	Performed Visits	ES
16.2.2.1	Major Protocol Deviations	ES
16.2.2.2	Minor Protocol Deviations	ES
16.2.3	Subjects Excluded from Analysis Populations and Reasons for Exclusion	ES
16.2.4.1	Demographic Data	SAF
16.2.5.1	Prior Medical Conditions / Aesthetic Facial Procedures	SAF

Listing	Title	Analysis Population
16.2.5.2	Concomitant Medical Conditions / Aesthetic Facial Procedures	SAF
16.2.5.3	Prior Non-Pharmacological Procedures	SAF
16.2.5.4	Concomitant Non-Pharmacological Procedures	SAF
16.2.5.5	Prior Medication	SAF
16.2.5.6	Concomitant Medication	SAF
16.2.7.1	Application of Investigational Medical Device: Baseline Treatment (Initial Treatment Phase)	SAF
16.2.7.2	Application of Investigational Medical Device: Touch-Up Treatment 1 (Initial Treatment Phase)	SAF
16.2.7.3	Application of Investigational Medical Device: Repeat-treatment (Repeat-treatment Phase)	SAF
16.2.7.4	Application of Investigational Medical Device: Touch-Up Treatment 2 (Repeat-treatment Phase)	SAF
16.2.7.5	Injection volume	
16.2.8.1	MVDSS Assessments	SAF
16.2.9.1	3D Volumetric Measurements	SAF
16.2.9.2	NLF-SRS	SAF
16.2.9.3	Modified GAIS Values (Subject and Blinded Evaluator at the Site)	SAF
16.2.9.4	FACE-Q Satisfaction with Outcome	SAF
16.2.9.5	FACE-Q Satisfaction with Cheeks	SAF
16.2.9.6	NPRS	SAF
16.2.10.1	Adverse Events	SAF
16.2.10.2.1	AEs leading to Discontinuation of Injection	SAF
16.2.10.2.2	AEs leading to Withdrawal of Subject	SAF
16.2.10.3	Serious Adverse Events (including Death)	SAF
16.2.10.4	Adverse Device Effects	SAF
16.2.10.5	Adverse Events of Special Interest	SAF
16.2.10.6	User/Other Person AEs	SAF
16.2.10.7	Device Deficiencies – Subject AEs	SAF
16.2.10.8	Device Deficiencies	SAF
16.2.10.9	Symptoms of Interest (Diary)	SAF
16.2.10.10	Injection Site Reactions (Diary)	SAF
16.2.11.1	Visual Examination	SAF
16.2.11.2	Visual Examination: Subjects with Snellen Test not performed adequately	SAF
16.2.12	Neurological Examination	SAF

Listing	Title	Analysis Population
16.2.13	Urine Pregnancy Test	SAF
16.2.14	Covid-19	SAF
16.2.15	Comments on CRF	

12.3. Layout of Tables and Listings

Issue	Specification
Basic layout of 'End-of-text' tables and listings (header, footnote)	3 horizontal lines per page: one above column headers, one below column headers, one below the body of the table or listing (footnotes below this last line). If necessary, additional lines can be added to ensure clarity. Footnotes for all tables and listings: `Program xxx.SAS, executed on DDMONYYYY at HH:MM`
= Page margins based on DIN-A4 sized page	For landscape: Top 3 cm, bottom 2 cm, left 2.5 cm, right 2 cm For portrait: Top 2.5 cm, bottom 2 cm, left 3 cm, right 2 cm
Column header	First letter of column capitalized (if applicable)
Subject or Patient as label?	Subject
Order in subject data listings	Subjects by Treatment group, Subject number and Visit (if applicable)
Labels and order of treatment groups	First saypha VOLUME Lidocaine, then [redacted]
Labels and order of visits	as appropriate
Labels for descriptive statistics for continuous variables	Use n, Mean, SD, Min, Q1, Median, Q3, Max (instead of N, arithmetic mean, standard deviation, minimum value, 1st quartile, median, 3rd quartile, and maximum value)
Display of categorical variables	Display all categories present in the data
In case a category does not occur	Display absolute frequency 0 (instead of "-") "-" should only be used if the category or table cell (e.g. concerning analysis results) is impossible
Display of absolute frequencies and percentages in tables	Frequencies are presented right aligned, followed by left aligned percentages in brackets. Percentages are presented with one decimal place, 0 and 100 percentages without any decimal place: xx (xx.x) x (x.x) 0 (0) Xxx (100) Percentages greater than 0 but rounded to 0.0 will be written as '<0.1'; percentages smaller than 100 but rounded to 100.0 will be written as '>99.9'.
P-values	P-values will be quoted with four decimal places; p-values which round to 0 will be reported as '<0.0001', p-values rounding to 1 will be displayed as '>0.9999'.

