Statistical Analysis Plan for Interventional Studies

Sponsor Name: Croma- Pharma GmbH

Clinical Investigation Plan Number: CPH-301-201200F

Protocol Title: A randomized, subject- and evaluating investigator-blinded, controlled, multicenter, split-face, comparison clinical investigation to evaluate effectiveness and safety of Princess® FILLER Lidocaine in the correction of nasolabial folds

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Author(s): [redacted]

NCT03990883

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

[redacted]

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Glossary of Abbreviations

Abbreviation	Description
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASADE	Anticipated Serious Adverse Device Effect
ATC	Anatomical Therapeutic Chemical
BDDE	1,4-butanediol diglycidyl ether
BDRM	Blinded Data Review Meeting
BMI	Body Mass index
CE	European Conformity
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
FACE-Q	Patient-Reported Outcome (PRO) Questionnaires Measuring Experience and Outcomes of Aesthetic Facial Procedures
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic Acid
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IMD	Investigational Medical Device

Abbreviation	Description
ISO	International Organization for Standardization
Max	Maximum
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed-Effect Model for Repeated Measure
N/A	Not Applicable
NA	Not Applicable
NC	Non-Compliance
NLF-SRS	NLF Severity Rating Scale
NLF(s)	Nasolabial fold(s)
NPRS	Numeric Pain Rating Scale
PD	Protocol Deviation
PPS	Per-Protocol Analysis Set
PT	Preferred Term
QC	Quality Control
RBC	Red Blood Cell
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TFL	Table, Figure and Listing
U(S)ADE	Unanticipated (Serious) Adverse Device Effect
UV	Ultraviolet
WHO	World Health Organization

Abbreviation	Description
w/w	Weight/weight

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

1.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

1.2. Timings of Analyses

The primary analysis of safety and effectiveness is planned after all subjects complete the final study visit or terminate early from the study.

2. Study Objectives

2.1. Primary Objective

To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of nasolabial folds (NLFs) compared to Juvéderm® Ultra XC, based on the independent blinded evaluating investigator live assessment using the Nasolabial Folds Severity Rating Scale (NLF-SRS) at Week 24 after initial treatment and relative to Baseline assessments.

2.2. Secondary Objective(s)

1. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvéderm® Ultra XC, based on the independent blinded photographic reviewers assessments of photographs from Baseline and Week 24 after initial treatment
2. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvéderm® Ultra XC, based on the treating investigator live assessments at Week 24 after initial treatment, relative to Baseline assessments
3. To evaluate aesthetic improvement over Baseline after treatment using Global Aesthetic Improvement Score (GAIS), based on the independent blinded evaluating investigator assessment at Week 24 after initial treatment
4. To evaluate aesthetic improvement over Baseline after treatment using GAIS, based on the subject assessment at Week 24 after initial treatment

2.3. Additional Objectives

1. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared with Juvéderm® Ultra XC, based on the independent blinded evaluating investigator live assessments at Week 12, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) after initial treatment relative to Baseline assessments
2. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvéderm® Ultra XC, based on the independent blinded photographic reviewers assessments of photographs from Baseline and Week 12, 36, 48 and Visit 7c after initial treatment
3. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvéderm® Ultra XC, based on the treating investigator live assessments at Week 12, 36, 48 and Visit 7c after initial treatment relative to Baseline assessments
4. To evaluate aesthetic improvement over Baseline after treatment using GAIS, based on the independent blinded evaluating investigator assessments at Week 12, 36, 48 and Visit 7c after initial treatment
5. To evaluate aesthetic improvement over Baseline after treatment using GAIS, based on the subject assessments at Week 12, 36, 48 and Visit 7c after initial treatment
6. To assess subject satisfaction with aesthetic outcome after treatment at Week 12, 24, 36, 48 and Visit 7c after initial treatment
7. To assess subject appearance appraisal of nasolabial folds after treatment at Week 12, 24, 36, 48 and Visit 7c after initial treatment compared to Baseline
8. To evaluate subject's perception of pain after initial and repeat-treatment with Princess® FILLER Lidocaine and Juvéderm® Ultra XC
9. Time from initial to repeat-treatment for each treatment group

10. To assess injection volume (initial, touch-up and repeat-treatments, separate assessments) needed for optimal correction for Princess® FILLER Lidocaine and Juvéderm® Ultra XC

2.4. Safety Objectives

To assess frequency, severity, seriousness and causal relationship of adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs) and serious adverse device effects (SADEs) during the entire clinical investigation period including subject complaints recorded in the subject diaries during four weeks after initial- and touch-up-treatments, in comparison with Juvéderm® Ultra XC and during four weeks after repeat-treatments, for Princess® FILLER Lidocaine.

2.5. Brief Description

This is a randomized, subject- and evaluating investigator-blinded, controlled, multicenter, split-face comparison clinical investigation of Princess® FILLER Lidocaine compared to Juvéderm® Ultra XC in the treatment of moderate to severe NLFs.

Eligible subjects will be randomized at Baseline (Visit 2/Day 0) in a 1:1 ratio to Group A or Group B and will receive an injection of Princess® FILLER Lidocaine and an injection of Juvéderm® Ultra XC as folows:

Group A:

- Princess® FILLER Lidocaine on left NLF
- Juvéderm® Ultra XC on right NLF

Group B:

- Juvéderm® Ultra XC on left NLF
- Princess® FILLER Lidocaine on right NLF

The left NLF will be treated first and the right NLF thereafter.

The initial treatment will be administered at Baseline (Visit 2/Day 0) after randomization.

A touch-up treatment may be done at Visit 3a (Week 2) if an optimal aesthetic correction has not been achieved after initial treatment, as evaluated by the treating investigator. A touch-up treatment will be performed using the same type of device as initially applied.

A repeat-treatment may be done at Visit 6 (Week 36) or Visit 7 (Week 48) or Visit 7c (post repeat-treatment hold follow-up visit), if in the opinion of the treating investigator, the subject has returned to sufficient severity of NLFs that would have qualified them for enrollment into the clinical investigation initially. A repeat-treatment will be performed with Princess® FILLER Lidocaine on both NLFs.

Repeat-treatment:
Subjects who received repeat-treatment at Visit 6 (Week 36) or Visit 7 (Week 48) or Visit 7c (post repeat-treatment hold follow-up visit) will be included in the repeat-treatment subgroup, and the demographic, other baseline characteristics, medication, and applicable safety data will be analyzed by Group A, Group B, and repeat-treatment subgroup.

Subjects who received a repeat-treatment at Visit 6 (Week 36) will come back for safety follow-up visits at Visit 8a (Week 40) and at Visit 9a (Week 48). For these subjects, Visit 9a will be their end of study visit. Subjects who received a repeat-treatment at Visit 7 (Week 48) will come back for safety follow-up visits at Visit 8b (Week 52) and at Visit 9b (Week 60). For these subjects, Visit 9b will be their end of study

visit.Subjects who received a repeat-treatment at Visit 7c will come back for safety follow-up visits at Visit 8c (Week 4 after Visit 7c) and at Visit 9c (Week 12 after Visit 7c). For these subjects Visit 9c will be their end of study visit. Subjects, who do not qualify for any repeat-retreatment, will have their end of study visit at Visit 7c.

Follow-up visits for effectiveness will be performed at Week 2, 12, 24, 36, 48, and Visit 7c after initial treatment. Follow-up visits for safety will be performed at Week 2, 4, 6 (only if touch-up treatment occurred at Week 2), 12,24,36/48, 48/60, and at Visit 8c (Week 4 after Visit 7c), Visit 9c (Week 12 after Visit 7c) after initial treatment. In addition, subjects will be contacted by phone on Day 3 (±24 hours) after initial, touch-up and repeat-treatments for a safety check-up. Also at the end of each treatment session, subjects will receive a diary to record the injection site reactions, as well as the incidence of adverse events associated with unintended intravascular injection over the following four weeks after initial-, touch-up- and repeat-treatments.

NLFs severity will be independently evaluated (live assessment) by the treating investigator and by the independent blinded evaluating investigator, using the 5-point NLF-SRS (0 as None/minimal, 1 as Mild, 2 as Moderate, 3 as Severe, and 4 as Extreme).

The aesthetic improvement will be assessed by the subject and by the independent blinded evaluating investigator (separated assessments) using the GAIS.

In addition, NLFs severity will be assessed from photographs by three independent blinded photographic reviewers.

Subject satisfaction will be assessed by FACE-Q questionnaires on “Satisfaction with Outcome” and “Appraisal of Nasolabial Folds”.

Pain assessment will be done after initial and repeat-treatment in 15 min increments (starting 15 min after last injection and for 60 min post-treatment).

In order to evaluate any potential vision changes, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) will be additionally performed at Baseline (Visit 2) and at Week 4 (Visit 3b). Subjects receiving touch-up treatment (Week 2/Visit 3a) and subjects receiving repeat-treatment (Week 36/Visit 6 or Week 48/Visit 7 or Visit 7c) will be examined the same way as they would be at the Baseline (prior to- and 30 min after the treatment) and additional examinations will be performed four weeks after the treatment (at Week 6/Visit 3c after touch-up treatment and at Week 40/Visit 8a or at Week 52/Visit 8b or at Week 4 after Visit 7c/Visit 8c) and 12 weeks after repeat-treatment (at Week 48/Visit 9a or at Week 60/Visit 9b or at Week 12 after Visit 7c/Visit 9c).

The effectiveness of the investigational device will be assessed according to changes in NLFs severity compared to Baseline using the 5-point NLF-SRS, as assessed by the independent blinded evaluating investigator, the treating investigator and three independent blinded photographic reviewers, and compared to the results obtained using Juvéderm® XC.

2.6. Subject Selection

Approximately 270 subjects will be randomized (300 screened; accounting for a screening failure rate of around 10%) to obtain at least 240 evaluable subjects, accounting for a combined drop-out and major protocol deviations rate of approximately 10%. The investigation is planned to be conducted at approximately 10 – 12 US sites with enrollment target of 23-27 subjects per site. Competitive recruitment will be allowed to stimulate enrollment, but no site will be allowed to enroll more than 54 subjects (20%) unless prior approval of the sponsor is given; in this case, the maximum number of subjects per site is capped at 68 (25%). This will maintain adequate balance between the investigational sites.

