CLINICAL INVESTIGATION PLAN

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

NCT03990883

Clinical investigation plan no.:	CPH-301-201200F
Sponsor:	Croma-Pharma GmbH Industriezeile 6 2100 Leobendorf, Austria
Clinical investigation plan version:	Version 7.0
Clinical investigation plan date:	15 Mar 2021

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

SPONSOR RELATED CONTACT DETAILS

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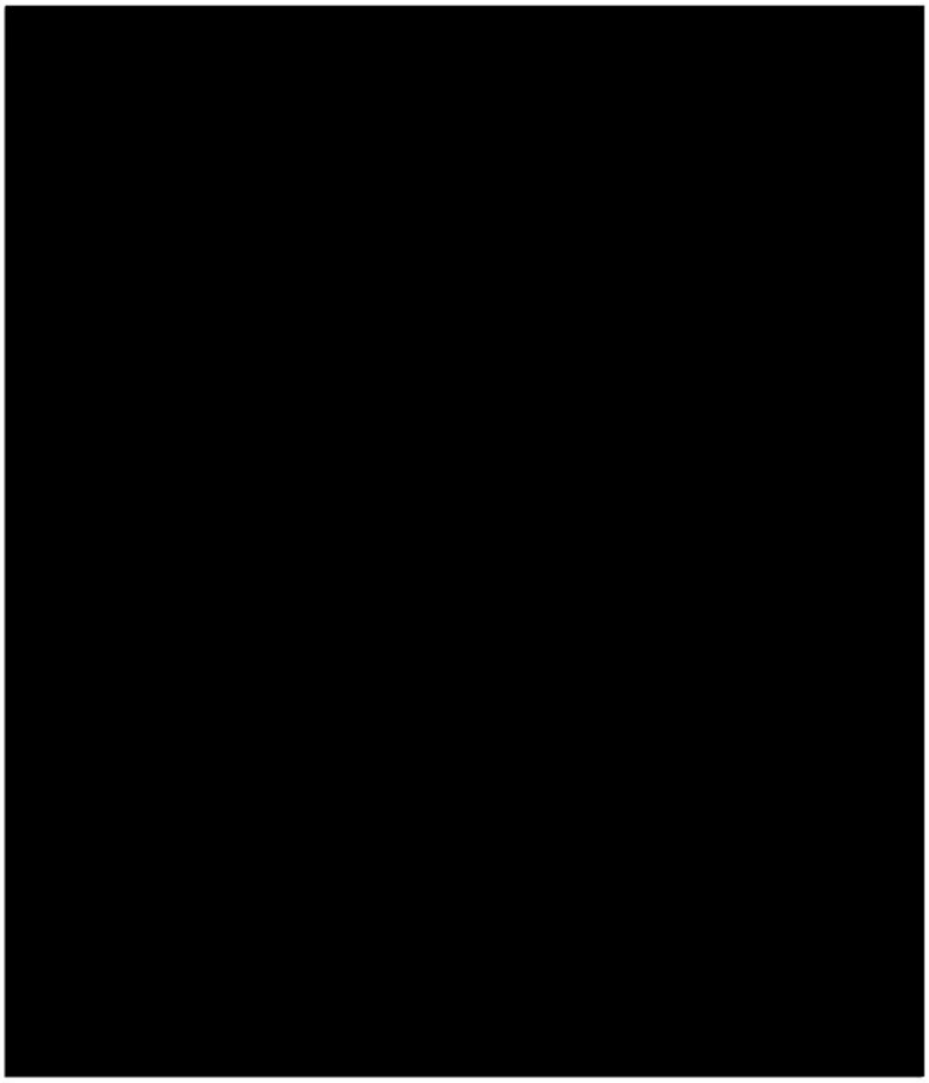
A randomized, subject- and evaluator-blinded, controlled, multicenter, split-face, comparison clinical investigation to evaluate effectiveness and safety of Princess® FILLER Lidocaine in the correction of nasolabial folds

SPONSOR SIGNATURE PAGE

This clinical investigation will be conducted in compliance with the clinical investigation plan (CIP) and the following regulatory requirements:

- International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects - Good clinical practice (GCP)
- Declaration of Helsinki, current revision
- The International Conference on Harmonisation harmonized tripartite guideline regarding Good Clinical Practice (GCP) (E6 Consolidated Guidance, April 1996)
- Applicable sections of the national laws and regulations

By acting in accordance with this CIP, the investigators and the clinical investigation site personnel fulfil the requirements of the International Standard ISO 14155:2011.
The clinical investigation will not commence until a favourable opinion from the Food and Drug Administration (FDA) (Investigation Device Exemption, IDE) and from the respective Institutional Review Boards (IRBs) has been received. All additional requirements imposed by the IRB(s) will be followed. Insurance coverage for damages emerging from the clinical investigation will be provided according to applicable legal requirements.
For Sponsor:



PRINCIPAL INVESTIGATOR AGREEMENT PAGE FOR THE CLINICAL INVESTIGATIONAL PLAN

I agree:

- To assume responsibility for the proper conduct of the clinical investigation at this site, and to conduct the clinical investigation in compliance with this clinical investigational plan (CIP), any future amendments, and with any other clinical investigation conduct procedures provided by the sponsor or authorized representatives, as well as in accordance with the clinical investigation agreement, respective laws and regulations, including GCP, and all applicable regulatory requirements.
- Not to implement any deviations from or changes to the CIP (including CIP amendments) without instructions and agreement from the sponsor and prior review and favorable opinion from the Ethics Committee and approval from the Competent Authority, if applicable, except where necessary to eliminate an immediate hazard to the subject(s), or for administrative aspects of the clinical investigation (where permitted by all applicable regulatory requirements).
- That I am familiar with the appropriate use of the investigational medical device (IMD) as described in this CIP and any other information provided by the sponsor including, but not limited to, the current Investigator's Brochure or equivalent document provided by the sponsor.
- To ensure that all persons assisting me with the clinical investigations are adequately informed about the IMDs and of their clinical investigation-related duties and functions.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the clinical investigation product, and more generally about his/her financial ties with the sponsor. The sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.
- To keep any information related to this clinical investigation and any results of it as strictly confidential. I agree that this information will not be used for any other purpose other than the conduct of this clinical investigation.

Investigator's name: _____

Investigator's address:_____

_____

Governing IRB _____

_____

Investigator's signature: _____

Date: _____

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1 Abbreviations and definition of terms

ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
ASADE	Anticipated serious adverse device effect
BDDE	1,4-butanediol diglycidyl ether
CE	European Conformity
CFR	Code of Federal Regulations
CIP	Clinical investigation plan
CRA	Clinical research associate
eCRF	Electronic case report form
EU	European Union
FACE-Q	Patient-reported outcome questionnaires measuring experience and outcomes of aesthetic facial procedures
FAS	Full analysis set
FDA	Food and Drug Administration
FSFV	First subject first visit
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
HA	Hyaluronic acid
HIPAA	Health insurance portability and accountability act
IRB	Institutional review board
ICF	Informed consent form
IFU	Instructions for use
IMD	Investigational medical device
ISO	International Organization for Standardization
LSLV	Last subject last visit

MedDRA	Medical disctionary for regulatory activities
NLF(s)	Nasolabial fold(s)
NLF-SRS	Nasolabial Folds-Severity Rating Scale
NPRS	Numeric Pain Rating Scale
PPS	Per-protocol set
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAF	Safety analysis set
SOC	System organ class
SOP	Standard operating procedure
UADE	Unanticipated adverse device effect
US/USA	United States of America
UV	Ultraviolet

2 Clinical Investigation Synopsis

INVESTIGATIONAL MEDICINAL PRODUCT	
Clinical investigation Sponsor	Croma-Pharma GmbH Industriezeile 6 2100 Leobendorf, Austria
Name of Investigational Medical Device	Crosslinked Hyaluronic Acid (HA) 2.3% + 0.3% Lidocaine Hydrochloride i.d. (Trade name: Princess® FILLER Lidocaine)
CLINICAL CONDITION(S)/INDICATION(S)	
Moderate to severe facial wrinkles and folds, such as nasolabial folds (NLFs)	
PROTOCOL IDENTIFIER	CPH-301-201200F
PROTOCOL TITLE	A randomized, subject- and evaluating investigator-blinded, controlled, multi-center, split-face, comparison clinical investigation to evaluate effectiveness and safety of Princess® FILLER Lidocaine in the correction of nasolabial folds
Short title	FILIDO
CLINICAL INVESTIGATION PHASE	Pivotal
PLANNED CLINICAL INVESTIGATION PERIOD	
Initiation	Anticipated Q1 to Q2 2019 (FSFV)
Primary Completion	Anticipated Q3 2021 (LSLV)
Clinical investigation Completion	Anticipated Q4 2021
Duration	The duration of the clinical investigation will be a maximum of 104 weeks for each participating subject, including the temporary hold on repeat-treatment. The total expected duration of the

	clinical investigation (FSFV to LSLV) is up to 24 months with an expected recruitment period of about 20 weeks.
CLINICAL INVESTIGATION OBJECTIVES AND PURPOSE	
Clinical investigation Purpose	To demonstrate the effectiveness and safety of Princess® FILLER Lidocaine in the correction of moderate to severe NLFs
Objectives	<u>Primary objective:</u> To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs in comparison 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, relative to Baseline assessments <u>Secondary objectives:</u> 1. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs and 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 and 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 a 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 <u>Additional objectives:</u> 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 with 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 NLFs 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 <u>Safety objectives:</u> Frequency, severity, seriousness and causal relationship of adverse events (AEs), adverse device effects (ADEs), serious adverse eents (SAEs) and serious adverse device effects (SADEs) during the entire clinical investigation period including subject complaints will be recorded in the subject diaries during four weeks after initial-, touch-up-treatments, in comparison with Juvéderm® Ultra XC. Frequency, severity, seriousness and causal relationship of AEs, ADEs, SAEs and SADEs during the entire clinical investigation period including subject complaints will be recorded in the subject diaries during four weeks after repeat-treatments, for Princess® FILLER Lidocaine
CLINICAL INVESTIGATION DESIGN	
Clinical Investigation Type	Interventional
Control Type	Non-inferiority clinical investigation
Indication Type	Treatment

Blinding/Masking	Subject- and independent evaluating investigator-blinded
Design	The clinical investigation is a randomized, subject- and independent evaluating investigator-blinded, active treatment controlled, multicenter, paired (split-face) clinical investigation. The clinical investigation will comprise two treatment groups 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 NFL Eligible subjects will be randomized at Baseline (Visit 2) in a 1:1 ratio to Group A or Group B; according to the randomization scheme. The subjects of each group will undergo bilateral treatments with Princess® FILLER Lidocaine and Juvéderm® Ultra XC for the correction of moderate to severe NLFs. Baseline Severity of NLFs will be determined at Screening by the treating investigator in conjunction with the independent blinded evaluating investigator. Subjects will be blinded to the treatment administered (they will be blindfolded during the administration of devices). The treating investigator and the independent blinded evaluating investigator will independently assess treatment effect in correction of the NLFs using the Nasolabial Folds Severity Rating Scale (NLF-SRS). Independent blinded photographic reviews will be done for the same time points. The treatment will be administered at the Baseline visit (Day 0) after randomization. The left NFL will be treated first and the right NLF thereafter. Subjects will return for effectiveness follow-up assessments two, twelve and 24 weeks after the initial treatment.

	At the first follow-up visit (Week 2), a touch-up treatment may be done 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. On Week 36 and/or Week 48 after initial treatment, an evaluation for repeat-treatment will take place; subjects will be offered an optional repeat-treatment (Visit 6 or 7), if in the opinion of the treating investigator, they have returned to sufficient severity of NLFs that would have qualified them for enrollment into the clinical investigation initially. The subjects do NOT have to return to their Baseline severity to be permitted to receive a repeat-treatment. At Week 36, an evaluation for repeat-treatment will take place; subjects qualifying for a repeat-treatment will receive it during the same visit (Visit 6) and will come back for a safety follow-up visit four and twelve weeks later (Week 40/Visit 8a and Week 48/Visit 9a). For these subjects, Visit 9a will be their end of study visit. Subjects which are not qualifying for a repeat-treatment at Week 36 will be evaluated again at Week 48 (Visit 7); qualified subjects will then receive a repeat-treatment during Visit 7 and will be followed-up for safety four and twelve weeks later (Week 52/Visit 8b and Week 60/Visit 9b). For these subjects, Visit 9b will be their end of study visit. Subjects, who do not qualify for any retreatment, will have their end of study visit at Visit 7. The repeat-treatment will be performed with Princess® FILLER Lidocaine on both NLFs. Follow-up visits for effectiveness will be performed at Week 2, 12, 24, 36 and/or 48 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 and 48/60 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 serious adverse events associated with unintended intravascular injection over the following (four weeks after initial-, touch-up- and repeat-treatments. Subject satisfaction with the outcome of the treatment will be assessed with GAIS and the patient-reported outcome questionnaires measuring experience and outcomes of aesthetic facial procedures (FACE-Q) questionnaires. Pain assessment will be performed after initial and repeat-treatment (15 min after last injection and at 15 min-intervals 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 (prior to- and 30 min after any treatment) 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) will be examined the same way as they would be at the Baseline (prior to- and 30 min after the treatment) and an additional examination 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 after repeat-treatment and at Week 48/Visit 9a or at Week 60/Visit 9b after repeat-treatment). Subjects with clinically significant changes in visual examinations considered to be related to a vascular injection of the dermal filler will be treated per standard of care for intravascular injection of dermal filler. The subject will be withdrawn from the study and the need for stopping the study will be reviewed.