Issue	Specification
Display of 2-sided confidence intervals	[lower limit ; upper limit]
Display of 1-sided confidence intervals	[lower limit ; infinity)
Display of units	Presentation case-sensitive and in round brackets, e.g. Concentration (mg/dL)

12.4. Example SAS-Code

Primary Endpoint Analysis

The SAS code for computing the p-values and CIs for the primary endpoint analysis using a Farrington manning statistic will look like

```
PROC FREQ data=Example;
TABLES Resp_Mvdss*trt /
   riskdiff (noninf margin=.1 method=fm ) alpha=0.025;
RUN;
```

The code for performing deriving the CIs according to Miettinen and Nurminen will look like:

```
PROC FREQ data=proba;
   TABLES Mvdss_weekX*trt / riskdiff (cl=mn);
RUN;
```

For performing multiple imputation, in a first step, a monotone missing data pattern is created by MCMC for the MVDSS variables ordered by visit and treatment, like:

```
PROC MI nimpute=100 seed= 12345 out=dat_mon;
  BY treatment;
  MCMC impute = monotone;
  VAR Base_ Day7 ... Week24;
RUN;
```

Afterwards, for each imputation obtained in the first step a pattern-mixture model under the MNAR assumption is applied, based on all complete cases, like:

```
PROC MI data= dat_mon nimpute=1 out=mi_mvn simple;
  VAR Base_ Day7_...  Week24;
  BY _imputation_ treatment;
  MONOTONE method=reg;
  MNAR  model (Week24 / modelobs=CCMV);
RUN;
```

After that, the point estimates and corresponding standard errors are calculated by imputed dataset (merged pairwise), like:

```
ODS OUTPUT BINOMIAL=prop;

PROC FREQ data=datain_mi;
   TABLES trt*data / riskdiff;
```

```
   BY _Imputation_;
RUN;
```

After manipulating the output data set for further processing (resulting in a dataset prop_diff), MIANALYZE is performed for pooling of point estimates and standard errors into a single point estimate with associated 95% CIs:

```
PROC MIANALYZE DATA=prop_diff;
  MODELEFFECTS prop_diff;
  STDERR se_diff;
  ODS OUTPUT PARAMETERESTIMATES=mian_prop_diff;
RUN;
```

Subgroup analysis:

For the binary regression models investigating heterogeneity of treatment effects, code will look like:

```
PROC GENMOD data= example;
   CLASS trt age;
   MODEL response = trt age trt*age / dist=bin link=id lrci;
RUN;
```

12.5. Conversion Tables for FACE-Q™ Questionnaires

Satisfaction with outcome:

Instructions: Higher scores reflect a better outcome. If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best).

[redacted]

[redacted]

Satisfaction with cheeks:

Instructions: Higher scores reflect a better outcome. If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best).

[redacted]

12.6. Table of 'In Text' TFLs

Not applicable

12.7. Shells for TFLs

Shells for TFLs will be delivered in an extra document.

12.8. Raw Statistical Output

N/A

12.9. Deliverables

The following documents will be handed over to Croma-Pharma GmbH after study completion:

- A document containing all end-of text tables
- A document containing all end-of text figures
- A document containing all subject data listings
- A document containing the raw statistical output (Multiple Imputation)

Croma Volido SAP Final 2.0

Final Audit Report 2025-02-07

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