2.6.1. Inclusion Criteria

Subjects who meet **ALL** the following criteria are eligible for this clinical investigation:

1. Male or female subjects aged ≥ 22 years at Screening Visit
2. Subjects with two fully visible, approximately symmetrical moderate to severe nasolabial folds (same severity) with severity scores of 2 or 3 (moderate or severe) on the 5-point NLF-SRS for both NLFs as judged by the treating investigator in conjunction with the independent blinded evaluating investigator
3. Females of childbearing potential must have a negative urine pregnancy test at injection visits and must agree to use an adequate method of contraception for the duration of the clinical investigation
4. Healthy skin in the nasolabial area and free of diseases that could interfere in cutaneous aging evaluation and/or injection
5. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation, including botulinum toxin injections (except glabella or forehead botulinum toxin treatment)
6. Subjects having understood the purpose and conduct of the clinical investigation, having given written informed consent, and are willing and able to adhere to the Clinical Investigation Plan (CIP)

2.6.2. Exclusion Criteria

Subjects who meet **ANY** of the following criteria are **NOT** eligible for this study:

1. For females: pregnant and/or lactating or planning to become pregnant during the clinical investigation
2. History of allergies or hypersensitivity to hyaluronic acid preparations, lidocaine or anesthetics of any amide-based anesthetic
3. Since Juvéderm® Ultra XC contains trace amounts of Gram-positive bacterial proteins, subjects with history of allergies to such material can not be included in this clinical investigation
4. Tendency to keloid formation, hypertrophic scars and/or pigmentation disorders
5. Known human immune deficiency virus-positive individuals
6. Presence of infectious, inflammatory or proliferative cancerous or pre-cancerous lesions in the area to be treated
7. Recurrent herpes simplex in the treatment area
8. History or presence of any autoimmune or connective tissue disease, or current treatment with immunomodulating therapy
9. Uncontrolled (or instable) diabetes mellitus or systemic diseases
10. Facial plastic surgery, tissue augmentation with silicone, fat or another non-absorbable substance (permanent fillers) in the area of device application
11. Implantation of facial dermal fillers in the treatment area in the preceding twelve months
12. Skin of the nasolabial region affected by aesthetic treatments (e.g. laser therapy, absorbable and non-absorbable sutures (threads), microneedling and/or botulinum toxin within the last twelve

months, dermabrasion and mesotherapy within the last six months, chemical peeling within the last three months) or planning to undergo such procedures during the clinical investigation
13. Facial lipolysis, including submental fat treatments, within last month prior to enrollment and during the clinical investigation
14. Bariatric surgery within 12 months prior to enrollment and during the clinical investigation
15. History of bleeding disorder and/or use of anticoagulant, antiplatelet or thrombolytic medication from ten days pre- to three days post injection
16. Planned dental/oral surgery or modification (bridge-work, implants) within two weeks prior to injection and to a minimum of four weeks post injection
17. Any medical condition prohibiting the inclusion in the clinical investigation according to the judgment of the treating investigator
18. Previous enrollment in this clinical investigation
19. Current participation in another clinical investigation, or treatment with any investigational drug/medical device within 30 days prior to clinical investigation enrollment, or five half-lives of the investigational drug, whichever is longer
20. Any dependency of the subject to the treating investigator, the blinded independent evaluating investigator or clinical investigation site (e.g. employees of the sponsor), or subjects who are employees or relatives of the treating investigator and/or the independent blinded evaluating investigator
21. Subjects who have one of the following assessments during the visual examinations at Baseline: Snellen visual acuity test worse than 20/40 (with corrective eyewear, if applicable), abnormal confrontational visual field test, or abnormal ocular motility test.

2.6.3. Inclusion Criteria - Repeat-treatment

Subjects who meet **ALL** the following criteria are eligible for a repeat-treatment:

1. In the opinion of the treating investigator, the subject has returned to sufficient severity of both NLFs that would have qualified him for enrollment into the clinical investigation initially (note that the subject does not have to return to his Baseline severity to be permitted to receive a repeat treatment)
2. Subjects with NLFs with severity scores of 2 or 3 on the 5 point NLF-SRS for both NLFs as judged by the treating investigator in conjunction with the independent blinded evaluating investigator (note that it is not necessary for the treating and evaluating investigator to agree on the same rating)
3. Females of childbearing age must have a negative urine pregnancy test at the repeat-treatment visit and must agree to continue to use an adequate method of contraception for the duration of the clinical investigation
4. Healthy skin in the nasolabial area and free of diseases that could interfere in cutaneous aging evaluation and/or injection

2.6.4. Exclusion Criteria - Repeat-treatment

Subjects who meet **ANY** of the following criteria are **NOT** eligible for a repeat-treatment:

1. Occurrence of a serious adverse event or adverse event of special interest (i.e. changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes, changes in peripheral vision], skin changing color around the eyelids or around the site of injection) during or after the initial injection and/or touch-up injection
2. Subjects who experienced visual changes or other serious medical conditions during or after the initial/touch-up injection
3. Subjects who have one of the following assessments during the visual examinations:
    - Snellen acuity test worse than 20/40 (with corrective eyewear, if applicable)

- Abnormal confrontational visual field test
- Abnormal ocular motility test

4. Subjects who became pregnant since start of the study or are planning to become pregnant during the clinical investigation
5. Known human immune deficiency virus-positive individuals
6. Presence of infectious, inflammatory or proliferative cancerous or pre-cancerous lesions in the area to be treated
7. Development of recurrent herpes simplex in the treatment area since study start
8. Development of any autoimmune or connective tissue disease since start of participation in the study, or current treatment with immunomodulating therapy
9. Development of uncontrolled (or instable) diabetes mellitus or any other systemic disease since study start
10. Development of a bleeding disorder since study start or use of anticoagulant, antiplatelet or thrombolytic medication from ten days pre- to three days post injection
11. Planned dental/oral surgery or modification (bridge-work, implants) within 2 weeks prior to injection and to a minimum of four weeks post injection
12. Any medical condition prohibiting the inclusion for repeat treatment according to the judgement of the treating investigator

2.7. Determination of Sample Size

The primary effectiveness outcome measure will be evaluated by the one-sided 95% confidence interval of the difference between paired proportions p_A-p_B. At this, p_A is the response rate for Princess® FILLER Lidocaine and p_B is the response rate for Juvéderm® Ultra XC. Thus, a negative value of this difference means that the response rate of Princess® FILLER Lidocaine is lower than the response rate for Juvéderm® Ultra XC. Princess® FILLER Lidocaine will be considered non-inferior to Juvéderm® Ultra XC if the lower confidence limit does not exceed the non-inferiority margin of -10%.

Further assumptions for sample size calculation:

- Response rate at Week 24 for Juvéderm® Ultra XC is 88%
- Response rate at Week 24 for Princess® FILLER Lidocaine is 87%
- Proportion of subjects with response only in one NLF: 21.9% (88.0% * 13.0% + 87.0% * 12.0% = 21.9%)
- Proportion of subjects with response in both NLFs: 76.5% (88.0% * 87.0% = 76.5%)

The latter two proportions were calculated on the basis of the response rates for Princess® FILLER Lidocaine and Juvéderm® Ultra XC assuming that the two NLFs of one subject are independent. Since there should be a concordant correlation between the two nasolabial folds of one subject, this assumption is considered to be conservative.

Based on these assumptions, 222 subjects will be necessary in order to achieve a power of 90%.

Sample size calculation was done using nQuery Advisor® 7.0. The result is based on 1600 simulations using the Newcombe-Wilson score method to construct the confidence interval.

2.8. Treatment Assignment and Blinding

Randomization will be performed at Baseline (Visit 2) per clinical investigation site via interactive web response system (IWRS). Each participant will receive Princess® FILLER Lidocaine in one NLF and Juvéderm® Ultra XC in the contralateral NLF, with allocation of respective fillers to the sides randomized as follows:

Group A:

- Princess® FILLER Lidocaine on left NLF
- Juvéderm® Ultra XC on right NLF

Group B:

- Juvéderm® Ultra XC on left NLF
- Princess® FILLER Lidocaine on right NLF

The treating investigator performing the treatment will be aware of the device injected (unblinded treating investigator).

The independent blinded evaluating investigator will not be aware of the device injected.

The subject will be blinded using a blindfold.

Moreover, an evaluation of NLFs severity by three independent blinded photographic reviewers using the 5-point NLF-SRS and based on photographs will take place at the end of the clinical investigation. Each of the three independent blinded photographic reviewers will review all photographs. These independent blinded photographic reviewers, will not be aware of the treatment allocation. They will be dislocated from the clinical investigational sites, will have no access to randomization schedule, and will not discuss any findings with the treating investigators or independent blinded evaluating investigators during the clinical investigation and until the final database lock.

The randomization assignment should not be revealed before the database has been cleaned and closed.

Emergency unblinding

There will be no special procedure for emergency unblinding because the treating investigators will be aware of the treatment allocation, and the subjects will know that they have received a hyaluronic acid dermal filler with lidocaine, which is, in both cases, sufficient level of information needed in case of emergency.

2.9. Administration of Study Medication

On Day 0 (Visit 2), the Princess® FILLER Lidocaine will be injected to one NLF and the control Juvéderm® Ultra XC to the contralateral NLF of each subject, according to the randomization scheme; the left NLF will be treated first and the right NLF thereafter.

The decision to perform touch-up treatment is in the responsibility of the treating investigator and aim to obtain optimal aesthetic result, if not already achieved with the initial treatment.

A repeat-treatment will be performed with Princess® FILLER Lidocaine on both NLFs.

2.10. Study Procedures and Flowchart

All study assessments will be performed at the visits oultlined in the events schedules (Table 1).