	During the conduct of the trial, some subjects were not evaluated for repeat-treatment at Week 36 (Visit 6) and/or Week 48 (Visit 7) due to a hold on repeat-treatment. Therefore, a post repeat-treatment hold follow-up visit (Visit 7c) has been added in Clinical Investigation Plan Version 7.0 to allow subjects to return for evaluation and repeat-treatment (if eligible) after the end of the hold on repeat-treatment. Subsequent follow-up visits (Visit 8c [4 weeks after repeat-treatment] and Visit 9c [12 weeks after repeat-treatment]) have also been added. For subjects who receive repeat-treatment at Visit 7c, Visit 9c will be their end of study visit. For subjects who do not qualify for repeat-treatment at Visit 7c, Visit 7c will be their end of study visit.
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. <u>Primary outcome measure:</u> 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). <u>Secondary outcome measures:</u> Responder is defined as having at least one grade improvement over Baseline, on the 5-point NLF-SRS. 1. Responder is defined as having at least one grade improvement over Baseline, on the 5-point NLF-SRS.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 <u>Additional outcome measures:</u> Responder is defined as having at least one grade improvement over Baseline, on the 5-point NLF-SRS. 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 treatment with Princess® FILLER Lidocaine and with Juvéderm® Ultra XC, and Subject's perception of pain 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 (separate assessments) and recording of injection volume required to achieve optimal correction for Princess® FILLER Lidocaine and Juvéderm® Ultra XC at repeat-treatments (separate assessments) Safety outcome measures: Frequency, severity, seriousness and causal relationship of AEs, ADEs, SAEs and SADEs during the entire clinical investigation period including subject complaints will be recorded in the subject diaries during four weeks after initial-, touch-up-treatments, in comparison with Juvéderm® Ultra XC. Frequency, severity, seriousness and causal relationship of AEs, ADEs, SAEs and SADEs during the entire clinical investigation period including subject complaints will be recorded in the subject diaries during four weeks after repeat-treatments, for Princess® FILLER Lidocaine
SUBJECT SELECTION	
Targeted Accrual	Approx. 300 subjects to be screened/ 270 randomized subjects /240 evaluable subjects (accounting for a screening failure rate of approx. 10% as well as approx. 10% of subjects to be excluded from the Per-Protocol Set due to major protocol deviations or subjects lost to follow-up) Approximately 10-12 United States (US) sites planned
Number of Groups	Two groups: • 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 Starting with Week 36, both groups will receive Princess® FILLER Lidocaine only.
Inclusion Criteria at Screening/Baseline	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 NLFs (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 CIP
Exclusion Criteria at Screening/Baseline	Subjects who meet **ANY** of the following criteria are NOT eligible for this clinical investigation: 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 (HA) 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.

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
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
STATISTICAL ANALYSIS	
Sample Size Calculation	The primary effectiveness outcome measure will be evaluated by means of a one-sided 95% confidence interval for the difference in 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 for 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 exceeds 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 NLFs 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.
Analysis Data Sets	<u>Full Analysis Set (FAS)</u> The Full Analysis Set (FAS) consists of all randomized subjects who received at least one administration of Princess® FILLER Lidocaine and the control medical device at the same visit. Subjects who received only one treatment (only Princess® FILLER Lidocaine or only Juvéderm® Ultra XC) during initial treatment will be excluded from the FAS. <u>Per-Protocol Set (PPS)</u> The Per-Protocol Set (PPS) is defined as a subset of the subjects in the Full Analysis Set who had no major protocol deviations. <u>Safety Analysis Set (SAF)</u> 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 PPS and FAS will be both considered equally important for the primary analysis; the primary 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 sensitivity analysis based on the PPS can be considered confirmatory. Otherwise, this analysis has to be considered exploratory. Non-inferiority is demonstrated only if the results are consistent for both analysis data sets. All effectiveness analyses will be conducted for the FAS and subsequently for the PPS. Safety analyses will be based on the SAF.
General Statistical Considerations	The analysis of the primary effectiveness outcome measure using the FAS and the subsequent sensitivity analysis using the PPS, as

	well as the analyses of the secondary outcome measures 1 and 2, will be considered confirmatory within the bounds of the corresponding hierarchical testing procedure. All other analyses will be considered exploratory.
Planned Statistical Analysis	All effectiveness outcome measures will be tabulated by treatment group and visit. To calculate the primary outcome measure, the improvement over Baseline in the NLF-SRS grade assessed by the independent blinded evaluating investigator at Week 24 will be computed for each subject and treatment side by subtracting the NLF-SRS grade obtained at Week 24 from ipsilateral NLF-SRS grade obtained at Baseline. The response rate will then be calculated for each treatment group as the proportion of subjects with NLF-SRS improvement (i.e., reduction) of a $\geq$1 point. The primary effectiveness outcome measure will be evaluated by means of a one-sided 95% confidence interval for the difference in paired proportions p_A-p_B. At this, p_A is the response rate for Princess® FILLER Lidocaine and p_B is the response rate for Juvéderm® Ultra XC. Thus, a negative value for this difference means that the response rate of Princess® FILLER Lidocaine is lower than the response rate for Juvéderm® Ultra XC. Princess® FILLER Lidocaine will be considered non-inferior to Juvéderm® Ultra XC if the lower confidence limit exceeds the non-inferiority margin of -10% and thus if the null hypothesis H_0: p_A-$p_B \leq$ -10% can be rejected. In addition to this, the response rates for both treatment groups will be tabulated. The statistical analysis of the secondary and additional outcome measures will be described in detail in the statistical analysis plan. A hierarchical testing procedure will be applied for the analysis of the primary outcome measure, as well as the secondary outcome measures 1 and 2, in order to control multiplicity. For qualitative variables, the frequencies (absolute and relative) will be calculated

	and compared between the treatment groups. Quantitative parameters will be described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum per treatment group. In addition to this, mean value, 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. Secondary outcome measures 1 and 2 will be analyzed as described for the primary effectiveness outcome measure. Descriptive statistics will be used to summarize the remaining outcome measures. Adverse events will be summarized by treatment, preferred term and system organ class, and also by intensity, duration, causal relationship to the device or procedure, and seriousness.

2.1 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	X	X[10]		X[10]		X[10]	X[10]
Eligibility assessment	X	X[12]								X[5, 6]		X[5,6]			
Randomization		X[5]													
Treatment		X		X[7]						X[9]		X[9]			
Urine pregnancy test[d]	X	X[5]		X[6,8]						X[6,10]		X[6,10]			
NLF-SRS[e]	X							X	X	X[6]		X[6]			
Clinical photography[f]	X	X[5]						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[5]	X	X[6]	X	X	X	X	X	X[6]	X	X[6]	X	X	X[10]
Adverse events		X[5]	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[1,6]			
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[j]			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]

Abbreviations: C. = call; FACE-Q = Patient-reported outcome questionnaires measuring experience and outcomes of aesthetic facial procedures ; GAIS = Global Aesthetic Improvement Scale; NLF(s) = nasolabial folds; NLF-SRS = Nasolabial Folds-Severity Rating Scale; NPRS = Numeric Pain Rating Scale.

[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. Subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection.

[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 9.2 of the protocol

[5] The first Follow-up visit for repeat-treatment will take place 4 weeks (± 5 days) after repeat-treatment. The second Follow-up visit for repeat-treatment will take place 12 weeks (± 5 days) after repeat-treatment.

[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 (NLFs) 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 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 Investigators and administrative structure of the clinical investigation

Treating investigators:

This clinical investigation will be conducted at approximately ten to twelve clinical investigational sites in the United States (US). An updated list of investigators and investigation sites is kept separately from the Clinical Investigation Plan (CIP) and is available on request.

Independent blinded evaluating investigators:

An updated list of independent blinded evaluating investigators is kept separately from the CIP and is available on request

Governing IRB(s):

An updated list of governing Institutional Review Boards(s) (IRB[s]) is kept separately from the CIP and is available on request.

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Sponsor's CIP signatories:

[redacted]

[redacted]

Sponsor's medical expert:

[redacted]

Clinical project manager:

[redacted]

Photographic procedures and independent photographic assessment by three blinded photography reviewer(s):

[redacted]

Investigation monitoring:

[redacted]

Safety monitoring and reporting:

[redacted]

Data management:

[redacted]

Statistics:

[redacted]

4 Background Information and Scientific Rationale

4.1 Background Information Regarding Dermal Fillers

The facial signs of aging are characterized by the formation of wrinkles and folds, which result due to the loss of bone mass and soft tissue volume, the redistribution of fat, as well as decreased skin elasticity and thickness (Donofrio, 2000; John & Price, 2009; Lowe, Maxwell, & Patnaik, 2005; Smith, 2008). With the natural process of aging, the endogenous hyaluronic acid (HA) is reduced, resulting in a less hydrated and consequently less elastic skin (Bogdan Allemann & Baumann, 2008). In the midface, furrowing and flattening of the central mid cheek occurs, with displacement medially exaggerating the depth of the nasolabial folds (NLFs) (Coleman & Grover, 2006; Mendelson & Jacobson, 2008; Raspaldo, 2008).

Dermal fillers serve as one of the most common and useful treatments for wrinkles and folds and appeal to the growing population keen to reverse the signs of aging (Raspaldo, 2008). Over the past two decades, soft tissue augmentation using injectable fillers, has become a standard clinical approach for correcting age-related facial defects (Raspaldo, 2008). Among these, HA-based fillers appear to be ideal, due to their low immunogenic potential and relatively long-lasting effect. HA is a naturally occurring glycosaminoglycan which exhibits no species and no tissue specificity and is an essential component of the extracellular matrix in adult tissue (Carruthers, Glogau, Blitzer, & Facial Aesthetics Consensus Group, 2008; John & Price, 2009; Rao, Chi, & Goldman, 2005; Vedamurthy, 2004). In the skin, it is located among the collagen fibers. It has a hydrophilic capability (Bogdan Allemann & Baumann, 2008; John & Price, 2009), promoting skin hydration and contributing to skin turgidity (John & Price, 2009). In dermal fillers, the HA molecules are chemically cross-linked in order to improve consistency and to increase the intradermal residence time of the filler (Landau, 2011). A wide range of HA-based dermal fillers are currently on the market differing in terms of source material, concentration, method and degree of cross-linking, viscosity, consistency, stiffness and injection force (Sundaram & Cassuto, 2013). Due to their favourable risk/benefit profile, HA products are the most widely used dermal fillers in Europe and the USA. HA fillers have also been used successfully to correct debilitating scars (Halachmi, Ben Amitai, & Lapidoth, 2013; Hasson & Romero, 2010; Khan, Richards, & Rashid, 2012; Richards & Rashid, 2011), facial lipoatrophy (Bugge, Negaard, Skeie, & Bergersen, 2007; Gooderham & Solish, 2005; Pavicic,

Ruzicka, Korting, & Gauglitz, 2010; Ross & Malhotra, 2010) and morphological facial asymmetry (Choi et al., 2011; Myung, Lee, & Chang, 2012).

In order to improve the comfort of filler injections, the local anaesthetic lidocaine hydrochloride (the terms "lidocaine" and "lidocaine hydrochloride" are used interchangeably in this document) has been included in their formulation to reduce procedural pain and to bypass the need for additional anaesthesia (Weinkle et al., 2009). Clinical studies (F. Brandt, Bank, Cross, & Weiss, 2010; Few, Cox, Paradkar-Mitragotri, & Murphy, 2015; Glaser et al., 2015; Levy, De Boulle, & Raspaldo, 2009a, 2009b; Lupo, Smith, Thomas, Murphy, & Beddingfield, 2008; Philipp-Dormston et al., 2014; Prager & Micheels, 2015; Raspaldo, De Boulle, & Levy, 2010; Royo de la Torre et al., 2013; Wahl, 2008; Weinkle et al., 2009) have demonstrated that treatment with dermal fillers with lidocaine resulted in a statistically and clinically significant reduction in pain ($p < 0.0001$).

Princess® FILLER Lidocaine is a sterile, biodegradable, viscoelastic, clear, absorbable, isotonic and homogenized injectable HA gel implant produced by Croma-Pharma GmbH in Austria. Princess® FILLER Lidocaine contains HA at a concentration of 23 mg/mL in a physiologic buffer and is chemically cross-linked with 1,4-butanediol diglycidyl ether (BDDE) which covalently binds native HA molecules to each other with repeating bridges, creating a polymer 'network', transforming the viscous liquid into a gel. Compared with native HA, the cross-linked HA gel is considerably more resistant against enzymatic and free radical breakdown, so that its tissue residence time is dramatically increased. Native HA is added in order to adjust the rheological properties and injectability of the fillers (Kablik, Monheit, Yu, Chang, & Gershkovich, 2009; Tezel & Fredrickson, 2008). The cross-linking process is optimized so that the device is most suitable for injections into the mid to deep dermis. Lidocaine has been added to reduce procedural pain and to improve the comfort of filler injections.

Princess® FILLER Lidocaine is intended to correct moderate to severe facial wrinkles and folds and to increase lip volume. The device was also conceived for medical purposes in the European Union (EU), consistent with the current Medical Device Directive and aims to address reconstructive purposes in the treatment, for instance, of facial lipoatrophy, debilitating scars or morphological asymmetry. It is indicated to be injected into the mid to deep dermis (EU Instructions for Use [IFU], see Section 22.2).

Analysis of the effectiveness of dermal fillers is investigated by (1) Scale to assess NLFs severity before and after treatment, (2) Scale to assess aesthetic improvement after treatment, (3) Scales to assess pain during and directly after treatment and (4) Assessment of subject satisfaction with treatment/outcome. The used scale for wrinkle severity assessment for the treatment of NLFs in this clinical investigation is the Nasolabial Fold Severity Rating Scale (NLF-SRS). The NLF-SRS is a 5-point scale graded from 0 (no visible NLFs) to 4 (extremely deep and long NLFs), which has standardized verbal descriptions for each grade and corresponding visual photographs for comparison (see Section 10.1).

Effectiveness is also assessed with the widely used Global Aesthetic Improvement Scale (GAIS), which is a 5-point scale rating improvement in appearance, compared to pre-treatment (Narins et al., 2003), according to the following rating categories "worse," "no change," "improved," "much improved," and "very much improved."

Pain assessment is performed for both treatments (Princess® FILLER Lidocaine in comparison to Juvederm® Ultra XC) using a scale adapted from the 11-point Numeric Pain Rating scale (0 corresponds to no pain, and 10 to the worst pain imaginable).

Subject satisfaction with treatment is generally assessed using the patient-reported outcome questionnaires measuring experience and outcomes of aesthetic facial procedures (FACE-Q) questionnaires.

Data from pivotal studies with dermal fillers which are clinically, technically and biologically equivalent to Princess® FILLER Lidocaine have consistently demonstrated a clinically significant reduction in wrinkle severity after treatment, often lasting up until twelve months after treatment (F. Brandt et al., 2010; Few et al., 2015; Glaser et al., 2015; Levy et al., 2009a, 2009b; Lupo et al., 2008; Philipp-Dormston et al., 2014; Prager & Micheels, 2015; Raspaldo et al., 2010; Royo de la Torre et al., 2013; Wahl, 2008; Weinkle et al., 2009). Moreover, these studies have confirmed that equivalent dermal fillers are safe and well tolerated, mostly reporting mild adverse events (AEs), which resolve quickly.

Princess® FILLER Lidocaine obtained the European Conformity (CE) mark in 2016. [redacted]

[redacted]

Two clinical investigations have been performed evaluating the safety and effectiveness of Princess® FILLER for the treatment of NLFs (Arruda, Costa, Pereira, de Oliveira Pereira, & Assumpção, 2013; Landau, 2011). The studies confirmed a significant decrease ($p<0.05$ Wilcoxon signed rank test) in wrinkle severity after treatment with Princess® FILLER, which lasted up to 1 year after treatment. The treatment was safe and well tolerated, with minor AEs related to treatment (erythema/edema at the injection site, ecchymosis, hematoma and local pain), all of which were mild to moderate in intensity, of short to medium duration and had completely resolved by the end of the clinical investigation.