Table 1 Schedule of Clinical Investigation Procedures and Assessments

					Follow-up for initial -/touch-up treatment					Evaluation for repeat-treatment/repeat-treatment[4]				Follow-up for repeat- treatment[5]	
	Screen-ing[1]	Baseline[1]	Day 3	Touch-up	Day 3 after touch-up treatment	4 Weeks Follow-up	6 Weeks Follow-up	12 Weeks Follow-up	24 Weeks Follow-up	36 Weeks Follow-up[13]	Day 3 after Repeat treatment	48 Weeks Follow-up[13]	Day 3 after Repeat treatment	4 Weeks Follow up after repeat-treatment at Visit 6 or 7	12 Weeks Follow up after repeat-treatment at Visit 6 or 7
	Visit 1	Visit 2	Phone C. [11]	Visit 3a[2]	Phone C.[3,11]	Visit 3b	Visit 3c	Visit 4	Visit 5	Visit 6	Phone C. [11]	Visit 7	Phone C. [11]	Visit 8a/8b	Visit 9a/9b
	Day-14 to Day 0	Day 0	Day 3 (± 1 day)	Week 2 (± 3 days)	Day 3 after Visit 3a (± 1 day)	Week 4 (± 5 days)	Week 6 (± 5 days)	Week 12 (±5 days)	Week 24 (±5 days)	Week 36 (±5 days)	Day 3 after Visit 6 (± 1 day)	Week 48 (±5 days)	Day 3 after Visit 7 (± 1 day)	Week 40 OR Week 52 (± 5 days)	Week 48 (±5 days) OR Week 60(±5 days)
Procedure															
Informed consent	X														
Medical /aesthetic procedures history[a]	X														
Demographics[b]	X														
Fitzpatrick skin type	X														
Body weight		X		X		X	X	X	X	X		X		X	X
Visual examinations[c]		X		X[2]		X	X[8]			X[10]		X[10]		X[10]	X[10]
Eligibility assessment	X									X[5, 6]		X[5,6]			
Randomization		X[6]													
Treatment		X		X[7]						X[9]		X[9]			
Urine pregnancy test[d]	X	X[6]		X[6,8]						X[6,10]		X[6,10]			
NLF-SRS[e]	X							X	X	X[6]		X[6]			
Clinical photography[f]	X	X[6]						X	X	X[6]		X[6]			
FACE-Q subject "Satisfaction with Outcome"[g]								X	X	X[6]		X[6]			
FACE-Q subject appearance "Appraisal of NLFs"[h]		X[6]						X	X	X[6]		X[6]			
GAIS[i] independent blinded evaluating investigator								X	X	X[6]		X[6]			
GAIS[i] subject								X	X	X[6]		X[6]			
Dispense subject diary		X		X		X[8]				X[10]		X[10]			
Collect subject diary[j]				X		X	X[8]							X[10]	
Evaluation of pain[k]		X								X[10]		X[10]			
Injection volume		X		X[7]						X[9]		X[9]			
Concomitant medications/procedures		X[6]	X	X[6]	X	X	X	X	X	X[6]	X	X[6]	X	X	X[10]
Adverse events		X[6]	X	X[6]	X	X	X	X	X	X[6]	X	X[6]	X	X	X[10]

	Evaluation for repeat-treatment after repeat treatment hold/repeat-treatment[4, 13]		**Follow-up for repeat- treatment[5]**	
	Post repeat-treatment hold Follow-up	**Day 3 after Repeat treatment at Visit 7c**	**4 Weeks Follow up after repeat-treatment at Visit 7c**	**12 Weeks Follow up after repeat-treatment at Visit7c**
	Visit 7c	**Phone C.[11]**	**Visit 8c**	**Visit 9c**
	-	**Day 3 after Visit 7c (± 1 day)**	**Week 4 after Visit 7c (± 5 days)**	**Week 12 after Visit 7c (± 5 days)**
Procedure				
Informed consent				
Medical /aesthetic procedures history[a]				
Demographics[b]				
Fitzpatrick skin type				
Body weight	X		X	X
Visual examinations[c]	X[10]		X[10]	X[10]
Eligibility assessment	X[5,6]			
Randomization				
Treatment	X[9]			
Urine pregnancy test[d]	X[6,10]			
NLF-SRS[e]	X[6]			
Clinical photography[f]	X[6]			
FACE-Q subject "Satisfaction with Outcome"[g]	X[6]			
FACE-Q subject appearance "Appraisal of NLFs"[h]	X[6]			
GAIS[i] independent blinded evaluating investigator	X[6]			
GAIS[i] subject	X[6]			
Dispense subject diary	X[10]			
Collect subject diary[i]			X[10]	
Evaluation of pain[k]	X[10]			
Injection volume	X[9]			
Concomitant medications/procedures	X[6]	X	X	X[10]
Adverse events	X[6]	X	X	X[10]

1	Screening and Baseline visits may be performed as one visit
2	Evaluation at Week 2 if a touch-up treatment is needed for optimal correction
3	Concerning only subjects who received a touch-up treatment
4	Evaluation if a repeat-treatment is needed will be performed at Week 36 (Visit 6) AND/OR at Week 48 (Visit 7) AND/OR Post repeat-treatment hold Follow-up (Visit 7c) according to the criteria presented in Section 2.6 of the protocol
5	The first Follow-up visit for repeat-treatment will take place four4 weeks (± 5 days) after repeat-treatment, i.e. at Week 40 (Visit 8a) for repeat-treatment at Week 36, and at Week 52 (Visit 8b) for repeat-treatment at Week 48. The. The second Follow-up visit for repeat-treatment will take place twelve12 weeks ((±(± 5 days) after repeat-treatment, i.e. at Week 48 (Visit 9a) for repeat-treatment at Week 36, and at Week 60) (Visit 9b) for repeat treatment at Week 48.
6	Prior to the treatment or any procedure, as applicable
7	Touch-up treatment if appropriate for optimal correction
8	Only if touch-up treatment occurred at Week 2
9	Repeat-treatment at Week 36 (Visit 6) OR Week 48 (Visit 7) OR Post repeat-treatment hold Follow-up (Visit 7c)
10	Only if repeat-treatment occurred at Week 36 (Visit 6) OR Week 48 (Visit 7) OR Post repeat-treatment hold Follow-up (Visit 7c)
11	All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection
12	Exclusion criterion based on visual examinations at Baseline
13	If a subject was not evaluated for repeat-treatment at Week 36 (Visit 6) and/or Week 48 (Visit 7) due to the hold on repeat-treatment, the subject could attend Visit 7c for evaluation and repeat -treatment (if eligible)
a	Includes information on prior medication, defined as all medication taken/received within the previous ten days
b	Includes date of birth, sex, race and ethnicity
c	Visual examinations (including Snellen visual accuity, confrontational visual fields and ocular motility) to be performed at Baseline and at Week 4; in case of touch-up treatment, to be done as well at Week 2 and at Week 6; in case of repeat-treatment, to be perfomed at 4 and 12 weeks after repeat-treatment visit. To be performed prior to- and 30 min after any treatment after all other assessments. The subject should wear the same corrective eyewear (i.e. glasses/contact lenses) at each assessment, if appropriate. The definition of clinically significant changes and action to be taken is presented in Section 10.8.4 of the protocol.
d	In women of childbearing potential only, including those who are postmenopausal for less than twelve months
e	Evaluation and grading of nasolabial folds severity by the treating investigator and by the independent blinded evaluating investigator (separate assessments) will be done using the 5-point NLF-SRS. The Baseline severity is the severity grade assigned at Screening as determined by the treating investigator in conjunction with the independent blinded evaluator. The left and right cheek will be separately evaluated.
f	Clinical photography will be performed; the evaluation and grading of nasolabial folds severity by the independent blinded photographic reviewers using the 5-point NLF-SRS and based on photographs will take place at the end of the clinical investigation. The left and right cheek will be separately evaluated
g	Evaluation of subject satisfaction using the FACE-Q questionnaire “Satisfaction with Outcome”
h	Evaluation of subject appearance appraisal using the FACE-Q questionnaire on ”Appraisal of Nasolabial Folds”
i	Evaluation of aesthetic improvement using the Global Aesthetic Improvement Scale (GAIS)
j	Subject diary to be collected and reviewed two and four weeks after initial-/touch-up treatment, and four weeks after repeat-treatment
k	Starting 15 min after last injection and at 15 min-intervals for 60 min post-treatment using the adapted NPRS.

3. Outcome Measures

The outcome measures will be separately evaluated for the left and right side of the face.

Responder is defined as having at least one grade improvement over Baseline, on the 5-point NLF-SRS.

3.1. Primary Effectiveness Outcome Measures

The percentage of responders based on the independent blinded evaluating investigator live assessment at Week 24 after initial treatment and compared to Juvéderm® Ultra XC. NLF-SRS scores are ranked as 0 (None/minimal), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Extreme).

3.2. Secondary Effectiveness Outcome Measures

1. The percentage of responders based on the independent blinded photographic reviewers assessments at Week 24 after initial treatment, compared to Juvéderm® Ultra XC and based on photographs
2. The percentage of responders based on the treating investigator live assessment at Week 24 after initial treatment and compared to Juvéderm® Ultra XC
3. The percentage of subjects with an improvement over Baseline (subjects who have been rated as “very much improved” or “much improved” or “improved”), based on the independent blinded evaluating investigator assessment at Week 24 after initial treatment and using the 5-point GAIS
4. The percentage of subjects with an improvement over Baseline (subjects who have been rated as “very much improved” or “much improved” or “improved”), based on subject assessment at Week 24 after initial treatment and using the 5-point GAIS

3.3. Additional Effectiveness Outcome Measures

1. The percentage of responders based on the independent blinded evaluating investigator live assessment at Week 12, 36, 48 and Visit 7c after initial treatment and compared to Juvéderm® Ultra XC
2. The percentage of responders based on the independent blinded photographic reviewers assessments at Week 12, 36, 48 and Visit 7c after initial treatment, compared to Juvéderm® Ultra XC and based on photographs
3. The percentage of responders based on the treating investigator live assessment at Week 12, 36, 48 and Visit 7c after initial treatment and compared to Juvéderm® Ultra XC
4. The percentage of subjects with an improvement over Baseline (subjects who have been rated as “very much improved” or “much improved” or “improved”), based on the independent blinded evaluating investigator assessment at Week 12, 36, 48 and Visit 7c after initial treatment and using the 5-point GAIS
5. The percentage of subjects with an improvement over Baseline (subjects who have been rated as “very much improved” or “much improved” or “improved”), based on subject assessment at Week 12, 36, 48 and Visit 7c after initial treatment and using the 5-point GAIS
6. The extent of subject satisfaction with outcome of the treatment, as assessed by the Face-Q questionnaire “Satisfaction with Outcome” at Week 12, 24, 36, 48 and Visit 7c after initial treatment
7. Subject appearance appraisal after treatment as assessed by the Face-Q questionnaire “Appraisal of Nasolabial Folds” at Week 12, 24, 36, 48 and Visit 7c after initial treatment, relative to Baseline
8. Subject’s perception of pain after initial with Princess® FILLER Lidocaine and with Juvéderm® Ultra XC and after repeat-treatment with Princess® FILLER Lidocaine, using a scale adapted from the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable.