Additionally, Princess® FILLER was evaluated in a post-market clinical follow-up study (FLASH 1), in order to evaluate its performance and safety for the correction of facial lipoatrophy, morphological asymmetry of the face or debilitating scars. The study showed treatment with Princess® FILLER to be safe, well tolerated and efficacious in the treatment of facial lipoatrophy, morphological asymmetry and debilitating scars and confirmed the effectiveness of the investigational device over a six-month period. The treatment outcome was

[1] Source PMS Report 2017

declared highly successful by investigators, patients and independent reviewer. There were no serious adverse events (SAEs) in the study, and only few adverse device effects (ADEs) were recorded; apart from two events of headache, all ADEs were limited to the injection site and have already been described in the literature as common adverse effects of crosslinked HA dermal fillers.

Hence, the studies demonstrated the safety and effectiveness of Princess® FILLER in the treatment of NLFs and confirmed the favourable benefit/risk ratio evident from Post-Market Surveillance.

The current clinical investigation will assess the safety and effectiveness of Princess® FILLER Lidocaine in the correction of moderate to severe NLFs.

4.2 Clinical Condition/Indication

The indication for Princess® FILLER Lidocaine to be studied in this clinical investigation is correction of moderate to severe NLFs.

The device is not yet approved in the US, while in Europe the label is stating the following: Princess® FILLER Lidocaine is intended to correct moderate to severe facial wrinkles and folds and to increase lip volume; the device was also conceived for medical purposes and aims to address reconstructive purposes in the treatment, for instance, of facial lipoatrophy, debilitating scars or morphological asymmetry; it is indicated to be injected into the mid to deep dermis (EU IFU, see Section 22.2).

Juvéderm® Ultra XC is indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as NLFs) (see Section 22.3).

In this clinical investigation, both investigational medical devices (IMDs) will only be used to treat NLFs.

4.3 Description of the Investigational Medical Devices

4.3.1 Princess® FILLER Lidocaine

Princess® FILLER Lidocaine is a biodegradable HA filler for soft tissue augmentation. It is a sterile, viscoelastic, clear, transparent, isotonic and homogenized, injectable gel implant. Princess® FILLER Lidocaine consists of cross-linked HA, obtained from *Streptococcus equi*

bacteria, formulated to a concentration of 23 mg/mL in a physiologic buffer. The gel is produced with HA molecules of biofermentative origin which are cross-linked via BDDE. The formulation additionally contains 0.3% of the medicinal product lidocaine hydrochloride as an ancillary substance.

The device is intended for single use, it is sterile, non-active, and without measuring function. No materials of human or animal origin are used during manufacture or as raw materials.

The device is intended to correct moderate to severe facial wrinkles and folds and to increase lip volume. The device was also conceived for medical purposes and aims to address reconstructive purposes in the treatment, for instance, of facial lipoatrophy, debilitating scars or morphological asymmetry. It is indicated to be injected into the mid to deep dermis (EU IFU, see Section 22.2).

Biodegradation of cross-linked HA occurs through different pathways (e.g. enzymatic, temperature, free radicals), and its longevity *in vivo* is thus limited. Degradation of BDDE cross-linked HA is isovolemic, i.e. it remains most of its initial filler volume throughout the degradation phase (F. S. Brandt & Cazzaniga, 2008). The benefit of the fillers is via a volume effect and by attracting and binding water. When fully degraded, it is absorbed without any fibrosis or remaining implant product (F. S. Brandt & Cazzaniga, 2008). Metabolism by-products are water and carbon dioxide.

Princess® FILLER Lidocaine is provided in steam sterilized syringes containing 1.0 mL of the injectable gel implant. The syringes are packed in boxes also containing two 27 G ½″ disposable sterile needles. Batch numbers, attached to the boxes, are used to ensure traceability.

The maximal recommended dosage is up to 10 mL per treatment session and up to 20 mL per subject per year.

For more information please refer to the Investigator's Brochure.

Manufacturer of Princess® FILLER Lidocaine: Croma-Pharma GmbH, Industriezeile 6, 2100 Leobendorf, Austria.

Manufacturer of the needle: [redacted].

4.3.2 Juvéderm® Ultra XC

Juvéderm® Ultra XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of cross-linked HA produced by *Streptococcus* species of bacteria, formulated to a concentration of 24 mg/mL and 0.3% weight/weight lidocaine in a physiologic buffer.

Juvéderm® Ultra XC is indicated for injection into the mid-to-deep dermis for correction of moderate to severe facial wrinkles and folds (such as NLFs).

Juvéderm® Ultra XC injectable gel is supplied in syringes containing 1.0 mL of the injectable gel implant with 30G needles.

The maximal recommended dosage is up to 10 mL per treatment session and up to 20 mL per subject per year. Cave, the treatment with Juvéderm® Ultra XC should be limited to 20 mL per 60 kg (130 lbs) body mass per year, as stated in the IFU (US IFU, see Section 22.2).

Manufacturer of Juvéderm Ultra XC: Allergan US.

4.4 Non-clinical and Clinical Summaries

4.4.1 Pre-clinical Experience and Biocompatibility

The device is manufactured in compliance with International Organization for Standardization (ISO) 13485 and Good Manufacturing Practice. The chemical, physical and biological properties of Princess® FILLER Lidocaine were extensively characterized during development. Compliance with ISO 14630 "Non-active surgical implants – general requirements" was demonstrated. Princess® FILLER Lidocaine was classified as an implantable medical device in permanent contact with tissues or bones according to ISO 10993-1. [redacted]

[redacted]

4.4.2 Clinical experience

Over the past two decades, soft tissue augmentation using injectable fillers, has become a standard clinical approach for correcting age-related facial defects. Among these, HA-based fillers appear to be ideal due to their low immunogenic potential and relatively long-lasting effect. Moreover, due to their very favorable risk/benefit profile, HA products are the most widely used dermal fillers in Europe and the USA.

Since their introduction, these devices have been proven to be safe, effective and easy to use (Beasley, Weiss, & Weiss, 2009). Princess® FILLER Lidocaine carries the European Conformity (CE) mark and has been on the European market since 2016. Princess® FILLER (without lidocaine) obtained the CE mark in 2008.

4.4.3 Clinical Summary

Clinical data is not yet available for Princess® FILLER Lidocaine, however data is available for Princess® FILLER, which is virtually the same dermal filler without lidocaine. Clinical studies with Princess® FILLER, conducted in the course of post-marketing activities in Europe, confirmed that the device is safe and effective.

<u>Post-marketing study 1:</u> "[redacted] for the treatment of nasolabial folds".

This clinical investigation was performed in 30 subjects with NLFs, aged 30 to 60 years. At the start of the investigation, 76% of subjects had moderate and 24% of subjects had severe wrinkles. One year post-injection of HA, 8% of subjects presented with severe, 56% with moderate, and 36% mild wrinkles with changes being statistically significant. Other effectiveness outcome measures confirmed these positive results and most subjects (88%) were willing to repeat the treatment at the end of the clinical investigation. Collagen levels and elastic fibers were not significantly changed after the treatment. The AEs with positive causal nexus were: local erythema/edema, ecchymosis, hematoma and local pain. They presented mild to

[redacted]

moderate intensity, and short to medium duration. The AEs were rare and resolved completely, thus demonstrating the safety of the device (Arruda et al., 2013).

Post-marketing study 2: "An open-label study of the safety and efficacy of Princess FILLER for the correction of moderate to severe wrinkles".

This clinical investigation was performed in 71 subjects with different indications (NLFs, marionette lines and glabellar lines). The evaluation of the wrinkle severity score showed a significant immediate improvement of the wrinkles as well as a long lasting effect after administration of Princess® FILLER. On a 4-point scale (from 1, mild, to 4, severe) average wrinkle severity was reduced from 2.17 before treatment to 1.16 and 1.7 one month and nine months post-injection, respectively. More than 70% of the subjects reported that their expectations had been reached at 240 days (end of follow-up period). Short term reactions were transient and related to the injection procedure (e.g. redness, swelling and pain). No long term adverse reactions were reported, confirming that the device was well tolerated (Landau, 2011).

Therefore, both studies demonstrated the safety and effectiveness of Princess® FILLER in the treatment of NLFs.

Post-marketing study 3: "Prospective, open label, non-comparative, multicentre, post-market clinical follow-up study of the Princess® FILLER performance and safety for correction of facial lipoatrophy, morphological asymmetry of the face, or debilitating scars (CPH-410-201259, FLASH 1)"

Princess® FILLER was evaluated in a post-market clinical follow-up study (FLASH 1, see Section 6.2.1), in order to evaluate its performance and safety for the correction of facial lipoatrophy, morphological asymmetry of the face, or debilitating scars. The study showed treatment with Princess® FILLER to be safe, well tolerated and efficacious in the treatment of facial lipoatrophy, morphological asymmetry and debilitating scars and confirmed the effectiveness of the investigational device over a six-month period. The treatment outcome was declared highly successful by investigators, patients and independent reviewer. There were no SAEs in the study, and only few ADEs were recorded; apart from two events of headache, all ADEs were limited to the injection site and have already been described in the literature as common adverse effects of crosslinked HA dermal fillers.

4.5 Clinical investigation Rationale

The current clinical investigation is designed to support regulatory approval in the US and to obtain clinical safety and effectiveness data for the dermal filler Princess® FILLER Lidocaine in the treatment of NLFs.

A non-inferiority investigation to assess the safety and effectiveness of Princess® FILLER Lidocaine in comparison with Juvéderm® Ultra XC is considered appropriate and in line with current FDA guidance. Each subject will receive Princess® FILLER Lidocaine to correct one NLF and Juvéderm® Ultra XC to correct the contralateral NLF. NLFs severity will be assessed with the NLF-SRS, which is an new objective and validated measurement tool for NLFs severity assessments developed recently for Croma-Pharma GmbH by Canfield Scientific Inc. Since the effects of HA dermal fillers have been reported to last from four to twelve months (Downie, Grimes, & Callender, 2013; Goodman et al., 2011; Nast et al., 2011) the follow-up period for effectiveness will be 36 weeks, with an option for repeat-treatment at 36 or 48 weeks.

The clinical investigation schedule includes a single treatment per subject, which is sufficient to provide optimal correction as determined by the treating investigator, with an option for touch-up treatment two weeks later to address any possible under-correction and a repeat-treatment at Week 36 or Week 48, if repeat-treatment is not needed at Week 36. The schedule includes visits at 2, 12, 24 and 36 and or 48 weeks after treatment for effectiveness and safety evaluation, as well as weeks 40 and/or 52 for safety evaluation.

The marketed product Juvéderm® Ultra XC is used as comparator in this clinical investigation, since containing the same lidocaine hydrochloride concentrations as Croma-Pharma GmbH's product and approved for the treatment of NLFs. Moreover, Juvéderm® Ultra XC is comparable to Princess® FILLER Lidocaine regarding its composition and intended use.

A non-inferiority investigation to assess the safety and effectiveness of Princess® FILLER Lidocaine in comparison to Juvéderm® Ultra XC is considered appropriate and in line with current FDA guidance.

5 Clinical Investigation Purpose and Objectives

5.1 Purpose

To evaluate the effectiveness and safety of Princess® FILLER Lidocaine in the correction of moderate to severe NLFs compared to Juvederm® Ultra XC.

5.2 Primary Objective

The primary objective is to assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvederm® Ultra XC, based on the independent blinded evaluating investigator live assessment using the NLF-SRS at Week 24 after initial treatment and relative to Baseline assessments.

5.3 Secondary Objectives

1. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvederm® 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 Juvederm® 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 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

5.4 Additional Objectives

1. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvederm® 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 and relative to Baseline assessments
2. To assess the effectiveness of Princess® FILLER Lidocaine in reducing the severity of NLFs compared to Juvederm® 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 Juvederm® Ultra XC, based on the treating investigator live assessments at Week 12, 36, 48 and Visit 7c after initial treatment and 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, and/or 48 and Visit 7c after initial treatment
7. To assess subject appearance appraisal of NLFs after treatment at Week 12, 24, 36, and/or 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 Juvederm® Ultra XC
9. To assess 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 Juvederm® Ultra XC

5.5 Safety Objectives

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

6 Risks and Benefits of the Investigational Device and Clinical Investigation

6.1 Potential Risks

In general HA fillers are the most frequently used dermal fillers and are considered the most predictable, having been shown to be safe and well-tolerated, with studies reporting mild adverse events which resolve quickly. Risks associated with the clinical investigation IMDs may include common, short-term events like discomfort, redness, swelling or bruising (DeLorenzi, 2013).

Less likely and uncommon events may include short-term events like injection site necrosis or hypersensitivity or medium-term events like visibility of injectant (blanched, bluish or white papule or lumps) or nodule formation (DeLorenzi, 2013; Funt & Pavicic, 2013; Ibrahim, Overman, Arndt, & Dover, 2017).

Rare but serious adverse events associated with the unintended intravascular injection of dermal fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, which are leading to stroke, skin necrosis, and damage to underlying facial structures (Beleznay et al., 2015). Possibly unrelated events like headache, sinusitis, respiratory symptoms, itching, acne and herpes simplex reactivation have been occasionally reported after treatment with dermal fillers (Bugge et al., 2007; DeLorenzi, 2013; Funt & Pavicic, 2013; Gazzola, Pasini, & Cavallini, 2012; Requena et al., 2011).

The risks will be mitigated by following strategies:

- engagement of investigators who are experienced in use of dermal fillers for correction of NLFs to ensure correct application of the investigational device
- regular follow-up assessments throughout the study duration, which will allow for timely recognition and management of potential AEs
- evaluation of vision changes through visual examinations before and after treatment
- protocols at each investigational site for immediate intervention in the event of unintended vascular injection
- phone calls for safety follow-up: the subjects will be contacted by phone three days after initial, touch-up and repeat-treatments to check their health condition, and will be

also instructed to immediately contact the treating investigator in case of any health concern occurring between the scheduled visits.

6.2 Potential Benefits

Treatment with Princess® FILLER Lidocaine should reduce the severity of NLFs in subjects by using an easy-to-perform and minimally invasive procedure, with a short downtime and resulting in immediate and long-lasting effects. The addition of lidocaine should lead to a more comfortable and pain-free procedure.

6.3 Risk / Benefit Rationale

Dermal fillers formulated using non-animal stabilized HA, such as Princess® FILLER Lidocaine, are considered very safe and effective and have been widely used for soft tissue augmentation. As these products are non-allergenic, allergy testing before treatment is not necessary.

The expected benefits (reduction or ablation of NLFs) have been previously demonstrated in clinical practice (see Section 4.1). For dermal aesthetic applications more than four thousand subjects have been treated with equivalent or similar devices in controlled and uncontrolled studies with follow-up durations ranging from six to 18 months, thus confirming the safety and effectiveness of dermal fillers.

The inclusion of lidocaine in other dermal fillers has resulted in a statistically and clinically significant reduction in pain (F. Brandt et al., 2010; Royo de la Torre et al., 2013), leading to a more comfortable injection experience. Lidocaine hydrochloride is rapidly released from the device after injection and, due to its short half-life of around 90 minutes, quickly eliminated from the body.

[redacted] Thus, the safety profile of the device in dermal applications is well

[3] PMS data from 2008 to 2017 inclusive

[4] PMS data from 2016 to 2017 inclusive

established and no serious ADEs are expected if injected correctly by an adequately trained and experienced user with appropriate knowledge of facial anatomy. Please refer to the Investigator's Brochure for a list of possible adverse events associated with the use of dermal fillers.

From clinical investigations to date, effectiveness has been reported to be immediate and long-lasting. The treatment is also expected to positively influence the emotional and social wellbeing of the subjects. Thus, the benefits for the subjects participating in this clinical investigation outweigh the possible risks.

7 Design of the Clinical Investigation

7.1 Description of the Clinical Investigation Design

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

Eligible subjects will undergo baseline assessments, where the baseline severity of NLFs (the left side and right side been separately evaluated) will be assessed live by the treating investigator in conjunction with the independent blinded evaluating investigator. Each subject will receive an injection of Princess® FILLER Lidocaine (Group A: left NLF; Group B: right NLF) and an injection of Juvederm® Ultra XC (Group A: right NLF; Group B: left NLF) at Visit 2 (Day 0, Baseline). A touch-up treatment may be performed at Visit 3a two weeks (± 3 days) after initial treatment, if optimal aesthetic correction was not achieved after the first injection at Baseline. Follow-up assessments for safety and effectiveness will be performed at Week 2 (optional touch-up), Week 12, 24, 36 and/or 48 (for details see Section 2.1). At Visit 6 and/or Visit 7 and/or Visit 7c (see end of this section for details on this visit), an evaluation for repeat-treatment is scheduled, followed by repeat-treatment as well during these visits if needed. The repeat-treatment will be performed with Princess® FILLER Lidocaine on both NLFs.

In that case safety visits are then scheduled four weeks after the repeat-treatment (at Week 40/Visit 8a or Week 52/Visit 8b or Visit 8c) and twelve weeks after the repeat-treatment (at Week 48/Visit 9a or Week 60/Visit 9b or Visit 9c) (see end of this section for details on Visit 8c and Visit 9c). Additional safety follow-up assessments will be performed on the phone three days (± 24 hours) after initial, touch-up and repeat-treatments, only for subjects who received this treatment. At the end of each treatment session, subjects will receive a diary to record the injection site reactions, as well as the incidence of AEs associated with unintended intravascular injection over the following four weeks after initial-, touch-up- and repeat-treatments.

NLFs severity will be evaluated (live assessment) by the treating investigator and by the independent blinded evaluating investigator, using the NLF-SRS. 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 vision changes, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) will be performed at Baseline (Visit 2) and at Week 4 (Visit 3b); visual examinations will be done as well at Week 2 (Visit 3a) and at Week 6 (Visit 3c) for subjects who received touch-up treatment, and also at Week 40 (Visit 8a) or at Week 52 (Visit 8b) or at Visit 8c for subjects having received repeat-treatment respectively at Week 36 (Visit 6) or at Week 48 (Visit 7) or at Visit 7c. These assessments will be done prior to- and 30 min after any treatment. Further details on visual examinations and the action to be taken in case of clinically significant changes are provided in Section 10.8.

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 Juvederm® XC.

Note: During the conduct of the trial, some subjects were not evaluated for repeat-treatment at Week 36 (Visit 6) and/or Week 48 (Visit 7) due to a hold on repeat-treatment. Therefore, a post repeat-treatment hold follow-up visit (Visit 7c, no visit window) has been added in CIP Version 7.0 to allow subjects to return for evaluation following the end of the hold on repeat-treatment. Subsequent follow up visits (Visit 8c [4 weeks after repeat-treatment] and Visit 9c [12 weeks after repeat-treatment]) have also been added.

7.2 Population to be Studied

A total of approximately 300 subjects of either gender, over 22 years of age inclusive at Screening, who meet all the inclusion criteria and do not meet any exclusion criteria and who provide written informed consent, will be enrolled in the clinical investigation.

7.3 Outcome Measures

7.3.1 Effectiveness Outcome Measures

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

7.3.1.1 Primary outcome measure:

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

7.3.1.2 Secondary Outcome Measures:

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

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 Juvederm® 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

7.3.1.3 Additional Outcome Measures:

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

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 Juvederm® 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 assessments at Week 12, 36, 48 and Visit 7c after initial treatment and compared to Juvederm® 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 assessments 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 assessments at Week 12, 36, 48 and Visit 7c after initial treatment and using the 5-point GAIS
6. The extend 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 treatment with Princess® FILLER Lidocaine and with Juvéderm® Ultra XC, and Subject's perception of pain 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 (separate assessments) and recording of injection volume required to achieve optimal correction for Princess® FILLER Lidocaine at repeat-treatments (separate assessments)

7.3.2 Safety Outcome Measures

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

All effectiveness and safety outcome measures are standard measurements. The 5-point NLF-SRS, used to assess the primary effectiveness outcome measure, is an objective and validated measurement tool for NLFs severity assessment (see Section 10.1).

7.4 Subject Identification

Each site will be assigned a unique site identification code; additionally, at each site, the treating investigator will assign an unique subject identification number in ascending order e.g. 001, 002, 003 etc.

Subjects will be enrolled until the planned sample size is achieved. Drop-outs will not be replaced.

7.5 Screening Failures

Data for screening failures (eligible subjects who did not receive investigational device for whatever reason) will be collected in source documentation at the site, documented in the Screening log and entered into the electronic case report form (eCRF), including the reason for the failure.

7.6 Randomization 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 followed:

- 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. To check if the independent blinded evaluating investigator has been successfully blinded, the following questions will be asked after the initial treatment:

- *Can you guess which of the two fillers the subject has received into the left nasolabial fold?*
- *If Yes, which one?*
- *Why do you deem that the subject has received that filler into the left nasolabial fold?*

The subject will be blinded using a blindfold. To check if the subject has been successfully blinded, the following questions will be asked after the initial treatment:

- *Can you guess which of the two fillers you've received into the left nasolabial fold?*
- *If Yes, which one?*
- *Why do you deem that you've received that filler into the left nasolabial fold?*

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

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 HA dermal filler with lidocaine, which is, in both cases, sufficient level of information needed in case of emergency.

8 Investigational Medical Devices

8.1 Packaging and Labeling

Princess® FILLER Lidocaine is provided in syringes containing 1.0 mL of the injectable gel implant, together with two 27 G ½″ disposable sterile needles.

Juvéderm® Ultra XC injectable gel is supplied in syringes containing 1.0 mL of the injectable gel implant with 30 G needles.

Both devices will be labeled according to applicable guidelines and national legal requirements.

8.2 Storage and Handling

Both Princess® FILLER Lidocaine and Juvéderm® Ultra XC must be stored at 2 to 25°C in a dry place in the original box, protected from light, heat and frost. There are incompatibilities between sodium hyaluronate and quaternary ammonium compounds such as benzalkonium chloride solutions. Therefore, Princess® FILLER Lidocaine or Juvéderm® Ultra XC should never be placed in contact with these substances, or with medical-surgical instruments that have been in contact with these substances.

8.3 Administration of the Device

8.3.1 Preparation of Administration

The IMDs must not be used if the packaging is opened or damaged. Upon opening of the packaging, the devices should not be re-sterilized or reused.

For more information please refer to the respective Instructions for Use (see Section 22.2).

The skin to be treated should be thoroughly cleaned and disinfected prior to injection of the device and appropriate aseptic technique should be employed throughout the procedure.

Prior to use the device, the luer-lock adapter should be held securely and the tip cap should be removed by twisting and pulling carefully, which should prevent formation of bubbles. The syringe should be held and the enclosed needle firmly attached. The needle should be secured tightly by twisting clockwise. The syringe is held correctly if the backstop opens at the back, toward the hand in which it is held.

8.3.2 Injection Technique

The injection technique used is essential for the success of treatment. Therefore, all participating treating investigators will receive, or must have previously received, specific training in injection techniques for filling NLFs; such specific training in the injection technique will be documented in the Trial Master File.

The investigational device should be injected into the mid- to deep dermis. Superficial injections, near the interface of the epidermis and papillary dermis, can result in visible white, yellow, or blue nodules, which may be persistent. Deep injections into the subcutaneous fat may result in loss of the filler in the vast subcutaneous space, requiring larger volumes.

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

After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular.

After the first small amount of material has been injected into the subject, it is suggested to wait a full three seconds to allow the lidocaine to take effect before proceeding with the rest of the injection (Juvéderm® IFU, see Section 22.3).

Different injection techniques can be employed based on investigator's preference and characteristics of the defect under correction. These include:

Retrograde technique: introduction of the entire needle along the fold or skin depression and injecting while slowly withdrawing the needle.

Fan technique: introduction of the entire needle along the fold or skin depression and injecting while slowly withdrawing the needle. The fan technique consists in introducing the needle as for the retrograde technique, and injecting the gel while withdrawing the needle, without removing its tip from the skin; then, changing the direction of the needle and injecting a new line. Repeating this process several times will achieve a fan pattern. This technique allows filling a large area and creating or restoring facial volume from a single injection point.

Lateral movements of the needle must be avoided since these may result in a fanlike dissection of the sub-epidermal plane, increasing the incidence of local AEs like bruising, swelling, redness, pain, or tenderness at the injection site.

The device should only be used with the needle and syringe provided by the manufacturer.
The device should be injected slowly with the least amount of possible pressure for the same reason. If the needle is blocked, the pressure on the plunger rod should not be increased, but the injection stopped and the needle replaced.

If a larger volume of the filler is needed to achieve the correction, small volumes should be injected in two or more sessions, instead of high volumes in one session.

The injection must be stopped just before the needle is pulled out of the skin to prevent leakage of the device or placement too superficially in the skin.

The needle must not be manipulated or bent, if the needle is blocked, pressure on the plunger rod should not be increased, instead injection should be stopped and the needle replaced.

After use the syringe, needle and remaining contents should be disposed appropriately and the device should never be re-used.

8.3.3 Touch-up treatment

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.

8.3.4 Applied volume of the device

The dosage (volume) of filler to be administered will depend on the depth of the NLF to be corrected, with the goal of optimal correction of the respective NLF with the respective HA filler during the first injection session, and will be decided in each case by the treating investigator. The severity of each NLF, as well as The total volume injected per treatment for each NLF and device, will be recorded in the eCRF. The devices should be injected according to the respective IFU (see Sections 22.2 and 22.3) and will not exceed 10 mL per treatment session.

The maximal recommended Princess® FILLER Lidocaine dosage is up to 10 mL per treatment session and up to 20 mL per subject per year.

Juvéderm® Ultra XC should be limited to 20 mL per 60 kg (130 lbs) body mass per year.

8.4 Precautions and Warnings, Prohibited Medications/Treatments and Restrictions

8.4.1 Precautions and Warnings

- The device must not be used if the expiry date has lapsed, if the packaging or contents are damaged, or if the gel in the syringe appears inhomogenous and/or cloudy
- The device should not be injected into blood vessels, bones, tendons, ligaments, nerves, muscles or naevi
- Immediately stop the injection if a subject exhibits any signs or symptoms associated with injection into a blood vessel, such as changes in vision, signs of a stroke (including sudden difficulty speaking, numbness or weakness in their face, arms or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance (or blanching) of the skin, or unusual pain during or shortly after the procedure
- In case of a vascular event, emergency treatment must be sought, and high dose hyaluronidase (Alam et al., 2008), vigorous massage and heat (gauze with hot water) should be applied. In addition, topical 2% nitroglycerin paste may encourage vasodilatation (Belazay et al., 2015)
- The device should never be placed in contact with quaternary ammonium compounds (such as benzalkonium chloride solutions) or with medical-surgical instruments that have been in contact with these substances

<u>Upon completion of device administration</u>

- After injection the investigator may apply a light massage for uniform distribution of the filler
- Application of ice packs for 5-10 min. post injection is optional and may reduce redness and swelling; this have to be recorded in the clinical investigation eCRF(s) along with any other concomitant medication/treatment
- The subject should be requested to stay in the office for a period of at least 30 minutes after the injection to assess pain following injection and to detect possible blanching caused by arterial occlusions

- The health care professionals must be familiar with the signs and symptoms associated with vascular occlusion, and have a plan detailing how to treat the subject in the event of vascular occlusion; this may include on-site treatment and/or immediate referral to another health care professional for treatment. For instance, in the event of blindness or any ophthalmic signs or symptoms, subjects have to undergo immediate evaluation by a ophthalmology specialist. Ophthalmology specialists (ideally a Retinal Specialist, if readily available) near each investigational site who are able to immediately examine subjects should be identified and informed about the clinical investigation procedure. Additionally, a specific treatment protocol in case of unintended intravascular injection that is consistent with those recognized by national, professional societies should be in place at each investigational site.
- The following information will be recorded in the eCRF(s) for each of the treatments administered: date of application, the side of application, injection technique, exact start time and end time of injection, injected volume of the device (see Section 8.3.4) and device ID.

8.4.2 Prohibited Medications/Treatments

The following medications/treatments will be prohibited:

- From ten days before Day 0 (Baseline) until three days post-injection: use of anticoagulant, antiplatelet or thrombolytic medication
- Current treatment with immunomodulating therapy

8.4.3 Restrictions

- Subjects must be advised not to apply any make-up for twelve hours after the injection
- Subjects should avoid prolonged exposure to sunlight and ultraviolet (UV) for one week after injection
- Subjects should abstain from use of saunas or Turkish baths for one week after the injection
- Subjects should abstain from frequent solarium visits
- Subjects should abstain from consuming alcohol, nicotine –containing products one hour before and after injection

- Subjects should not massage the treatment site or apply pressure to the area for one week following the injection, to avoid the possible risk of device mobility
- Subjects should avoid strenuous exercise within 24 hours after injection

8.5 Rescue Medication

In case of overcorrection, commercially available hyaluronidase should be used at the discretion of the treating investigator, in accordance with the American Society for Dermatologic Surgery guidelines (Alam et al., 2008).