9. Time from initial to repeat-treatment for each treatment group will be assessed by tabulating the following rates:
   - repeat-treatment at Week 36
   - repeat-treatment at Week 48
   - repeat-treatment at Visit 7c
   - no repeat-treatment
10. Recording of injection volume required to achieve optimal correction for Princess® FILLER Lidocaine and Juvéderm® Ultra XC at initial and touch-up treatments and recording of injection volume required to achieve optimal correction for Princess® FILLER Lidocaine at repeat-treatments (separate assessments)

3.4. Safety Outcome Measures

Frequency, severity, seriousness and causal relationship of AEs, ADEs, SAEs and SADEs during the entire clinical investigation period including subject complaints recorded in the subject diaries during four weeks after initial- and touch-up- treatments, in comparison with Juvéderm® Ultra XC and during four weeks after repeat-treatments, for Princess® FILLER Lidocaine.

4. Analysis Sets

4.1. Screened / Randomized Set

The Screened Set will include all subjects who give informed consent and are screened. Unless specified otherwise, this set will be used for summaries of subject disposition.

The Randomized Set will include all subjects randomized. Unless specified otherwise, this set will be used for all subject listings with exception of the listing presenting screening failures and the respective reason(s) for screen failure.

4.2. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized subjects who received Princess® FILLER Lidocaine AND the control Juvéderm® Ultra XC at the same visit as initial treatment; subjects who receive only one treatment (only Princess® FILLER Lidocaine or only Juvéderm® Ultra XC) during initial treatment will be excluded from the FAS. The analyses based on the FAS will use the randomized treatment groups.

The FAS will be used for effectiveness, demographic, and other baseline characteristics analyses.

4.3. Per-Protocol Set

The Per-Protocol Set (PPS) is defined as a subset of the subjects in the FAS who had no major protocol deviations upto Week 24. Subjects with randomization errors will be considered as major protocol deviations and excluded from PPS.

The PPS will be used for effectiveness analysis.

4.4. Safety Analysis Set

The Safety Analysis Set (SAF) comprises all subjects who were randomized and received at least one treatment (i.e., any dose of Princess® FILLER Lidocaine or the control medical device). The analyses based on the SAF will use the actual treatment groups.

The SAF will be used for all analyses of safety endpoints.

4.5. Protocol Deviation and Non-Compliances

Non-compliances are unplanned deviations from applicable regulations, guidelines, other standards, controlled documents, contractual agreements, and/or protocol or project specific requirements. Any change, divergence, or departure from the study design or procedures defined in the protocol; a subset of non-compliances occurring at an individual subject level, or deviations that are related to COVID-19 are defined as protocol deviations (PDs).

All subjects who comply with criteria for inclusion into FAS, PPS and SAF, as defined in section 4, will be included in respective analyses.

Protocol deviations will be identified (in a blind manner) and discussed throughout the study. Prior to database lock, all protocol deviations will be listed in a blinded manner. Their relevance (minor / major) and their impact on the effectiveness assessments, i.e., with respect to exclusion of subjects from PPS and/or FAS will be evaluated in the Blind Data Review Meeting (BDRM). Possible major protocol deviations may include but are not limited to deviations related to premature termination, the inclusion and exclusion criteria, and prohibited concomitant treatments.

For the preparation of the BDRM, subject listings will be generated with all protocol deviations and non-compliances identified from eCRF entries and from monitoring documentation system. These listings

will be reviewed by Croma Pharma and SH study team. The final decision with regards to protocol deviations and populations will be taken in the BDRM.

The number and percentage of subjects with a protocol deviation by type of deviation category will be presented by treatment group. In addition, protocol deviations related to COVID-19 will be summarized in a similar fashion.

All protocol deviations will be provided in a by-subject listing with the categorization of minor or major. Protocol deviations related to COVID-19 will be listed separately.

Primary reasons and categories of the PDs at individual subject levels are:

- Concomitant Medication
- Dosing
- Enrollment Criteria
- Informed Consent
- Laboratory
- Non-compliance
- Other
- Regulatory
- Visit Schedule
- Visit/Procedure Required

5. Estimands

5.1. Primary Effectiveness Endpoint

The estimand for the primary effectiveness endpoint is defined as follows:

- Treatment: Princess® FILLER Lidocaine and Juvéderm® Ultra XC for the treatment of NLF (both sides) in each subject.
- Population: Of all subjects defined by the study inclusion / exclusion criteria, the analysis population will include subjects who were randomized to the study treatment and received both treatments (Princess® FILLER Lidocaine and the control medical device) as initial treatment at the same visit (FAS population).
- Variable: A binary variable indicating the subject is alive and has a NLF-SRS response based on the independent blinded evaluating investigator live assessment using the NLF-SRS at Week 24 after initial treatment and relative to baseline assessments. NLF-SRS responder with regards to each specific NLF is defined as a subject with at least one grade improvement from baseline in NLF-SRS in that NLF.
- Intercurrent events:
    - The intercurrent event 'death' is very unlikely in this study, however, in case of death prior to Week 24, this will be considered as non-response following the composite strategy.
    - Major protocol deviations impacting the NLF-SRS assessment will be handled using the treatment-policy strategy, i.e., the NLF-SRS value at Week 24 will be used for categorization of response.
- Population-level summary: Paired difference of NLF-SRS response rates between Princess® FILLER Lidocaine and the control medical device for non-inferiority comparison.

Study discontinuation (due to any reason) prior to Week 24 is not considered as an intercurrent event, however this will lead to missing Week 24 values, which will be imputed using single imputation strategy as non-response for the primary analysis of this estimand. Subjects with missing NLF-SRS value at Baseline will be considered as non-response for the primary analysis of this estimand.

5.2. Key Secondary Effectiveness Endpoint 1

The estimand for the key secondary effectiveness endpoint 1 is defined as follows:

- Treatment: Princess® FILLER Lidocaine and Juvéderm® Ultra XC for the treatment of NLF (both sides) in each subject.
- Population: Of all subjects defined by the study inclusion / exclusion criteria, the analysis population will include subjects who were randomized to the study treatment and received both treatments (Princess® FILLER Lidocaine and the control medical device) as initial treatment at the same visit (FAS population).
- Variable: A binary variable indicating the subject is alive and has NLF-SRS response based on the independent blinded photographic reviewers (I, II,and III) assessments of photograph (NLF severity) using the NLF-SRS at Week 24 after initial treatment compared to baseline. NLF-SRS responder with regards to each specific NLF is defined as a subject with at least one grade improvement from baseline in NLF-SRS in that NLF.
- Intercurrent events:
    - The intercurrent event 'death' is very unlikely in this study, however, in case of death prior to Week 24, this will be considered as non-response following the composite strategy.

    - Major protocol deviations impacting the NLF-SRS assessment will be handled using the treatment-policy strategy, i.e., the NLF-SRS value at Week 24 will be used for categorization of response.
- Population-level summary: Paired difference of NLF-SRS response rates between Princess® FILLER Lidocaine and the control medical device for non-inferiority comparison.

Missing data imputation for this estimand will be performed as described for the primary estimand.

5.3. Key Secondary Effectiveness Endpoint 2

The estimand for the key secondary effectiveness endpoint 2 is defined as follows:

- Treatment: Princess® FILLER Lidocaine and Juvéderm® Ultra XC for the treatment of NLF (both sides) in each subject.
- Population: Of all subjects defined by the study inclusion / exclusion criteria, the analysis population will include subjects who were randomized to the study treatment and received both treatments (Princess® FILLER Lidocaine and the control medical device) as initial treatment at the same visit (FAS population).
- Variable: A binary variable indicating subject is alive and has NLF-SRS response based on the treating investigator live assessment using the NLF-SRS at Week 24 after initial treatment compared to baseline. NLF-SRS responder with regards to each specific NLF is defined as a subject with at least one grade improvement from baseline in NLF-SRS in that NLF.
- Intercurrent events:
    - The intercurrent event ‘death’ is very unlikely in this study, however, in case of death prior to Week 24, this will be considered as non-response following the composite strategy.
    - Major protocol deviations impacting the NLF-SRS assessment will be handled using the treatment-policy strategy, i.e., the NLF-SRS value at Week 24 will be used for categorization of response.
- Population-level summary: Paired difference of NLF-SRS response rates between Princess® FILLER Lidocaine and the control medical device for non-inferiority comparison.

Missing data imputation for this estimand will be performed as described for the primary estimand.

6. General Aspects for Statistical Analysis

6.1. General Methods

- All analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4.
- Unless otherwise specified, summaries for disposition and demography will be presented by treatment group and overall, all other summaries will be presented by treatment/treatment group.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects. Summary statistics will be presented to the following degree of precision (seeTable 2):

Table 2 Reporting Precision

Statistics	Degree of Precision
Mean, Median, Confidence limit boundaries	One more decimal place than the raw data e.g. if data is displayed to 3 decimal places: data=0.xxx, output=0.xxxx
Standard deviation (SD)	Two more decimal places than the raw data e.g. if data is displayed to 3 decimal places: data=0.xxx, output=0.xxxxx
Minimum, Maximum	The same number of decimal places as the raw data
P-value	Rounded to 3 decimal places and formatted as 0.xxx; P-values smaller than 0.001 as '<0.001'; P-values smaller than 0.0001 as '<0.0001'
Percent	One decimal place

- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.

6.2. Key Definitions

The study day is the day relative to the date of first administration of Investigational Medical Device (IMD), where Day 1 is the day of first administration of IMD.

The first dose date is defined as the first non-missing date where an administration of IMD was recorded. The last dose date is defined as the last non-missing date where an administration of IMD was recorded.

For on-treatment events (on or after first dosing day), Study Day = Event Date - date of first administration of IMD + 1; and for pre-treatment events (prior to first dosing day), Study Day = Event Date - administration of IMD.

Unless otherwise specified, baseline is the last non-missing observation before the administration of IMD, which is expected to be Day 1, or Screening if the Day 1 data are not available.

6.3. Missing Data

For safety analysis missing data will not be estimated and/or imputed in any way. All subjects who withdraw prematurely from the study will be documented and the reason for withdrawal will be reported in the Clinical investigation report. All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to analysis data sets.

In case of an AE/ ADE with partial/ missing start/ stop dates, the rules outlined in Section 9.3 will be applied.

Subjects with missing NLF-SRS grades at Baseline and/or at Week 24 will be considered as non-responders for the primary analysis. Since it is very unlikely that the assessment of only one NLF will be missing, presumably either no or both assessments will be available for one subject at a certain time point. Therefore, this imputation method will probably decrease the response rate in both treatment groups simultaneously. Due to the fact that the sample size calculation was based on rather high response rates (88% for Juvéderm® Ultra XC and 87% for Princess® FILLER Lidocaine), lower response rates will make it more difficult to demonstrate non-inferiority of Princess® FILLER Lidocaine and thus this approach is considered to be conservative. In addition to this approach, a complete case analysis (using the available data without any imputation), a best-case analysis (missing values for Princess® FILLER Lidocaine will be considered as a response, missing values for Juvéderm® Ultra XC will be considered as a non-response), a worst-case analysis (missing values for Princess® FILLER Lidocaine will be considered as a non-response, missing values for Juvéderm® Ultra XC will be considered as a response), and a tipping point analysis will be conducted as sensitivity analyses.