If the subject complains of ocular pain or vision changes, they should be immediatey refered to an ophthamolgy specialist.

8.6 Medical Device Accountability

The assumed average volume of such device to be administred for this indication is 2.0 mL per fold for the initial treatment, 1.0 mL per fold for potential additional touch-up treatment and 2.0 mL per fold for potential repeat treatment. Considering the number of subjects to be enrolled (270 subjects), it is anticipated that maximum of 1,860 units of Princess® FILLER Lidocaine, as well as the 900 units of the control device, will be used during this clinical investigation.

The clinical investigation material must not be used outside the context of this CIP. Documentation of receipt, dispensing and return of all IMDs must be performed by the principal investigator or his/her designee. It is the principal investigator's responsibility to ensure that all clinical investigation materials are kept in a secure location, with access limited to individuals authorized by the principal investigator. At the end of the investigation, all remaining clinical investigation material should be destroyed on site, following the site-specific destruction procedure after a monitor has verified all accountability documentation. If the site does not have an appropriate destruction process, the material must be returned to the sponsor designee . Records on investigational device delivery to the center, the inventory at the site, the use by each subject, and return to the sponsor must be maintained by the principal investigator or designee. Forms will be provided to enhance device accountability.

As the preparations are for use of the treating investigator only, compliance will be controlled by the drug accountability log and empty packages only. Empty or used syringes will not be returned to the sponsor, but will be destroyed as per investigational sites's procedures.

9 Subject Selection, Withdrawal and Discontinuation

9.1 Inclusion and Exclusion Criteria – Screening/Baseline

9.1.1 Inclusion Criteria

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

1. Male or female subjects, 22 years of age or older, at the Screening visit
2. Subjects with two fully visible, approximately symmetrical moderate to severe NLFs (same severity) with severity scores of 2 or 3 on the 5- point NLF-SRS for both NLF 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
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 glabellar or forehead botulinum toxin treatment)
6. Subjects having understood the purpose and conduct of the clinical investigation and having given written informed consent

9.1.2 Exclusion Criteria

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

1. For females: pregnant and/or lactating or planning to become pregnant during the clinical investigation
2. History of allergies or hypersensitivity to HA 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. Re-current 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) 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 lypolysis, including submental fat treatments, within last month prior to enrollment and during the clinical investigation
14. Bariatric surgery within 12 months prior to enrollement and during the clinical investigation
15. History of bleeding disorders 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 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
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.

9.2 Inclusion and Exclusion Criteria – Repeat-treatment

9.2.1 Inclusion Criteria

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

9.2.2 Exclusion Criteria

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

1. Occurrence of an SAE or adverse event of special interest (AESI; i.e., changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes, change 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

9.3 Subject Withdrawal and Discontinuation

Each subject has the right to withdraw his/her consent to participate in the clinical investigation at any time and without giving reasons.

Subjects may be discontinued for the following reasons:

- Lost to Follow-Up
- Consent withdrawal (the treating investigator must try to find out and document the reasons for withdrawal of consent)
- Safety reasons including abnormal and clinically significant changes in visual examinations (see Section 10.8.4)
- Treating investigator's decision
- Poor compliance and/or disregard of the treating investigator's instructions
- Major CIP violation

In case of early withdrawal, reasons, circumstances and findings should be described as completely as possible on the "Early Termination" page in the CRF respecting the subject's privacy. Subjects who are withdrawn prematurely should undergo an early termination visit with the assessments that are scheduled for Week 40 (Visit 8a) or Week 52 (Visit 8b) or Visit 8c.

In accordance with similar studies in this indication, the expected lost to follow-up rate is estimated to reach approximately 5% and repeat treatments will be offered in this clinical investigation to further decrease the amount of lost to follow-up subjects. Due to the split face design, minimal attrition bias is expected.

9.4 Subject Enrollment, Number and Duration of Subject's Participation

Subjects who have signed the informed consent form (ICF) and comply with all inclusion and exclusion criteria will be enrolled, and undergo treatment at Visit 2 on Day 0. Screening and Baseline may be combined in one visit. If full correction is not achieved after the initial treatment, subjects may receive a touch up treatment 2 weeks later and can receive repeat-treatment (with Princess® Filler Lidocaine only) at Week 36 (Visit 6) or Week 48 (Visit 7) or Visit 7c. Each subject is expected to be in the clinical investigation for a maximum of 104 weeks including the temporary hold on repeat-treatment.

Approximately 300 subjects will be screened in the USA; the enrollment of a total of approximately 270 subjects is planned in order to obtain at least 240 evaluable subjects randomized in an 1:1 ratio to each clinical investigation group (accounting for a screening failure rate of approximately 10%, as well as approximately 10% of subjects to be excluded from the Per-Protocol Set due to major protocol deviations or subjects lost to follow-up).

The clinical investigation is planned to be conducted at approximately 10-12 US sites with enrolment target of 23-27 subjects per site. Competitive recruitment may 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.

10 Clinical investigation Procedures and Assessments

10.1 Nasolabial Folds-Severity Rating Scale (NLF-SRS)

The Baseline severity of NLFs will be assessed by the treating investigator in conjunction with the independent blinded evaluating investigator at Screening using the NLF-SRS. Subjects can be included with two fully visible, approximately symmetrical moderate to severe NLFs (same severity) with severity scores of 2 or 3 on the 5- point NLF-SRS for both NLF as judged by the treating investigator in conjunction with the independent blinded evaluating investigator. It is essential that the subject qualifies on both evaluator assessment as having a rating of 2 or 3 on the 5-point NLF-SRS, both investigators do not need to be full agreement as long as they agree that the subject has at rating of 2 or 3. The NLF-SRS is a validated 5-point rating scale ranging from Grade 0 (none) to Grade 4 (extreme) as outlined in Table 1; this scale have been developed and validated by Canfield Scientific Inc. for Croma-Pharma GmbH. Additional information on how NLFs severity should be evaluated for the standardized treating investigator's live assessment and for the standardized live assessment by the independent blinded evaluating investigator will be outlined in the manual.

After enrollment, live assessments, using the NLF-SRS, will be performed by the treating investigator and the independent blinded evaluating investigator (separate assessments) at Week 12 (Visit 4), at Week 24 (Visit 5), at Week 36 (Visit 6) and/or at Week 48 (Visit 7) and/or at 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 treating investigator and the independent blinded evaluating investigator will be trained on the 5-point NLF-SRS prior to the study start, during the investigator meeting, a live WebEx with a sponsor medical consultant, or through review of a recording of the WebEx. Additional open questions will be answered during the pre-study visits; further training on the scale will be also performed during site pre-study visits, if needed. The independent blinded photographic reviewers will be trained on the 5-point NLF-SRS prior to their assessments of the photographs.

Table 1: Nasolabial Folds-Severity Rating Scale (NLF-SRS)

Grade	Definition
0	**None/minimal:** No visible/minimal NLFs
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

10.2 Global Aesthetic Improvement Scale (GAIS)

The GAIS is a 5-point scale that rates global aesthetic improvement from the pre-treatment appearance. The ratings are "worse", "no change", "improved", "much improved", and "very much improved" and will be judged by the evaluating investigator (Table 2). Additional information will be available in manuals for independent blinded evaluating investigators and for subjects.

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/or at Visit 7c. At Week 36 (Visit 6), Week 48 (Visit 7), and/or 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 2: Global Aesthetic Improvement Scale

Grade		Definition
1	**Very much improved**	Optimal aesthetic results 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).

10.3 Subject Satisfaction using Face-Q Questionnaires

FACE-Q, User's Manual, version 1.0, January 2015 (see Section 22.1).

10.3.1 Satisfaction with Outcome

In the section of the User's manual, "Process of Care Scales", the questionnaire about the "Satisfaction with Outcome" will be used: This scale measures a subject's satisfaction with the result of their most recent procedure.

"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) and/or at Week 48 (Visit 7) and/or Visit 7c.

Separate assessments will be performed for the left and the right side of the face.

10.3.2 Appraisal of Nasolabial Folds

In the section of the User's manual, "Appearance Appraisal Scales", the questionnaire about the "Appraisal of Nasolabial Folds" will be used.

"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) and/or at Week 48 (Visit 7) and/or Visit 7c.

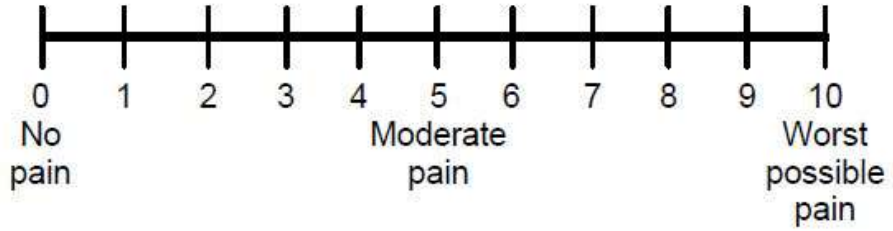
Separate assessments will be performed for the left and the right side of the face.

10.4 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 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 repeat-treatments) using the adapted NPRS.



10.5 Injection Volume

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

10.6 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

10.7 Clinical Photography

Clinical photography of the subject's face will be taken at Screening (Visit 1), on Day 0 (Baseline) and at Week 12, 24, 36 and/or 48 and/or Visit 7c after initial treatment (at Visit 2, 4, 5, 6 and/or 7 and/or 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.

10.8 Visual Examinations

Visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) will be performed at the study site by the examiner (i.e. treating investigator or authorized designee) prior to- and 30 min after any treatment (after all other assessments have been performed) at:

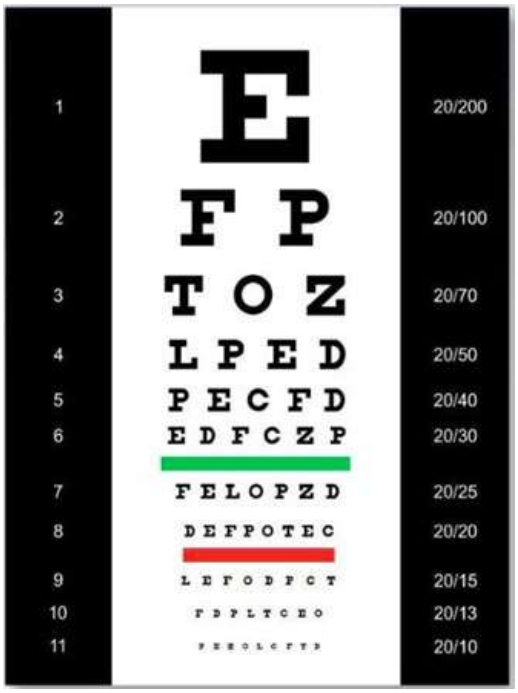
- Baseline (Visit 2)
- Week 2 (Visit 3a) (only in case of touch-up treatment)
- Week 4 (Visit 3b)
- Week 6 (Visit 3c) (only in case touch-up treatment was performed at Week 2 [Visit 3a])
- Week 36 (Visit 6) or Week 48 (Visit 7) or Visit 7c (only in case of repeat-treatment)
- Week 40 (Visit 8a) or Week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

All visual examination results and the use of corrective eyewear (i.e., glasses/contact lenses) will be recorded on the eCRF.

10.8.1 Snellen Visual Acuity

Visual acuity for each eye will be assessed using the standard Snellen hanging wall chart (Figure 1).

Figure 1: Standard Snellen Hanging Wall Chart



The assessment will be carried out as follows:

- The standard Snellen hanging wall chart will be read with the subject standing at a distance of 20 feet (6 meters).
- Each eye will be tested independently (i.e. one eye will be covered while the other eye will be used to read).
- If applicable, the subject should wear the same corrective eye wear (i.e. glasses/contact lenses) at each assessment.
- The ability to read every line on the chart does not need to be assessed. It is acceptable to move directly to the smaller characters, where appropriate.
- The numbers at the end of the line indicate the subject's visual acuity compared with a subject with normal visual acuity:
    - Normal limits are 20/25 or better, with no acuity difference between the eyes
    - The larger the denominator, the worse the acuity
    - 20/200 = subject sees at 20 ft (6 meters) what an individual with normal visual acuity sees at 200 ft (60 meters)
    - Results will be recorded in the eCRF as normal or abnormal alongside the actual Snellen results in numerical form for both eyes

10.8.2 Confrontational Visual Fields

The confrontational visual fields will be used to assess peripheral vision for each eye. The assessments will be made as follows:

Correct positioning

- The examiner should be eye level with the subject, separated by approximately 8 to 12 inches (20 to 30 cm).
- The subject should remove corrective eyewear (i.e. glasses/contact lenses).
- The examiner will cover one eye and the subject will cover the one opposite. The open eyes should then be staring directly at one another.

Technique

- The examiner will present finger(s) in each of 4 quadrants, taking care not to position fingers in overlapping quadrates.
- With head stationary the subject will be asked to correctly identify the number of fingers.
- All 4 quadrants (upper and lower, temporal and nasal) must be tested.
- The test will be repeated with the opposite eye open.

10.8.3 Ocular Motility

The movements and alignment of eyes will be tested for each eye by evaluation of ocular motility as follows:

- The examiner will stand in front of the subject.
- The subject should remove corrective eyewear (i.e. glasses/contact lenses).
- The subject will be asked follow examiner’s finger with their eyes while keeping their head in one position.
- The examiner will trace an imaginary "H" or rectangular shape in front of them, making sure that the finger moves far enough out and up/down so that all appropriate eye movements can be seen (lateral up, lateral down, medial down, medial up).
- Then the finger will be brought directly in towards the subject's nose. This will cause the subject to look cross-eyed and the pupils should constrict (accommodation).
- The eyes should be able to easily and smoothly follow the examiner’s finger.
- The results of the test will be documented for both the left and the right eye.

10.8.4 Abnormal Visual Examinations

The following results from visual examinations at Baseline will be considered abnormal and will exclude the subject from participation in the study:

- **Snellen acuity test**: any result worse than 20/40 (with corrections, if applicable)
- **Confrontational visual field test**: abnormal is defined as the inability of the subject to correctly identify/count the examiner’s fingers in one or more quadrants in one or both eyes.

- **Ocular motility**: abnormal is defined as the inability of the subject to follow the finger of the tester smoothly; inability to focus on the finger as it points to the nose; any unexpected and/or uncontrolled eye movements such as nystagmus or divergent or unilateral strabismus

Should any of the vision assessments (Snellen visual acuity, confrontational visual test field, or ocular motility) suddenly worsen after the injection of the filler, the treating investigator must examine the subject to exclude vascular injection and contact an eye specialist if necessary.