6.4. Visit Windows

There are no plans to derive visit windows; visits will be used in the analyses as reported on the electronic Case Report Form (eCRF).

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

The number of subjects in each of the 3 study populations (FAS, PPS, SAF) will be summarized; the number of subjects screened will also be summarized.

Screen-failure subjects (ie, subjects screened but not treated) and the associated reasons for screen failure will be tabulated overall for all screened subjects. The number and percentage of subjects who complete the study in the FAS will be tabulated. The reasons for withdrawal from the study as recorded on the termination pages of the eCRFs will be summarized with number and percentage. All subjects who withdrew during the study will be listed by discontinuation reason for the FAS.

7.2. Demographic and Other Baseline Characteristics

The following demographic data will be collected at Screening or baseline (Day 0/Visit 2):

- Age (years) = (Inform consent date - date of birth + 1) / 365.25 and truncated to complete years
- Sex (%)
- Race (%)
- Ethnicity (%)
- Fitzpatrick skin type (Type I ~ Type VI) (%)
- Body weight (kg)

Demographic data and baseline characteristics will be statistically described for subjects in the FAS and listed in the SAF by groups (i.e., Group A, Group B and the repeat-treatment subgroup). If difference between FAS & PPS is more than 5%, then demographic data and baseline characteristics will be statistically described for subjects in the FAS and PPS, respectively.

7.3. Medical/Aesthetic Procedures History

Medical/aesthetic procedures history will be collected at Screening, from subject interview and medical records (if available), covering relevant past medical history with particular reference to:

- Diseases and medical conditions addressed in exclusion criteria
- Previous aesthetic and surgical procedures in the treatment area
- All medications taken by the subject in the previous ten days (regularly or occasionally), including over-the-counter and herbal medicines, and with special attention to immune therapies, anticoagulant drugs, antiplatelet drugs, and analgesics

Medical/aesthetic procedures history will be statistically described by system organ classes (SOC) and preferred terms (PTs) for groups in the FAS by groups (i.e., Group A, Group B and the repeat-treatment subgroup), and be listed for subjects in the SAF.

7.4. Prior and Concomitant Medications/Treatments

Prior medications/treatments are defined as all medications/treatments taken/received within ten days (whether continuing or not) prior to Day 0. Particular attention should be made to identify the use of anti-coagulation or anti-platelet agents (e.g. acetylsalicylic acid).

Concomitant medications/treatments is defined as all medication taken/received from Day 0 (including medication taken immediately pre-injection and post-injection) until the last visit.

Medications missing both start and stop dates, or having a start date prior to the first dose of study product and missing the stop date, or having a stop date on or after the last dose of study product and missing start date will be counted as concomitant.

For partial dates, the following approach will be taken:

- If the start day is missing but the start month and year are complete, a medication will be excluded as being concomitant only if the start month/year is before the month/year of study product administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study product administration.
- If the start day and month are missing but the start year is complete, a medication will be excluded as concomitant only if the start year is before the year of study product administration and if the stop date (either: full date, month and year if missing day, or year if missing month and day) is before study product administration.

Prior and concomitant medications will be coded using the WHO Drug Dictionary, and subject incidence will be tabulated by Anatomic Therapeutic Class (ATC) Level 2 and preferred term (PT) for FAS by groups (i.e., Group A, Group B and the repeat-treatment subgroup), and be listed for subjects in the SAF. Subjects will be counted only once for each ATC or PT in the event that they have multiple records of the same ATC or PT in the database.

8. Effectiveness

The FAS and the PPS will be both considered equally important for the primary analysis. The primary effectiveness analysis will be performed with the FAS; if Princess® FILLER Lidocaine can be considered non-inferior to Juvéderm® Ultra XC according to this analysis, the results of the non-inferority comparison based on the PPS can be considered confirmatory. Otherwise, the results of this analysis has to be considered exploratory. Overall non-inferiority is demonstrated only if the results are consistent for both analysis data sets. All secondary and additional effectiveness analyses will be conducted for the FAS and PPS.

A hierarchical testing procedure will be applied for the analysis of the primary outcome measure, as well as the key secondary outcome measures, in order to control multiplicity. At this, the following order will be used:

1. Analysis of primary effectiveness based on FAS
2. Analysis of primary effectiveness based on PPS
3. Analysis of key secondary effectiveness # 1 based on FAS
4. Analysis of key secondary effectiveness # 1 based on PPS
5. Analysis of key secondary effectiveness # 2 based on FAS
6. Analysis of key secondary effectiveness # 2 based on PPS

All statistical presentation will be done by treatment group (Princess® FILLER Lidocaine and Juvéderm® Ultra XC). For the primary analysis of the estimands of the primary effectiveness and of key secondary effectiveness endpoints, missing Week 24 assessments of NFL-SRS will be imputed by single imputation as no response. As sensitivity analyses, a best-case analysis (missing values for Princess® FILLER Lidocaine will be considered as a response, missing values for Juvéderm® Ultra XC will be considered as a non-response), a worst-case analysis (missing values for Princess® FILLER Lidocaine will be considered as a non-response, missing values for Juvéderm® Ultra XC will be considered as a response) will be performed on the FAS. Additionally, a tipping point analysis will be conducted on FAS to investigate the robustness of the results, and a complete-case analysis (includes subjects without any missing data) will be performed as supportive analysis.

For qualitative variables the frequencies (absolute and relative) will be calculated and compared between the treatment groups. Quantitative parameters will be summarized by mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum per treatment group. In addition to this, mean value (incl. two-sided 95% confidence interval), standard deviation, minimum, first quartile, median, third quartile, and maximum will also be provided for the difference in quantitative parameters between the two treatment sides of a subject. The key secondary outcome measures 1 and 2 will be analyzed as described for the primary effectiveness outcome measure. Kappa statistics will be calculated in order to assess inter-rater consistency among the three independent blinded photographic reviewers.

8.1. Evaluation Methods and Response Rate

8.1.1. Nasolabial Folds (NLF) Severity Rating Scale (NLF-SRS)

NLF-SRS is a five-point scale graded from 0 (None/minimal: No visible wrinkles) to 4 (Extreme: Extremely deep and long fold with skin redundancy) see Table 3. After enrollment, live assessments

using the NLF-SRS, will be performed by the treating investigator and the independent blinded evaluating investigator in conjunction at Baseline and as separate assessments at Week 12 (Visit 4), at Week 24 (Visit 5), at Week 36 (Visit 6), at Week 48 (Visit 7) and the post repeat-treatment hold follow-up visit (Visit 7c). Photographic assessments using the NLF-SRS will be performed at the end of the clinical investigation by three blinded independent photographic reviewers. The left and the right NLF will be graded separately.

Table 3 NLF Severity Rating Scale (NLF-SRS)

NLF-SRS grade	Definition
0	None/minimal: No visible/minimal nasolabial folds
1	Mild: shallow but visible nasolabial fold with a slight indentation
2	Moderate: moderately deep nasolabial fold
3	Severe: very deep nasolabial fold with prominent facial feature
4	Extreme: Extremely deep and long nasolabial fold with skin redundancy

8.1.2. Global Aesthetic Improvement Scale (GAIS)

The GAIS is a five-point scale that rates global aesthetic improvement from the pre-treatment appearance (Narins et al., 2003). The scale is presented in Table 4.

The GAIS assessment will be performed separately by the independent blinded evaluating investigator and the subject at Week 12 (Visit 4), at Week 24 (Visit 5), at Week 36 (Visit 6), at Week 48 (Visit 7), and the post repeat-treatment hold follow-up visit (Visit 7c). At Week 36, Week 48, and Visit 7c GAIS assessments will be performed prior to repeat-treatment. Separate assessments will be performed for the left and the right side of the face.

Table 4 Global Aesthetic Improvement Scale (GAIS)

Grade	Definition
1 Very much improved	Optimal aesthetic result for the implant in this subject.
2 Much improved	Marked improvement in appearance from initial condition, but not completely optimal for this subject. A touch-up would slightly improve the result.
3 Improved	Obvious improvement in appearance from the clinical condition, but a touch-up or retreatment is indicated.
4 No change	The appearance is essentially the same as the original condition.
5 Worse	The appearance is worse than the original condition.

Cited from (Narins et al., 2003)

8.1.3. Satisfaction with Outcome

FACE-Q Subject Satisfaction with Outcome Questionnaire, see Appendix 2, will be used to measure subjects satisfaction with the results of their most recent procedure.

“FACE-Q Subject Satisfaction with Outcome” assessments will be performed by the subject at Week 12 (Visit 4), at Week 24 (Visit 5), at Week 36 (Visit 6), at Week 48 (Visit 7), and the post repeat-treatment hold follow-up visit (Visit 7c). Separate assessments will be performed for the left and the right side of the face.

Satisfaction with Outcome Conversion Table:

The FACE-Q Subject Satisfaction with Outcome Questionnaire consists of 6 questions with answers ranging from 1 – "Definiteley disagree" over 2 – "Somewhat disagree" and 3 – "Somewhat agree" to 4 – "Definitely agree". The sum score can thus range from 6 to 24.

Higher scores reflect a better outcome. If missing data is less than 50% of the scales items, that is if at least 3 questions out of 6 questions are answered, insert the mean score of the completed items to the missing items. If less than 3 questions are answered, no sum score will be calculated. Use the conversion table below to convert the raw scale summed score into a equivalent Rasch transformed score from 0 (worst) to 100 (best).

Raw scale summed score	Equivalent Rasch transformed score (0-100)
6	0
7	19
8	24
9	28
10	31
11	35
12	38
13	41
14	45
15	48
16	52
17	55
18	59
19	63
20	68
21	73
22	79
23	87
24	100

8.1.4. Appraisal of Nasolabial Folds

FACE-Q Subject Appearance Appraisal of Nasolabial Folds Questionnaire, see Appendix 3, will be used to measure subjects appraisal of Nasolabial Folds with the results of their most recent procedure.

"FACE-Q Subject Appearance Appraisal of Nasolabial Folds" assessments will be performed by the subject at Week 12 (Visit 4), at Week 24 (Visit 5), at Week 36 (Visit 6), at Week 48 (Visit 7), the post repeat-treatment hold follow-up visit (Visit 7c). Separate assessments will be performed for the left and the right side of the face.