In addition, any one of the following changes in visual examinations after Baseline will be considered abnormal and clinically significant:

- **Snellen acuity test**: any change of 1 line or more
- **Confrontational visual field test**: change to the peripheral vision
- **Ocular motility**: change to ocular motility

If any of the above changes occur at any assessment, the change should be reported as an AE and the subject must be referred to an ophthalmologist to evaluate if the resulting change is related to a vascular injection of the dermal filler. If the ophthalmologist confirms that the the result is related to a vascular injection of the dermal filler, the subject should be treated per standard of care for intravascular injection of dermal filler. The subject will be withdrawn from the study and the need for stopping the study will be reviewed.

10.9 Other Assessments

Each of the following information have to be listed in the subject's medical record and recorded on the eCRF:

- **Demography**: includes date of birth, sex, race and ethnicity collected at Screening (Visit 1); every effort will be made to enroll male subjects in sufficient numbers.
- **Medical/aesthetic procedures history:** collected from both subject interview and medical records at Screening (Visit 1).

  Particular attention should be paid 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

All co-morbidities, major surgeries, aesthetic dermatology procedures in the previous year (e.g. skin resurfacing procedures, needling, mesotherapy, or similar), all medications taken within the previous ten days, and, in females, the date of the last period will be recorded in the eCRF.

- **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.

  At each visit or phone call, the subject must be asked about any new medication taken or changes in current medication, as well as any aesthetic procedure applied in the area treated with the investigational devices.

  On treatment days (Visit 2, 3a, 6 or 7 or 7c), information on concomitant medications/treatments will be collected before the dermal filler injection procedure.

  All prior and concomitant medications/treatments will be recorded in the eCRF

- **Fitzpatrick skin types**: to be documented at Screening (Visit 1); every effort will be made to include individuals with all Fitzpatrick skin types, included types V and VI.

- **Randomization:** will only occurr via IVRS/IWRS once eligibility has been confirmed by the site.

Treatment: Initial, touch-up with the assigned device following randomization scheme will be applied according to this CIP. The repeat-treatment will be performed with Princess® FILLER Lidocaine on both NLFs.

- **Adverse events:** Occurrence of adverse events will be collected at each visit after the initial treatment at Baseline (Visit 2), from Visit 2 to Visit 9a, 9b or 9c included (for more information, see Section 12).

- **Urine pregnancy test:** Required in women 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) and prior to repeat-treatment (Week 36/Visit 6, Week 48/Visit 7 or Visit 7c).

- **Weight measurement:** at Baseline (Day 0/Visit 2), at Visit 3a, 3b, 3c, 4 and 5, as well as at Visit 6, Visit 7 or Visit 7c upon evaluation for repeat-treatment; as well as Visit 8a/8b/8c or Visit 9a/9b/9c; weight measurement should be done to the nearest 0.1 kg and with the subjects standing barefoot and wearing light indoor clothing.

- **Subjects' daily safety diary:** to be dispensed to each subject at the end of each treatment session (and additionally at Week 4/Visit 3b for subjects having received touch-up treatment at Week 2/Visit 3a) in order to record injection site reactions, as well as the incidence of adverse events and AEs associated with the unintended intravascular injection; to be collected and reviewed two and four weeks after initial-/touch-up treatment (and additionally at Week 6/Visit 3c), and four weeks after repeat-treatment.

  The diary will include the following adverse events:

  - 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 color around the eyelids
  - Crusty or scabby skin around the eyelids
  - Headache
  - Fever
  - Dizziness
  - Confusion
  - Weakness or numbness in the arms or legs
  - Changes to consciousness or alertness
  - Difficulty speaking/speech impairment

- Face droop
- Changes to chewing and drinking
- Discomfort and discomfort with palpation
- Sensitivity to hot/cold liquids and foods

Furthermore, the subject diary will include specific instructions to seek immediate medical attention if any of the above symptoms or signs is observed.

10.10 Factors that may Compromise the Outcome

There are no anticipated factors that may compromise the outcome. Substantial body weight changes (more than 10% change from Baseline), UV and sunlight exposure, as well as acne may affect the results. Subjects with unhealthy skin will not be included (see Section 9.1). Subjects will be advised to abstain from prolonged UV exposure for one week after the treatment (see Section 8.4.3) or from excess body weight gain or loss.

10.11 Schedule of the Clinical Investigation

An overview of the schedule of the investigation is provided in Section 2.1. Subjects who have signed the ICF will be considered enrolled.

10.11.1 Screening (Visit 1)

After written informed consent is obtained, the following procedures and/or assessments will be performed at Screening (Visit 1), Day -14 to -3:

- Evaluation of inclusion and exclusion criteria (eligibility assessment)
- Urine pregnancy test in women of childbearing potential only, including those who are postmenopausal for less than twelve months
- Demography (date of birth, sex, race and ethnicity)
- Fitzpatrick skin type
- Medical history (including information on prior facial aesthetic or surgical procedures)
- Live evaluation of nasolabial fold severity by treating investigator in conjunction with the independent blinded evaluating investigator using the 5-point NLF-SRS
- Photography

10.11.2 Baseline (Visit 2)

The following procedures and/or assessments will be performed at Baseline (Visit 2), Day 0:

- Body weight measurement
- Visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) prior to- and 30 min after the treatment (see Section 10.8)
- Evaluation of eligibility criterion based on visual examinations
- Urine pregnancy test in women of childbearing potential only, including those who are postmenopausal for less than twelve months (prior to treatment)
- Randomization (prior to treatment)
- Treatment (initial treatment)
- Live assessment of nasolabial fold severity by treating investigator using NLF-SRS (prior to treatment)
- Live assessment of nasolabial fold severity by the independent blinded evaluating investigator using NLF-SRS (prior to treatment)
- Photography (prior to treatment)
- Evaluation of pain assessment by the subject using the adapted NPRS
- FACE-Q subject appearance appraisal questionnaire (“appraisal of nasolabial folds”) (prior to treatment)
- Dispense of subject diary
- Assessment of injection volume
- AEs (prior to treatment)
- Concomitant medications/procedures (prior to treatment)

10.11.3 Phone Contact after Visit 2

The following assessments will be performed at Day 3 (±24 hours) after Visit 2:

- AEs including if subjects are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection
- Concomitant medications/procedures

10.11.4 Week 2 (Visit 3a)

The following assessments will be performed at Week 2 (± 3 days) after initial treatment:

- Urine pregnancy test in women of childbearing potential only, including those who are postmenopausal for less than twelve months (in case of touch-up only and then prior to treatment)
- Body weight measurement
- In case of touch-up treatment, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility). prior to- and 30 min after treatment. For action to be taken in case of abnormal findings, see Section 10.8.4.
- Treatment (touch-up) if needed
- Collect and review of subject diary dispensed at Baseline (Visit 2)
- Dispense of new subject diary
- Assessment of injection volume (in case of touch-up)
- AEs (prior to treatment)
- Concomitant medications/procedures (prior to treatment)

10.11.5 Phone Contact after Visit 3a

The following assessments will be performed at Day 3 (±24 hours) after Visit 3a:

- AEs including if subjects are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection
- Concomitant medications/procedures

10.11.6 Week 4 (Visit 3b)

The following assessments will be performed at Week 4 (± 5 days) after initial treatment:

- Body weight measurement
- Visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility). For action to be taken in case of abnormal findings, see Section 10.8.4.
- Collect and review of subject diary dispensed at Week 2 (Visit 3a)
- Dispense of new subject diary (only in case touch-up treatment occurred at Week 2/Visit 3a)
- AEs
- Concomitant medications/procedures

10.11.7 Week 6 (Visit 3c)

The following assessments will be performed at Week 6 (± 5 days) after initial treatment:

- Body weight measurement
- In case touch-up was performed at Week 2 (Visit 3a), visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility). For action to be taken in case of abnormal findings, see Section 10.8.4.
- Collect and review of subject diary dispensed at Week 4 (Visit 3b)
- AEs
- Concomitant medications/procedures

10.11.8 Week 12 (Visit 4) and Week 24 (Visit 5)

The following assessments will be performed at Week 12 (± 5 days) and Week 24 (± 5 days) after initial treatment:

- Body weight measurement
- Live assessment of nasolabial fold severity by treating investigator using NLF-SRS
- Live assessment of nasolabial fold severity by the independent blinded evaluating investigator using NLF-SRS
- Assessment of GAIS over Baseline by the evaluating investigator and the subject
- Face-Q subject appearance appraisal questionnaire (“appraisal with nasolabial folds”)

- Face-Q subject satisfaction ("Satisfaction with Outcome")
- Photography
- AEs
- Concomitant medications/procedures

10.11.9 Week 36 (Visit 6) and/or Week 48 (Visit 7) and/or Visit 7c - Evaluation

A repeat-treatment will be performed, if the subject meets the criteria specified in Section 9.2.

The following assessments will be performed at evaluation for repeat-treatment at Week 36 (± 5 days) and/or Week 48 (± 5 days) after initial treatment and/or Visit 7c (no visit window):

- Body weight measurement
- Eligibility for repeat-treatment (see Section 9.2)
- Urine pregnancy test in women of childbearing potential only, including those who are postmenopausal for less than twelve months
- Live assessment of nasolabial fold severity by treating investigator using NLF-SRS
- Live assessment of nasolabial fold severity by the independent blinded evaluating investigator using NLF-SRS
- Assessment of GAIS over Baseline by the independent blinded evaluating investigator and the subject
- Face-Q subject satisfaction ("Satisfaction with Outcome")
- FACE-Q subject appearance appraisal questionnaire ("Appraisal with Nasolabial Folds")
- Photography
- AEs
- Concomitant medications/procedures

Some subjects were not assessed for repeat-treatment at Week 36 and/or Week 48 due to the hold on repeat-treatment. In this case, a subject can attend Visit 7c (no visit window) for evaluation and repeat-treatment as described above (if eligible).

10.11.10 Week 36 (Visit 6) and/or Week 48 (Visit 7) and/or Visit 7c - Repeat-Treatment

The following assessments will be performed at Week 36 (± 5 days) and/or Week 48 (± 5 days) after initial treatment and/or at Visit 7c (no visit window):

- In case of repeat-treatment at Week 36 (Visit 6), Week 48 (Visit 7) or Visit 7c, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) prior to- and 30 min after the treatment. For action to be taken in case of abnormal findings, see Section 10.8.4.
- Treatment
- Evaluation of pain assessment by the subject using the adapted NPRS
- Dispense of subject diary
- Assessment of injection volume

If the subject is being retreated at Week 36, subject qualifies for 4 Weeks Follow up after repeat-treatment at Week 40. If the subject is being retreated at Week 48, subject qualifies for 4 Weeks Follow up after repeat-treatment at Week 52. If the subject is being retreated at Visit 7c, subject qualifies for 4 Weeks Follow up after repeat-treatment at Visit 8c.

10.11.11 Phone Contact after Visit 6, Visit 7 or Visit 7c

The following assessments will be performed at Day 3 (± 24 hours) after Visit 6, Visit 7 or Visit 7c, if the subject received a repeat-treatment:

- AEs including if subjects are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection
- Concomitant medications/procedures

10.11.12 Week 40 (Visit 8a), Week 52 (Visit 8b) or Visit 8c

The following assessments will be performed at the end of clinical investigation visit at Week 40 (± 5 days), Week 52 (± 5 days) or Visit 8c (± 5 days), which are four weeks after repeat-treatment:

- In case repeat-treatment was performed at Week 36 (Visit 6) or Week 48 (Visit 7) or Visit 7c, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility). For action to be taken in case of abnormal findings, see Section 10.8.4.
- Body weight measurement
- Collect subject diary dispensed at repeat-treatment (Visit 6, Visit 7 or Visit 7c)
- AEs
- Concomitant medications/procedures

If the subject is not being treated at Week 36, no Week 40 Visit is necessary.

10.11.13 Week 48 (Visit 9a), Week 60 (Visit 9b) or Visit 9c

The following assessments will be performed at the end of clinical investigation visit at Week 48 (± 5 days), Week 60 (± 5 days) or Visit 9c (± 5 days), which are twelve weeks after repeat-treatment:

- In case repeat-treatment was performed at Week 36 (Visit 6), Week 48 (Visit 7) or Visit 7c, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility). For action to be taken in case of abnormal findings, see Section 10.8.4.
- Body weight measurement
- AEs
- Concomitant medications/procedures

For subjects who are not retreated at Week 36 (Visit 6) or Week 48 (Visit 7), the Week 48 Visit will be their end of study visit unless the subject returns for Visit 7c. For subjects who are not retreated at Visit 7c, Visit 7c will be their end of study visit. For subjects who are retreated at Week 36, the Week 48 Visit will be their end of study visit. For subjects who are retreated at Week 48, the Week 60 Visit will be their end of study visit. For subjects who are retreated at Visit 7c, Visit 9c (12 weeks after Visit 7c) will be their end of study visit.

10.12 Early Termination

In case a subject prematurely discontinues the clinical investigation, the subject will be asked to complete an early termination visit, where as many assessments as possible (which would normally be performed at the end of clinical investigation visit at Week 48, Week 60 or Visit 9c)

will be completed. If an early termination visit can't take place, the investigator or any member of the clinical investigation team should try to contact the subject, or his relatives, in order to collect adverse events and concomitant medications/treatments.

In case of early withdrawal, reasons, as well as circumstances and findings, should be collected and fully described on the "Early Termination" page in the eCRF.

10.13 Time-Windows

A time deviation of ± 5 days is allowed for each visit, except for phone contacts (+/- 24 hours) and for the touch-up visit at Week 2 (+/- 3 days). Clinical investigational sites must adhere to the Schedule of Clinical investigation Procedures and Assessments (see Section 2.1) and visit windows, and subjects must ensure they are available for those visits. However, if for practical reasons, e.g. bank holidays, a visit window cannot be met, a visit can be scheduled as close as possible to that visit window. However, any deviation from the visit schedule and its associated time windows will still be documented as a protocol deviation.

10.14 Medical Care upon Termination of the Clinical Investigation

Clinical investigation subjects will not receive any clinical investigation-specific treatment after the final visit. Any further treatment, if needed, will be proposed to the subject by the investigator at their discretion. After the final visit, subjects will not receive any further clinical investigation-specific treatment.

11 Monitoring Plan

The extent of monitoring and source data verification will be specified in a monitoring plan. 100% source data verification should be ensured in accordance to the monitoring plan.

Before clinical investigation initiation at a center, a clinical research associate (CRA) from the sponsor or sponsor's representative will discuss the CIP and eCRF with the treating investigators and their staff. The center must not enroll any subject before this initiation visit. During the clinical investigation, further monitoring visits will be performed according to ISO 14155:2011, the applicable standard operating procedures (SOP), and local regulations. The eCRFs will be reviewed against source data in accordance to the monitoring plan for adherence to the CIP, as well as for completeness, accuracy and consistency of data. Additionally, the CRA will check the progress of enrollment, and will ensure that the investigational device is stored, dispensed and accounted for according to respective specifications. Key clinical investigation personnel must be available to assist the CRA during these visits. The CRA informs the treating investigator or authorized designee of any eCRF entry error, omission, or illegibility. The CRA should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the treating investigator or by an authorized designee.

The treating investigators must permit the monitors access to those portions of the subject's primary medical records, which directly concern this clinical investigation.

It is the treating investigator's obligation to assure documentation of all relevant data in the subject's file, such as medical/aesthetic procedures history and concomitant diseases, date of enrollment into the clinical investigation, visit dates, results of examinations, application of medical device, and AEs and ADEs.

12 Assessment of Safety

12.1 Definitions of Adverse Events and Adverse Device Effects

Adverse Event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects, users or other persons. This definition includes events whether or not related to the IMDs and those events related to the procedures involved.

Adverse Device Effect (ADE)

An ADE is defined as an AE that is related to the use of the IMDs. This includes any AE resulting from insufficiencies or inadequacies in the IFU, the deployment, the implantation, the installation, the operation, or any malfunction of the IMDs. In addition, this includes any event that is a result of a use error or intentional misuse of the IMDs.

Those AEs occurring after provision of informed consent and prior to application of the IMDs will be recorded as part of the medical/aesthetic procedures history. Any medical condition that is present at the time that the subject is screened should be also considered as medical/aesthetic procedures history and not recorded as an AE (see Section 10.9). However, if the condition deteriorates at any time from date of administration of the IMDs during the clinical investigation, it should be recorded and reported as an AE.

For a list of anticipated AEs and anticipated ADEs please refer to Section 6.1. In addition, the following events could specify 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, change in peripheral vision)
- Skin changing color around the eyelids or around the site of injection

Serious Adverse Event (SAE)

An 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 structure 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 structure or a body function

- led to fetal distress, fetal death, or a congenital abnormality or birth defect
- is an important medical event

Note: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or require hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are: invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse. Hospitalization is defined as at least one overnight stay. Pre-planned hospitalizations (known already prior to signing the ICF) will not be considered an SAE, unless any of the above criteria are fulfilled over the course of the hospitalization due to unplanned complications.

A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.

Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 Code of Federal Regulations [CFR] 812.3[s]).

Investigators should report UADEs to the sponsor and to the IRB as follows: Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150[a]).

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46[b], 21 CFR 812.150[b]).

12.2 Documentation of Adverse Events

For each AE, the following must be reported: the date of onset, description of event (event term), event status or date of resolution, severity, action taken (none, medical and/or surgical), relationship to investigational device, relationship to procedure, and seriousness criteria. Each AE must be reported separately. The treating investigator must record all AEs on the ”AE” page of the CRF. For SAEs, the Serious Adverse Event Form must also be completed. A complete description of all AEs must also be available in the source documents.

AEs (or ADEs or SADEs) occurring after provision of informed consent and prior to application of the IMDs will be recorded as part of the medical /aesthetic procedures history. Any medical condition that is present at the time that the subject is screened should also be considered as medical/aesthetic procedures history (see Section 10.9) and not recorded as an AE (or ADE or SADE). However, if the condition deteriorates at any time during the clinical investigation from the date of administration of the IMDs, it should be recorded and reported as an AE.

In case the severity or seriousness of an AE changes, the most severe intensity or seriousness of the AE will be recorded and included in the analysis. Separate AEs will not be recorded for each intensity level.

Changes in the assessment of relationship to the IMDs or procedure should also be clearly documented.

Any medication necessary for the treatment of an AE must be recorded on the “Concomitant Medication” page of the CRF.

12.3 Assessment of Adverse Events

All AEs will be assessed in terms of seriousness, severity, outcome, relationship to the IMDs and relationship to procedures.

12.3.1 Assessment of Causality

Investigator is obligated to estimate the relationship between each AE/SAE and the IMD or clinical investigation procedure. Clinical judgment should be used and the relevant documents (e.g., IFU) consulted. The presence of confounding factors, such as concomitant medications/treatments, the natural history of the underlying disease and/or other concurrent illness or risk factors, shall also be considered. This has to be documented within the source data accordingly. The type of relationship should be determined using one of the following causality levels:

- **Definitely related:**

The AE/SAE is associated with the investigational device or with procedures beyond reasonable doubt when:

- the AE/SAE is a known side effect of the product category the device belongs to, or of similar devices and procedures
- the AE/SAE has a temporal relationship with investigational device use/application or procedures
- the AE/SAE involves a body-site or organ that the investigational device or procedures are applied to or have an effect on
- the AE/SAE follows a known response pattern to the medical device (if the response pattern is previously known)
- the discontinuation of medical device application (or reduction of the level of exposure), when clinically feasible, and reintroduction of its use (or increase of the level of exposure) impact on the event
- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out
- harm to the subject is due to error in use

- **Probably related:**

The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

- **Possibly related:**

The relationship with the use of the investigational device is weak, but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained, should also be classified as possible.

- **Unlikely related:**

The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

- **Not related:**

Relationship to the device or procedures can be excluded when:

  - the AE/SAE is not a known side effect of the product category the device belongs to or of similar devices and procedures
  - the AE/SAE has no temporal relationship with the use of the investigational device or the procedures
  - the AE/SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible
  - the discontinuation of medical device application or the reduction of the level of exposure (when clinically feasible) and reintroduction of its use (or increase of the level of exposure) do not impact on the event
  - the AE/SAE involves a body-site or an organ not expected to be affected by the device or procedure
  - the AE/SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors)

- harm to the subject are not clearly due to use error

The treating investigator will use his/her clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IMD administration will be considered and investigated. The treating investigator will also consult the IFU in the determination of his/her assessment.

If there is a disagreement between Sponsor and Investigator, queries will be sent in an attempt to reach a resolution. The queries will include a statement providing the rationale for the Sponsor assessment causality. Consequentely, a request for the rationale for the Investigator causality will be requested and a confirmation of their causality assessment.

In instances where there is a discrepancy in causality between the Investigator and the reviewing medic, for the causality of the event to the study device. The event will be considered as being related to the study device for the purposes of reporting.

12.3.2 Assessment of Severity

The following definitions for rating severity will be used:

- **Mild:** The AE is easily tolerated and does not interfere with daily activity
- **Moderate:** The AE interferes with daily activity but the subject is still able to function
- **Severe:** The AE is incapacitating and/or requires medical intervention

12.3.3 Adverse Event Outcome

The outcome of an AE will be assessed as follows:

- **Ongoing:** the event is ongoing at the time of reporting and the subject has still not recovered
- **Resolved:** the subject has fully recovered from the event, or the condition has returned to the level observed at Baseline
- **Resolved with Sequelae:** as a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralyzed)

- **Death:** the subject died due to the event
- **Unknown:** if outcome is not known or not reported

12.4 Adverse Event Monitoring and Assessment

Subjects will be monitored for AEs throughout the clinical investigation from signing the ICF until the final visit. Should an SAE occur after the final visit, which is considered at least possibly related to the IMD or procedure, such events should always be reported to Croma-Pharma GmbH or its representative, even after the end of the clinical investigation.

Subjects will be questioned concerning their well-being at all visits from screening through to the final visit. Furthermore, subject diaries will be provided to the subjects, and they will be instructed to note Injection site reactions, AEs and AESI. In addition, subjects will be encouraged to spontaneously report any AEs, ADEs or SAEs. Any subject with an AE, SAE or clinically significant abnormal test result will be evaluated by the treating investigator and will be treated and/or followed up as per local clinical practice. A physician, either at the investigative site or at a nearby hospital emergency room, will administer treatment for any SAEs. Where appropriate, medical tests and examinations may be performed to ensure that an AE has fully resolved.

If an Injection site reaction is not resolved at the time the by the time the diary is returned after 4 weeks (after treatment, touch-up treatment, retreatment), the injection site reaction might be classified as an AE s per investigator discretion.

By default, AEs ongoing at the termination visit will not be followed-up. However, SAEs which are ongoing at the End of Clinical investigation visit will be followed-up until recovery or normalization of changed laboratory parameters, or until the treating investigator determines that the subject's condition is stable or a plausible explanation has been provided, whichever occurs first.

All subjects excluded from repeat-treatment should continue to be followed until the resolution of all ongoing AEs, regardless of device relatedness.

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Whenever possible, a specific disease or syndrome, rather than

individual associated signs and symptoms, should be identified by the treating investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the treating investigator, it should be recorded as a separate AE on the CRF

When documenting AEs, standard medical terminology should be used in order to avoid the use of vague, ambiguous, or colloquial expressions. Each AE will be evaluated by the treating investigator for:

- Seriousness, as defined in Section 12.1.
- Severity, as defined in Section 12.3.2.
- Causal relationship to IMD or procedure, as defined in Section 12.3.1.
- Outcome, as defined in Section 12.3.3.

If the severity rating for an ongoing AE changes before the event resolves, the AE will be reported in an additional row in the AE log (or additional AE page) with complete information (i.e. start and stop date, severity, relationship, outcome etc.).

Reporting Serious Adverse Events All SAEs for all subjects occurring from the time of informed consent until the End of Clinical investigation visit must be reported to Croma-Pharma GmbH or their representative **within 24 hours** of knowledge of the occurrence. If considered at least possibly related to clinical investigation treatment, SAEs observed after the End of Clinical investigation must also be reported.

SAE Report Forms must be completed and faxed to the Safety department [redacted] within 24 hours of awareness of the event.

[redacted] will inform the sponsor about all SAEs without undue delay after receipt of the respective report from the treating investigator.

Reporting to IRBs and regulatory authorities will follow pertinent national legislation.

Any details about AE reporting and casuality assessement are described in the current valid version of device safety management plan.

12.4.1 Unanticipated Adverse Device Effects Reporting

A UADE is "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3[s]).

Investigators should report UADEs to the sponsor and to the IRB as follows: Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR812.150[a][1]).

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46[b], 21 CFR 812.150[b][1]).

Clinical investigation stopping rules in case of vascular occlusion:

Special care will be taken in case of vascular occlusion which is a rare, but serious, adverse event; this encompasses vascular embolic events which may lead to skin necrosis, vision loss or stroke.

In the event that such a complication occurs, the enrollment and treatment at the investigational site will be suspended and a root cause investigation has to be conducted to determine the cause of the event. If the investigator didn't properly follow the treatment procedure, he/she will be re-trained before being allowed to recruit further subjects.

In case this event was unanticipated and the investigator did follow the treatment procedure correctly, the entire clinical investigation has to be immediately suspended and no subjects

should be enrolled until the event can be properly characterized and an appropriate treatment strategy to avoid this unanticipated event can be devised.

For received reports containing any event relating to incidences of visual distrubances, in the form of a site query ('Device Safety Query for Additional Information' form, see SMP 9.5.4), the following information must be urgently requested:

- Depth of injection (i.e. subcutaneous or supraperiosteal)
- The injection volume
- The symptoms that were observed
- The time to event onset, and resolution
- Any interventions that were implemented
- The symptoms that were observed
- The time to event onset, and resolution
- Any interventions that were implemented

If a response to the aforementioned queries is not received within 24 hours, a follow up reminder will be sent, and the queries escalated to the Clinical Monitor and Project Manager.

12.5 Adverse Events/Serious Adverse Events Follow-up

The investigator will take all appropriate and necessary measures required for resolution of the AE. Should this include prohibited medication, the investigator will contact the Medical Monitor in order to seek advice.

All AEs must be followed-up by the investigator until recovery, or until the investigator determines that the subject's condition is stable, or until the last day of the clinical investigation at the site, whichever occurs first.

Any pregnancy must be followed-up until the pregnancy outcome on the pregnancy report form. If it is still on-going at the end of the clinical investigation, follow-up will be continued outside of the context of clinical investigation and pregnancy outcome (including pregnancy duration

and health status of a newborn or cause of premature termination, as applicable) will be reported to the Sponsor.

All SAEs judged to be related to the IMDs (SADEs) must be followed by the investigator until the subject has recovered, recovered with sequelae, died, or until the investigator determines that the subject's condition is stable, whichever occurs first. In case the clinical investigation ends before an SAE is resolved, the last status should be recorded. Every possibly effort should be made in order to follow up on SAEs until their resolution.

12.6 Visual Examinations

For details of visual examinations, see Section 10.8.

12.7 Device Deficiencies

12.7.1 Definition of a Device Deficiency

A device deficiency is defined as an inadequacy of an IMD with respect to its identity, quality, durability, reliability, safety or effectiveness. Deficiencies include malfunctions, use errors and inadequate labeling.

12.7.2 Recording and Reporting of Device Deficiencies

Device deficiencies should be reported to the Safety Department of [redacted] will forward the deficiency report to the sponsor within 24 hours after receipt of the respective report from the treating investigator.

Device deficiencies will be recorded as per relevant SOPs from the CRO. In case a device deficiency is associated with an AE, additionally, the corresponding AE documentation procedures must be adhered to (see Section 12.2).

12.7.3 Handling of Deficient Medical Devices

Any medical device alleged to be deficient must not be used by the treating investigator and must be returned to Croma-Pharma GmbH or its representative or destroyed according to the site's procedures, after device accountability has been performed.

13 Assessment of Effectiveness

Effectiveness will be determined using a well defined, valid and reliable scale, the NLF-SRS (outlined in Section 10.1). The scale and the proposed instructions for its use by treating investigators is outlined in the manual.

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

Scores are assessed as 1 (None/minimal), 2 (Mild), 3 (Moderate), 4 (Severe), 5 (Extreme).

14 Statistical Considerations

The statistical analyses will be described in detail in a statistical analysis plan.

14.1 Analysis Sets

The statistical analyses will be based on the following data sets:

Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all randomized subjects who received at least one administration of Princess® FILLER Lidocaine and the control medical device at the same visit; 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.

Per-Protocol Analysis Set (PPS)

The Per-Protocol Set (PPS) is defined as a subset of the subjects in the FAS who had no major protocol deviations. A possible per protocol analysis population bias will not be influenced by the exclusion criteria due to the split face design. The excluded subjects due to protocol deviations will be discussed in detail while the statistical analysis plan is being prepared and definitively ahead of the database lock in order to identify any possibly bias.

Safety Analysis Set (SAF)

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.

14.2 Statistical Analyses

The PPS and the FAS will be both considered equally important for the primary analysis; the primary 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 sensitivity analysis based on the PPS can be considered confirmatory. Otherwise, this analysis has to be considered exploratory. Non-inferiority is demonstrated only if the results are consistent for both analysis data sets.