Appraisal of Nasolabial Folds Conversion Table:

The FACE-Q Subject Appearance Appraisal of Nasolabial Folds Questionnaire consists of 5 questions with answers ranging from 1 – "Not at all" over 2 – "A little" and 3 – "Moderately" to 4 – "Extremely". The sum score can thus range from 5 to 20.

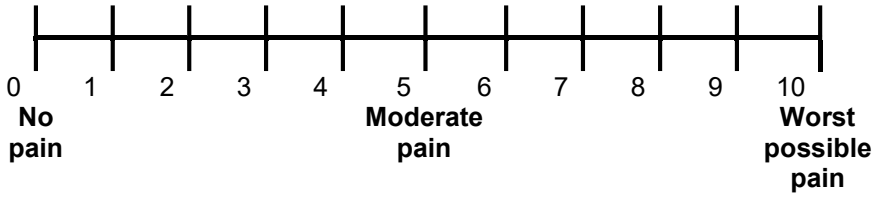
Ensure the data are rescored as follows: “Not at all” = 4; “A little” = 3; “Moderately” = 2; “Extremely” = 1. Higher scores reflect a better outcome. If missing data is less than 50% of the scales items, that is if at least 3 questions out of 5 questions are answered, insert the mean score of the completed items to the missing items. If less than 3 questions are answered, no sum score will be calculated. Use the conversion table below to convert the raw scale summed score into a equivalent Rasch transformed score from 0 (worst) to 100 (best).

Raw scale summed score	Equivalent Rasch transformed score (0-100)
5	0
6	10
7	18
8	24
9	30
10	36
11	42
12	47
13	52
14	58
15	63
16	69
17	76
18	83
19	91
20	100

8.1.5. Subject’s Evaluation of Pain

The subject’s perception of pain will be evaluated for treatments with Princess® FILLER Lidocaine and Juvéderm® Ultra XC. This evaluation will be assessed using a scale adapted from the 11-point Numeric Pain Rating Scale (NPRS), where "0" indicates "no pain" and "10" indicates “the worst pain imaginable".

The evaluation of subject’s pain will be done starting 15 min (+/- 3 min) after last injection and at 15 min-intervals (+/- 3 min) for 60 min (+/- 3 min) post-treatment (initial and repeattreatments) using the adapted NPRS. Separate assessments will be performed for the left and the right side of the face and overall. Overall assessment will be used for summary, and left, right side and overall assessments will be listed.



8.1.6. Injection Volume

For each subject, the total volume injected will be recorded separately for each treatment (initial, touch-up and repeat-treatments).

8.1.7. Time to Repeat-Treatment

For each subject, the time from initial treatment to repeat-treatment will be recorded for each investigational group and assessed by tabulating the following rates:

- Repeat-treatment at Week 36
- Repeat-treatment at Week 48
- Repeat-treatment at Visit 7c
- No repeat-treatment

8.1.8. Clinical Photography

Clinical photography of the subjects face will be taken at Screening (Visit 1), on Day 0 (Baseline) and at Week 12, 24, 36, 48, and Visit 7c after initial treatment (at Visit 2, 4, 5, 6, 7 and Visit 7c, respectively) under standardized conditions in accordance with the manual. On treatment days (initial- and/or repeat-treaments), the clinical photography will be performed prior to the treatment.

8.1.9. Response Rate for NLF-SRS

The response rate for week X in treatment group A is defined as follows:

$$Response\ rate = \frac{Number\ of\ Responders\ at\ Week\ X\ with\ treatment\ \ A}{Number\ of\ Responders\ at\ Week\ X\ with\ treatment\ \ A\ +\ Number\ of\ Non-Responders\ at\ Week\ X\ with\ treatment\ \ A}$$

The change from Baseline in NLF-SRS at Week X is calculated as follows (separately for the treatment groups):

$$= NLF-SRS_{Week\ X} - NLF-SRS_{Baseline}$$

'Responder' is defined as a subject with at least one grade improvement in NLF-SRS at Week X compare to Baseline.

Each subject's 'Response' for NLF-SRS will be assessed for both treatment groups, Princess® FILLER Lidocaine and Juvéderm® Ultra XC, in this split-face design.

8.1.10. Response Rate for GAIS

The aesthetic response rate based on GAIS assessment will be calculated considering the percentage of subjects that have been rated 'improved', 'much improved' or 'very much improved'.

Each subject's 'Response' for GAIS with regards to NLF will be assessed for both treatment groups, Princess® FILLER Lidocaine and Juvéderm® Ultra XC, in this split face design.

8.2. Primary Effectiveness Estimand and Analysis

The estimand for the primary effectiveness endpoint that is defined as a binary variable indicating the subject is alive and has a NLF-SRS response based on the independent blinded evaluating investigator live assessment using the NLF-SRS at Week 24 after initial treatment and relative to baseline assessments. NLF-SRS responder with regards to each specific NLF is defined as a subject with at least one grade improvement from baseline in NLF-SRS in that NLF. The shifts of the NLF-SRS grades (0 to 4) at Week 24 from baseline based on blinded independent evaluating investigator live assessment will be summarized for Princess® FILLER Lidocaine and Juvéderm® Ultra XC. A frequency table with the number and percentage of responders and non-responders at Week 24 will be presented for Princess® FILLER Lidocaine and Juvéderm® Ultra XC treatments. Additionally, summary of actual values and changes from baseline will be provided for Princess® FILLER Lidocaine and Juvéderm® Ultra XC treatments at all post-baseline timepoints.

8.2.1. Hypothesis Testing

The hypothesis to be tested for the estimand for the primary effectiveness endpoint is:

$$H_0: p_A - p_B \leq d_0 \quad \text{versus} \quad H_1: p_A - p_B > d_0$$

where, p_A is the response rate for Princess® FILLER Lidocaine, p_B is the response rate for Juvéderm® Ultra XC, and d_0 is the non-inferiority margin set at -10%.

A negative value for the difference p_A-p_B indicates that the response rate of Princess® FILLER Lidocaine is lower than the response rate for Juvéderm® Ultra XC.

The hypothesis testing of non-inferiority for paired proportions will be tested using a 1-sided, McNemar type test at an alpha of 0.025 with a delta of 0.10 (10%). Princess® FILLER Lidocaine will be considered non-inferior to Juvéderm® Ultra XC if the lower limit of the 2-sided 95% confidence interval (equivalent to the 1-sided 97.5% CI) for the difference between the proportions is greater than -10%.

McNemar type test using a GENMOD procedure and taking into account of paired data will be used for testing the non-inferiority of the rate difference in paired proportions considering non-inferiority margin (-10%).

SAS code for comparison of paired proportions could refer:

```
ods output parameterestimates=paramest;
proc genmod data=indiv;
   class id treatment;
   model response (event='1')=treatment/dist=binomial link=identity;
   repeated subject=id;
   lsmeans treatment/diff cl;
   lsmestimate treatment/cl lower testvalue=-0.1 alpha=0.025;
run;
```

Above analysis and confirmatory testing will be repeated on PPS.

8.2.2. Homogeneity & Treatment Effect

In order to assess the homogeneity of the primary effectiveness outcome measure and of the treatment effect among the clinical investigational sites, a generalized linear model with treatment, site, and treatment-by-site interaction as fixed effects and random subject effects will be fitted.

The generalized linear regression model in SAS statements could refer:

```
ods output parameterestimates=paramest;
proc genmod data=indiv;
   class id treatment site;
   model response (event='1')=treatment site treatment*site
   /dist=binomial link=identity;
   repeated subject=id;
   lsmeans treatment/diff cl;
run;
```

Where response=1 defines a responder and response=0 defines a non-responder.

Small clinical investigational sites with less than ten subjects will be pooled and a two-sided alpha level of 15% will be used to test for a treatment-by-site interaction. In case that the treatment-by-site interaction is not statistically significant (at the alpha level mentioned above), the treatment-by-site interaction will be removed from the mixed model and the confidence interval for the difference in proportions will be derived from this mixed model adjusted for site effects.

8.3. Key Secondary Effectiveness Estimands and Analyses

8.3.1. Key Secondary Effectiveness Estimand 1

The estimand for the key secondary effectiveness endpoint 1 that is defined as a binary variable indicating the subject is alive and has a NLF-SRS response based on the independent blinded photographic reviewers (I, II,and III) assessments of photograph (NLF severity) using the NLF-SRS at Week 24 after initial treatment and relative to baseline assessments. This endpoint will be analyzed as described in section 8.2. Median assessment from three independent blinded photographic reviewers (I, II, and III) will be used for this endpoint assessment.

The analyses performed on FAS will be repeated on PPS population.

8.3.2. Key Secondary Effectiveness Estimand 2

The estimand for the key secondary effectiveness endpoint 2 that is defined as a binary variable indicating the subject is alive and has a NLF-SRS response based on treating investigator live assessments of NLF severity using the NLF-SRS at Week 24 after initial treatment and relative to baseline assessments. This endpoint will be analyzed as described in section 8.2.

The analyses performed on FAS will be repeated on PPS population.

8.4. Sensitivity Analysis

Single imputation:

Best-case analysis will be conducted as sensitivity analysis for the primary outcome measure, as well as the key secondary outcome measures on the FAS and PPS. Missing values will be imputed using single imputation strategy for Princess® FILLER Lidocaine as a response, and for Juvéderm® Ultra XC as a non-response. This endpoint will be analyzed as described in section 8.2.1.

Similarly, worst-case analysis will be conducted as sensitivity analysis for the primary outcome measure, as well as the key secondary outcome measures on the FAS and PPS. Missing values will be imputed using single imputation strategy for Princess® FILLER Lidocaine as a non-response, and for Juvéderm® Ultra XC as a response. This endpoint will be analyzed as described in section 8.2.1.

Multiple imputation:

A sensitivity analysis will be conducted for the estimand of the primary outcome measure, as well as the key secondary outcome measures (NFL-SRS assessments) using a method of multiple imputation on the FAS and PPS, under the missing-at-random (MAR) assumption for all missing values at Week 24. If baseline is missing one side of the face, then impute from the other side of the face, but if baseline is missing for both sides of the face then impute using multiple imputation with the Markov Chain Monte Carlo (MCMC) method. Additionally, a tipping point analysis will be performed for the estimand of the primary outcome measure, as well as the key secondary outcome measures on the FAS, by performing a series of multiple imputations with adding an increasing shift value to the original NLF-SRS scale (discrete) of imputed subjects prior to performing the treatment comparison to investigate the impact of the deviation from MAR assumption. The number of completed datasets for each multiple imputation approach will be 100. The multiple imputations will be performed via SAS PROC MI procedure.

Impute: The missing values on the NLF-SRS scale (discrete) will be multiple imputed (using MAR assumptions) for each subject (with missing NLF-SRS post-baseline) with a set of 100 plausible values, thus 100 completed datasets will be produced. The multiple imputations will be done via SAS PROC MI. As per MAR assumption, all available observations with similar baseline characteristics from same treatment group are used to derive the imputation model.

The following statements use the MI procedure to impute missing values under the MAR assumption:

Achieve monotone missing data pattern for all visits:

```
proc mi data=datain seed=12345 nimpute=100 round=1 minimum=0 maximum=4
out=mono;
   class treatment;
   var treatment sex age base week12 week24;
   mcmc impute=monotone;
run;
```

Impute under the MAR assumption for all visits with monotone missing data pattern:

```
proc mi data=mono seed=12345 nimpute=1 round=1 minimum=0 maximum=4
out=outmi;
   by  _Imputation_;
   class treatment;
   var treatment sex age base week12 week24;
   monotone reg;
run;
```

Categorization of Response: The category of response/non-response for each subject will be derived based on the imputed NLF-SRS scale for the missings in each of the 100 completed datasets.

Analyze: The analysis method as described in section 8.2.1 will run in each of the 100 completed datasets using binary response data.

Combine: The analysis results / estimates resulting from 100 completed datasets will be combined using Rubin's combination rules (Rubin D.B., 2004) with SAS MIANALYZE procedure.

```
ods output parameterestimates=paramest;
proc mianalyze data=paramest;
   modeleffects estimate;
   STDERR stderr;
run;
```

Tipping point is a series of multiple imputations whereby a shift (here a positive shift) will be applied on the original NLF-SRS scale (discrete) of imputed subjects to the treatment group Princess® FILLER Lidocaine, which results then in the decrease of the number of responses in this group, and thus decreases the likelihood of non-inferiority against the control treatment Juvéderm® Ultra XC. This shift is only applied to subjects where missing values have been multiple imputed.

The positive shift of 1, 2, 3, 4 will be performed in each step, until the point is reached where the statistically significant non-inferiority switches to statistically non-significant: This respective shift where this happens is the tipping point.

A sample of SAS code for sensitivity analysis using the tipping-point method could refer to:

```
/*-----------------------------------------------------------*/
/*--- Performs multiple imputation analysis              ---*/
/*--- for specified shift parameters:                    ---*/
/*--- data= input data set                               ---*/
```

```
/*--- smin= min shift parameter                          ---*/
/*--- smax= max shift parameter                          ---*/
/*--- sinc= increment of the shift parameter             ---*/
/*--- outparams= output reg parameters                    ---*/
/*-------------------------------------------------------------*/

%macro miparams(data=, smin=, smax=, sinc=, outparams=);
ods select none;

data &outparams;
   set _null_;
run;

/*------------ # of shift values ------------*/

%let ncase= %sysevalf( (&smax-&smin)/&sinc, ceil);

/*---- Multiple imputation analysis for each shift ----*/
%do jc=0 %to &ncase;
   %let sj= %sysevalf( &smin + &jc * &sinc);

/*---- Generates 100 imputed data sets ----*/

proc mi data=&data seed=12345 nimpute=100 round=1 minimum=0 maximum=4
out=mono;
      class treatment;
      var treatment sex age base week12 week24;
      mcmc impute=monotone;
run;

proc mi data=mono seed=12345 nimpute=1 round=1 minimum=0 maximum=4 out=outmi;
      by  _Imputation;
      class treatment;
      var treatment sex age base week12 week24;
      monotone reg;
      mnar adjust( week24 / shift=&sj adjustobs=(treatment='1') );
run;

/*---- Categorization of response in imputed data sets ----*/

data outmi;
      set outmi;
      chg= week24 - base;
      if chg<0 then response=1;
      else response=0;
run;

  /*------ Perform genmod test -------*/

   ods output parameterestimates=paramest;
   proc genmod data=outmi;
```

```
      by  _Imputation_;
      class id treatment;
      model response (event='1')=treatment/dist=binomial link=identity;
      repeated subject=id;
      lsmeans treatment/diff cl;
      lsmestimate treatment/cl lower testvalue=-0.1 alpha=0.025;
   run;

  /*------ Combine genmod results -------*/

ods output parameterestimates=miparams;
proc mianalyze data=paramest;
      modeleffects estimate;
      STDERR stderr;
run;

data miparams;
      set miparams;
      Shift= &sj;
      keep Shift Probt;
   run;

/*----- Output multiple imputation results ----*/
   data &outparams;
      set &outparams miparams;
   run;

%end;

ods select all;
%mend miparams;
```

8.5. Supportive Analysis

Complete-case analysis which includes subjects without any missing data will be conducted as supportive analysis for the primary outcome measure, as well as the key secondary outcome measures on the FAS and PPS. This endpoint will be analyzed as described in section 8.2.1.

8.6. Other Secondary Effectiveness Endpoints and Analyses

8.6.1. GAIS Response Rate - Blinded Independent Evaluating Investigator

Aesthetic response rate based on blinded independent evaluating investigator assessment at Week 24 relative to Baseline using the GAIS. This endpoint will be analyzed descriptively presenting the response rate and one-sided 95% CIs using McNemar type test given in section 8.2.1.

8.6.2. GAIS Response Rate - Subject Assessment

Aesthetic response rate based on subject assessment at Week 24 relative to Baseline using the GAIS. This endpoint will be analyzed descriptively presenting the response rate and one-sided 95% CIs using McNemar type test given in section 8.2.1.

8.7. Additional Effectiveness Endpoints and Analyses

8.7.1. NLF-SRS Response Rate - Blinded Independent Evaluating Investigator

NLF-SRS response rate based on independent blinded evaluating investigator live assessments of NLF severity at Week 12, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) compared to Baseline using the NLF-SRS. This endpoint will be analyzed descriptively presenting the response rate and one-sided 95% Cs using McNemar type test given in section 8.2.1.

8.7.2. NLF-SRS Response Rate – Blinded Independent Photographic Reviewer

NLF-SRS response rate based on independent blinded photographic reviewers assessments of photograph (NLF severity) at Week 12, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) compared to Baseline using the NLF-SRS. This endpoint will be analyzed descriptively presenting the response rate and one-sided 95% CIs using McNemar type test given in section 8.2.1, and the individual independent ratings will also be analyzed using pairwise Kappa statistics to assess inter-rater consistency among the three independent blinded photographic reviewers.

The Kappa test for consistency in SAS statements could refer:

```
Proc freq  data=xxxxxxxxx;
   tables  Reviewer1 * (Reviewer2 Reviewer3) / agree;
   tables  Reviewer2 * Reviewer3 / agree;
   test kappa;
Run;
```

8.7.3. NLF-SRS Response Rate – Treating Investigator

NLF-SRS response rate based on treating investigator live assessments of NLF severity at Week 12, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) compared to Baseline using the NLF-SRS. This endpoint will be analyzed descriptively presenting the response rate and one-sided 95% CIs using McNemar type test given in section 8.2.1.

8.7.4. GAIS Response Rate - Blinded Independent Evaluating Investigator

Aesthetic response rate based on blinded independent evaluating investigator assessment at Week 12, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) relative to Baseline using the GAIS. This endpoint will be analyzed descriptively presenting the response rate and one-sided 95% CIs using McNemar type test given in section 8.2.1.

8.7.5. GAIS Response Rate - Subject Assessment

Aesthetic response rate based on subject assessment at Week 12, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) relative to Baseline using the GAIS. This endpoint will be analyzed descriptively presenting the response rate and one-sided 95% CIs using McNemar type test given in section 8.2.1.

8.7.6. FACE-Q Subject Satisfaction with Outcome

FACE-Q subject satisfaction with aesthetic outcome at Weeks 12, 24, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) relative to Baseline. For tabulation, Week 36, Week 48 and Visit 7c data will be combined into one additional virtual post repeat-treatment visit. This endpoint wil be analyzed using Wilcoxon signed-rank test.

SAS code for Wilcoxon signed-rank test could refer:

```
proc univariate data=xxxxx;
   var diff;
run;
```

8.7.7. FACE-Q Subject Appearance Appraisal of NLF

FACE-Q subject appearance appraisal of nasolabial folds at Weeks 12, 24, 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) relative to Baseline. For tabulation, Week 36, Week 48 and Visit 7c data will be combined into one additional virtual post repeat-treatment visit. This endpoint wil be analyzed using Wilcoxon signed-rank test.

8.7.8. Subjects Perception of Pain

Subjects' perception of pain will be compared between the treatment groups after initial treatment with Princess® FILLER Lidocaine and with Juvéderm® Ultra XC and after repeat treatment with Princess® FILLER Lidocaine, using a scale adapted from the 11-point Numeric Pain Rating Scale (NPRS), where 0 indicates 'no pain' and 10 indicates 'worst possible pain'. This endpoint will be analyzed using a longitudinal mixed model for repeated measures (MMRM) with fixed effects for treatment, timepoint, treatment-by-timepoint interaction, and baseline pain score as covariate. Subject will be the random effect. The unstructured covariance matrix for repeated observations within subjects will be used.

The least square (LS) means and standard error of each treatment, LS means differences including standard error, 95% confident interval (CI) and 2-sided p-values for the treatment difference for the pain scores at Weeks 36, 48 and the post repeat-treatment hold follow-up visit (Visit 7c) and for each scheduled time point will be presented in the tables.

SAS code for MMRM model could refer:

```
ods output lsmeans=lsmeans diffs=diffs tests3=test;
proc mixed data=xxxxxx method=REML;
   class subject treatment timepoint;
   model score=base treatment timepoint treatment*timepoint/ddfm=kr;
   repeated timepoint/sub=subject type=un;
   lsmean treatment*timepoint/pdiff cl;
run;
```

8.7.9. Time from Initial to Repeat-Treatment

Time (in days) from initial treatment to repeat-treatment for subjects received Princess® FILLER Lidocaine and Juvéderm® Ultra XC. This endpoint will be analyzed using descriptive statistics.

8.7.10. Injection Volume for Optimal Correction

Injection volume (initial, touch-up and repeat-treatments, separate assessments) needed for optimal correction for subjects received Princess® FILLER Lidocaine and Juvéderm® Ultra XC. This endpoint will be analyzed using descriptive statistics.

9. Safety

The population used for safety analyses will be the SAF. Safety will be assessed on the basis of adverse events (AEs), adverse device effects (ADEs) reports, serious adverse events (SAEs) and serious adverse device effects (SADEs).

9.1. Extent of Exposure

Injection volume (mL) administrated and number of syringes used will be summarized for the SAF using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) by treatment type (initial, touch-up, repeat, and total). In addition, injection volume (mL) administrated will be presented for overall treatment by treatment type (initial, touch-up, repeat, and total).

9.2. Treatment Compliance

N/A.

9.3. Adverse Events / Adverse Device Effects / Injection Site Responses

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects, users or other persons administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product. Treatment, Princess® FILLER Lidocaine or Juvederm® Ultra XC, was based on the AE side of face; if AE side is not applicable (N/A), the AE is considered to have happened to both sides of the face.

A Serious Adverse Event (SAE) is defined as an AE meeting one or more of the following conditions:

- Led to death;
- led to serious deterioration in health of the subject that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body stmcture or a body function, or
    - in subject hospitalization or prolonged hospitalization, or
    - medical or surgical Intervention to prevent life-threatening illness or injury or permanent impairment to a body stmcture or a body function
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect;
- Is an important medical event.

An Adverse Device Effect (ADE) is an adverse event related to the investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical devices. In addition, this includes any event that is a result of a use error or intentional misuse of the investigational medical devices.

A Serious Adverse Device Effect (SADE) is an ADE, in a participant, user or other person that results in any outcome listed in the definition of Serious Adverse Event. This includes device deficiencies that might have led to a Serious Adverse Event, in a participant, user, or other person if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

An unanticipated SADE (USADE) is defined as an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator's Brochure. Anticipated serious

adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. The following events could be specified as Adverse Events of Special Interest (AESI);

- Changes in vision (i.e. loss of vision, blurriness, double vision, pain in or around your eye, blindness, blind spots, problems moving the eyes)
- Skin changing colour around the eyelids or around the site of injection

Occurrence of AEs will be collected at each visit after the initial treatment at Baseline (Visit 2), from Visit 2 to Visit 9a or 9b or 9c included.

The AE and ADE reporting period for an enrolled participant will begin when the participant provides informed consent. TEAEs and treatment-emergent ADEs (TEADE) will be those defined as following dose administration. All TEAEs and TEADEs that occur during the AE and ADE reporting period specified in the protocol must be reported to InCarda, regardless of the relationship of the TEAE or TEADE to study treatment. Any known untoward event that occurs beyond the AE or ADE reporting period that the Principal Investigator considers possibly related to study treatment will be reported as an AE or ADE.

If the start date of an AE is partially or completely missing, the date will be compared as far as possible with the date of the start of administration of study product. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). The following general rules will be used:

- If the start day is missing but the start month and year are complete, an AE will be excluded as being treatment-emergent only if the start month/year is before the month/year of study product administration or if the stop date/time is before study product administration.
- If the start day and month are missing but the start year is complete, an AE will be excluded as being treatment-emergent only if the start year is before the year of study product administration or if the stop date/time is before study product administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before study product administration.

Device-related TEAEs/ TEADEs are defined as TEAEs/ TEADEs with possible or probable or definite relationship to study device.

Treatment-emergent AEs and ADEs will be summarized using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT), classified from verbatim terms. The incidence and percentage of participants with at least 1 occurrence of a PT will be included, according to the most severe grade using a 3-point scale (mild, moderate, severe). The number of events per PT will also be summarized. Causality (relationship to study treatment) will be summarized separately.

The number and percentage of subjects as well as number of events will be presented for the treatment-emergent AEs and ADEs summaries. For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum severity, a subject is counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, subjects may only contribute once to each PT and once to each SOC level.

Only injection site reaction AEs will be summarized by treatment group. However all AEs will be summarized by overall for both treatment groups together.

The incidence and frequency of treatment-emergent AEs, ADEs, SAEs, SADEs, and special interest AEs will be summarized by treatment group for injection site reaction AEs, and all AEs will be summarized by overall according to SOC and PT. AEs and ADEs will also be listed. The duration of AEs and ADEs will be determined and included in listings, along with the action taken and outcome.

Summaries presenting frequency of treatment-emergent AEs/ ADEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

AEs, ADEs, SAEs and SADEs will be listed by subject and treatment group for injection site reaction AEs, and overall for non injection site reaction AEs and then chronologically by date and time of onset. These listings will include all data collected in the eCRF, along with the derived variables: elapsed time since initial application, duration, and coded variables.

The following summaries will be provided:

- An overall summary of the number and percentage of treatment-emergent AEs and ADEs, serious TEAEs and TEADEs, severity TEAEs and TEADEs (unanticipated and anticipated), device-related TEAEs and TEADEs, procedure-related TEAEs and TEADEs, sepecial interest TEAEs, TEAEs and TEADEs leading to study withdrawal, and death;
- Treatment-emergent AEs and ADEs by SOC and PT;
- Treatment-emergent AEs and ADEs by SOC, PT and maximum severity;
- Treatment-emergent AEs and ADEs by SOC, PT and maximum relationship to study device/procedure;
- Treatment-emergent serious AEs and ADEs by SOC and PT;
- Study device/procedure related Treatment-emergent AEs and ADEs by SOC and PT;
- Special Interest Treatment-emergent AEs by SOC and PT;
- Treatment-emergent serious AEs and ADEs by SOC, PT and maximum relationship to study device/procedure;
- List of treatment-emergent AEs and ADEs Leading to study withdrawal.

TEAEs and TEADEs of the repeat-treatment subgroup from Week 36 or Week 48 or Visit 7c will be separately summarized.

Deaths, other serious and significant adverse events (if any) will be listed separately.

The number and percentage of subjects with injection site reactions by maximum severity, and duration of injection site reactions will be summarized by treatment group.

Injection site reactions will be listed. In addition, injection site reactions not resolved after 14 days (after initial treatment, touch-up treatment, repeat treatment), will be classified as an AE per investigator discretion, and all these AEs will be listed.

9.4. Visual Examination

Evaluation of vision changes (including left eye snellen visual acuity, right eye snellen visual acuity, left eye confrontational visual fields, right eye confrontational visual fields, left eye ocular motility and right eye ocular motility) will be performed prior to- and 30 min after any treatment at:

- Baseline (Visit 2)
- Week 2 (Visit 3a) (only in case of touch-up treatment)
- Week 4 (Visit 3b)
- Week 6 (Visit 3c) (only in case touch-up treatment was performed at Week 2 (Visit3a))
- Week 36 (Visit 6) or Week 48 (Visit 7) or Visit 7c (only in case of repeat-treatment)
- Week 40 (Visit 8a) or Week 52 (Visit 8b) (only in case repeat-treatment was performed respectively at Week 36 (Visit 6) or Week 48 (Visit 7))
- Week 48 (Visit 9a) or Week 60 (Visit 9b) (only in case repeat-treatment was performed respectively at Week 36 (Visit 6) or Week 48 (Visit 7))
- Visit 8c (Week 4 after Visit 7c) or Visit 9c (Week 12 after Visit 7c) (only in case repeat-treatment was performed post repeat treatment hold follow-up at Visit 7c)

The shifts of visual examination outcomes on treatment days from pre-treatment to post-treatment for each treatment visit, and on non-treatment days from baseline to post baseline visits will be summarized. Visual examination outcomes will also be listed by SAF.

9.5. Urine Pregnancy Test

Urine pregnancy test is required in female subjects of childbearing potential only, including those who are postmenopausal for less than twelve months. An urine pregnancy test (dip stick) will be performed at:

- Screening (Visit 1)
- prior to initial treatment (Day 0/Visit 2)
- prior to touch-up treatment (Week 2/Visit 3a)
- prior to repeat-treatment (Week 36/Visit 6 or Week 48/Visit 7 or Visit 7c)

Urine pregnancy test outcomes will be listed by SAF.

9.6. Body Weight

Body weight will be measured at Baseline (Day 0/Visit 2), Visit 3a, 3b, 3c, 4 and 5, as well as at Visit 6 or Visit 7 or Visit 7c upon evaluation for repeat-treatment; as well as Visit 8a/8b or Visit 9a/9b or Visit 8c/9c; weight measurement should be done to the nearest 0.1 kg and with the subjects standing barefoot and wearing light indoor clothing. Subjects will be advised to abstain from excess body weight gain or loss (±10% from Baseline).

Body weight measurements will be listed by SAF.

10. Interim Analyses

No interim analyses is planned for this study.

11. Changes from Analysis Planned in Protocol

Estimand approach is defined for the primary objective, and for the Key secondary objectives.

Secondary objectives 3, 4, and all additional objectives will be analysed by presenting the CIs and/or p-values.

12. Reference List

Narins, R. S., Brandt, F., Leyden, J., Lorenc, Z. P., Rubin, M., & Smith, S. (2003). A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatologic surgery*, *29*(6), 588-595.

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials: May2021.

13. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

The following items need to be clarified upfront with the sponsor and Medical Writing and modified as per study requirements.

- One SAS program can create several outputs, or a separate SAS program will be created for each output.
- One output file can contain several outputs.or each output will be stored in a separate file.
- Output files will be delivered in Word format or portable document format pdf.
- Numbering of TFLs will follow ICH E3 guidance

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

- Croma-Pharma GmbH Protocol CPH-301-201200F (Syneos Health study number 1007995)
- Draft/Final Run <date>
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis sets are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of effectiveness tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in a separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the

analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, drug class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC2 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907) .

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.”

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Listing 16.2.1.2	Subject Disposition	All Enrolled
Section 16.2.2 Protocol Deviations		
Listing 16.2.2.1	Protocol Deviations	All Enrolled
Listing 16.2.2.2	Protocol Deviations due to COVID-19	All Enrolled
Listing 16.2.2.3	Missing Visits due to COVID-19	All Enrolled
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Number	Title	Population
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Listing 16.2.6.3	Subject Satisfaction - FACE-Q Questionnaires	FAS
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NA

18. Shells

Refer to shells document titled “CIP_CPH-301-201200F_TFLs_Final_V3.0_15Aug2022.docx”.

19. Appendices

19.1. Appendix 1: NLF Severity Rating Scale (NLF-SRS)

19.2. Appendix 2: FACE-Q Subject Satisfaction with Outcome Questionnaire

SATISFACTION WITH OUTCOME

19.3. Appendix 3: FACE-Q Subject Appearance Appraisal of Nasolabial Folds Questionnaire

APPRAISAL OF NASOLABIAL FOLDS