All effectiveness analyses will be conducted for the FAS and subsequently for the PPS . Safety analyses will be based on the SAF.

Effectiveness

The primary effectiveness outcome measure will be evaluated by means of a one-sided 95% confidence interval for the difference in 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 Juvederm® Ultra XC. Thus, a negative value for this difference means that the response rate of Princess® FILLER Lidocaine is lower than the response rate for Juvederm® Ultra XC. Princess® FILLER Lidocaine will be considered non-inferior to Juvederm® Ultra XC if the lower confidence limit exceeds the non-inferiority margin of -10% and thus if the null hypothesis H0: p_A-$p_B \leq$ -10% can be rejected. In addition to this, the response rates for both treatment groups will be tabulated.

In order to assess the homogeneity of the primary effectiveness outcome measure and of the treatment effect among the clinical investigational sites, a mixed logistic regression model with treatment, site, and treatment-by-site interaction as fixed effects and random subject effects will be fitted. 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. If the treatment-by-site interaction effect is statistically significant (at the alpha level mentioned above), the treatment difference is not interpretable in the model. In this case, the treatment difference in the main effect model without adding the interaction effect is tested and in addition, the treatment difference by site will be presented and observed heterogeneities will be evaluated.

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 Juvederm® 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.

The statistical analysis of the secondary and additional outcome measures will be described in detail in the statistical analysis plan. A hierarchical testing procedure will be applied for the analysis of the primary outcome measure, as well as the secondary outcome measures 1 and 2, in order to control multiplicity. At this, the following order will be used:

1. Analysis of primary outcome measure based on FAS
2. Analysis of primary outcome measure based on PPS
3. Analysis of secondary outcome measure 1 based on FAS
4. Analysis of secondary outcome measure 1 based on PPS
5. Analysis of secondary outcome measure 2 based on FAS
6. Analysis of secondary outcome measure 2 based on PPS

For qualitative variables the frequencies (absolute and relative) will be calculated and compared between the treatment groups. Quantitative parameters will be described by declaring the 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 secondary outcome measures 1 and 2 will be analyzed as described for the primary effectiveness outcome measure. Descriptive statistics will be used to summarize the remaining outcome measures. Kappa statistics will be calculated in order to assess inter-rater consistency among the three independent blinded photographic reviewers.

Safety

Safety variables will be analyzed based on the SAF. Adverse events will be coded by the MedDRA. Incidence of AEs will be summarised by preferred term (PT) and system organ class

(SOC). AEs (SOC and PTs) will be summarised also by intensity, relationship to the IMDs or procedure and seriousness. All AEs will be properly listed (by subject, type, date, treatment and time since last treatment [first injection or touch-up]).

14.3 Sample Size Calculation

The primary effectiveness outcome measure will be evaluated by means of a one-sided 95% confidence interval for the difference in 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 Juvederm® Ultra XC. Thus, a negative value for this difference means that the response rate of Princess® FILLER Lidocaine is lower than the response rate for Juvederm® Ultra XC. Princess® FILLER Lidocaine will be considered non-inferior to Juvederm® Ultra XC if the lower confidence limit exceeds the non-inferiority margin of -10%.

Further assumptions for sample size calculation:

- Response rate at week 24 for Juvederm® Ultra XC is 88%
- Response rate at week 24 for Princess® FILLER Lidocaine is 87%
- Proportion of subjects with response only in one nasolabial fold: 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 Juvederm® Ultra XC assuming that the two NLFs of one subject are independent. Since there should be a concordant correlation between the two NLFs 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.

15 Data Handling and Record Keeping

15.1 Electronic Case Report Forms

An eCRF will be completed for each subject screened and included. Data generated after the subject has given informed consent must be recorded in the eCRF. The treating investigator is

responsible for ensuring accurate and proper completion of the eCRF according to the instructions in the eCRF. Data for all subjects screened for inclusion in the clinical investigation must be documented in the respective form provided by the sponsor.

Only treating investigators and authorized designees are allowed to make entries in the eCRF. The eCRF data should be entered within five days after obtaining it. The investigator or designee has to carefully answer queries issued by Data Management in the eCRF. Answered queries and changed data due to queries will be reviewed by Data Management and the monitor; required data will be required or verified accordingly.

Any source data corrections should be made in a way which does not obliterate the original entry. Treating investigators or designees must initial and date all corrections.

The treating investigator or designee must carefully answer queries issued by Data Management. Queries issued by Data Management must be carefully answered.

15.2 Data Management Procedures

All data management activities will be conducted by the sponsor's representative following their SOPs. The database will be built by the sponsor's representative.

Details on data handling will be described in the Data Management Plan. Computerized validation check programs on completeness, correctness, plausibility (such as range checks, cross-checks) will verify the data according to the Data Validation Plan. All identified discrepancies will be queried and addressed to the treating investigator.

Regarding self-evident corrections (such as spelling and header corrections) if applicable, treating investigator’s agreement will be obtained, that these will be made by the Data Manager and documented in the audit trail.

The sponsor’s representative will handle the data cleaning process, including logical check, medical checks, and query processes.

All changes will be tracked (audit trail). Sponsor approval prior to database lock is mandatory.

15.3 Data Retention

The treating investigator shall retain all clinical investigation records during the clinical investigation and for at least 15 years after the formal discontinuation, premature termination

or completion of clinical investigation. However, the treating investigator must contact the sponsor prior to destruction of any records or reports pertaining to the clinical investigation, in order to ensure they no longer need to be retained. In addition, the sponsor should be contacted if the treating investigator plans to leave the site so that arrangements can be made for transfer of records.

The medical files of clinical investigation subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

15.4 Clinical Investigation Report

Following completion of clinical investigation, the results will be evaluated and a clinical investigation report will be generated, including a summary of all available data, statistical measures, tabulated results, graphical results, and interpretations. This report will be submitted to regulatory authorities and ethics committees, as appropriate, within the timeframes defined per national regulation or by the IRB.

16 Regulatory and Ethical Considerations

16.1 Ethical Conduct of the Investigation

The treating investigator will ensure that this clinical investigation is conducted in full conformity with the current revision of the Declaration of Helsinki and in compliance with IRB informed consent regulations and ISO guideline 14155:2011 (Clinical investigation of medical devices for human subjects - Good Clinical Practice [GCP]). In addition, all local regulatory requirements will be followed.

16.2 Institutional Review Board (IRB)

Before the initiation of the clinical investigation, the final CIP, any amendments if applicable, the subject information sheet and ICF, as well as any additional documents which are required by national regulations and the IRB will be submitted to the competent IRB for review. A favorable opinion for the clinical investigation must be obtained from the IRB before any subject is enrolled at a center.

If appropriate, any additional requirements imposed by the IRB will be followed. Amendments to the clinical investigation documents will be notified to, or approved by, the IRB before implementation, if applicable.

16.3 Insurance

Insurance coverage for damages emerging from the clinical investigation will be provided according to applicable legal requirements. During the informed consent procedure, the treating investigator must inform the subject accordingly. Insurance details will be provided to the subject within the subject information sheet.

16.4 Informed Consent Process

Written informed consent must be obtained from each subject prior to initiation of any of the investigation-specific procedures, including collection of data for the study.

Before any clinical clinical investigation-related activities are performed, the treating investigator (or authorized designee) must review the ICF and explain the clinical investigation to potential clinical investigation subjects. The treating investigator must ensure that the subject

is fully informed about the aims, procedures, potential risks (including precautions and restrictions), any discomforts and expected benefits of the clinical investigation.

Before consenting, the subject must be left with ample time to consider and ask questions. It must be emphasized that participation is voluntary and that the subject has the right to withdraw from the clinical investigation at any time without prejudice. The subject must then sign and date the ICF prior to the conduct of any clinical investigation procedures. The treating investigator must sign and date the ICF as well.

A copy of the subject information sheet and ICF will be given to the subjects for their records. The rights and welfare of the clinical investigation subjects will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this clinical investigation.

If amendments to the final CIP affect the subject's participation in the clinical investigation (e.g. a change in any procedure), the subject information and ICF must be updated to incorporate modifications, and subjects must agree to sign the amended form indicating that they re-consent to participate in the clinical investigation.

16.5 Subject Confidentiality

The clinical investigation CIP, documentation, data, and all other information generated will be held in strict confidence. No information concerning the clinical investigation or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The treating investigator must receive written permission from the subject for direct access to the subject's data (including photographs taken) as part of the informed consent procedure. Any party (e.g. domestic and foreign regulatory authorities, monitors and auditors) with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirements, to maintain the confidentiality of the subject's identity and the sponsor's proprietary information. The data collected during the clinical investigation must be transferred to the sponsor only in pseudonymous form. The treating investigator will keep the original Subject Identification Log (including complete name and date of birth of each subject) in his/her file. The treating investigator must maintain these documents in strictest confidence.

Personal subject data will be kept confidential in compliance with Health Insurance Portability and Accountability Act (HIPAA) and other applicable international and national requirements.

Personal subject data transferred to Croma-Pharma GmbH in Austria should be in compliance with the European Data Protection Directive.

On CRFs, compensation documentation, or any other documents submitted to the sponsor or sponsor's representative, subjects must be identified only by their identification codes; use of subjects' names, addresses, telephone numbers, or similar information is prohibited. For GCP compliance, all subjects will be asked for consent regarding access to their personal clinical clinical investigation-related data for monitoring, audits, and inspections as well as regarding transmission and storage of their anonymous data; a respective statement will be part of the ICF. Professionals receiving access to source data for monitoring, audits and inspections must preserve strict confidentiality.

17 Amendments to and deviations from the CIP

17.1 Amendments

Any change to the CIP concerning the purpose of the clinical investigation, the clinical investigation design or the subject's eligibility must be made in the form of a written amendment to the CIP. Such amendments must be discussed and signed by the sponsor, the coordinating investigator, and the principal investigator(s) before implementation Amendments that might have an impact on subject-related clinical investigation procedures and/or the well-being of the subject require an additional ICF that must be signed by all subjects enrolled in the clinical investigation who are affected by the amendment.

17.2 Deviations

A CIP deviation is a failure to follow, intentionally or unintentionally, the requirements of the CIP. As required by national regulation or guidelines, requests for deviations and reports of deviations will be provided to the IRB if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

Under emergency circumstances, deviations from the CIP may proceed without prior approval by the sponsor and favorable opinion of the IRB if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the sponsor and the IRB as soon as possible in accordance with national regulations.

The investigator must maintain accurate, complete and current records of any deviation from the CIP, including the date and reason for each deviation.

The investigator shall notify the Sponsor and the reviewing IRB of any deviation from the CIP made to protect the life or physical well-being of a subject in emergency as soon as possible, but in no event later than five working days after the emergency occurred.

All CIP deviations will be listed and (if evaluable for analysis) will be discussed in a blind data review meeting prior to the statistical analysis.

No waivers to the CIP will be granted by the Sponsor.

18 Suspension or Premature Termination of the Clinical Investigation

The sponsor reserves the right to terminate the clinical investigation for any reason. The sponsor will provide instructions if assessments beyond the regular per protocol procedures should be necessary.

The sponsor may suspend enrollment or terminate the clinical investigation at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the protocol or other clinical research requirements.

A principal investigator, IRB, or FDA may also suspend or prematurely terminate the clinical investigation at the investigational sites for which they are responsible.

If the clinical investigation is prematurely terminated, the sponsor or the sponsor's representative will promptly inform the FDA of the termination and its reason(s); the treating investigator or the sponsor (or representative) will promptly inform the IRB as specified in applicable regulations.

In case of vascular occlusion, clinical investigation stopping rules are described in the Section 12.4.1.

19 Publication Policy

The clinical investigation will be posted on the “clinicaltrials.gov” site.

Moreover, the results of the clinical investigation may be published and/or presented at scientific meetings. However, results should not be published without prior written consent by the sponsor and such consent will not be unreasonably withheld. All manuscripts and abstracts, which refer to data originating from the clinical investigation, must be submitted to the sponsor for comments at least 90 days prior to submission for publication.

If the proposed publication contains any invention related to the clinical investigation, the sponsor is entitled to file respective patent applications and - on this ground - to delay the submission for publication or presentation of medical results.

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21 Revision History

Version	Date	Reason for Revision
7.0	**15.03.2021**	Updates to the following sections to account for the extension to the study duration because of the temporary hold on repeat-treatment: **2 Synopsis** - planned clinical investigation period **9.4 Subject Enrollment, Number and Duration of Subject's Participation** Updates to the following sections to include the additional visit for evaluation for repeat treatment (and receipt of repeat treatment if eligible) and the two follow-up visits if repeat treatment was received: **2 Synopsis -** additional objectives, design and additional outcome measures **2.1 Schedule of Clinical Investigation Procedures and Assessments** **5.4 Additional Objectives** **7.1 Description of Clinical Investigation Design** **7.3.1.3 Additional Outcome Measures** **9.3 Subject Withdrawal and Discontinuation** **9.4 Subject Enrollment, Number and Duration of Subject's Participation** **10.1 Nasolabial Folds-Severity Rating Scale (NLF-SRS)** **10.2 Global Aesthetic Improvement Scale (GAIS)** **10.3 Subject Satisfaction using Face-Q Questionnaires** **10.6 Time to Repeat-Treatment** **10.7 Clinical Photography** **10.8 Visual Examinations** **10.9 Other Assessments** **10.11.9 Week 36 (Visit 6) and/or Week 48 (Visit 7) and/or Visit 7c – Evaluation** **10.11.10 Week 36 (Visit 6) and/or Week 48 (Visit 7) and/or Visit 7c – Repeat-Treatment** **10.11.11 Phone Contact after Visit 6, Visit 7 or Visit 7c**

		10.11.12 Week 40 (Visit 8a), Week 52 (Visit 8b) or Visit 8c **10.11.13 Week 48 (Visit 9a), Week 60 (Visit 9b) or Visit 9c** **10.12 Early Termination** In addition, minor formatting changes were made throughout.
6.0 (not finalized)[a]	**04.11.2020**	**Update of the following sections as per FDA requests:** **Addition of Section 9.2 –** Inclusion and Exclusion Criteria for repeat treatment eligibility of subjects; existing criteria were formally summarized and additional exclusion criteria based on visual assessments were introduced **Addition of Section 10.8** as a separate section for description of Visual Assessments Updates throughout the entire protocol with a special emphasis on evaluation of potential changes to vision during or after device application: this includes updates to the **Synopsis (Section 2), the Schedule of Events (Section 2.1),** detailed description of study visits **(Schedule of Clinical Investigation, Section 10.11)** **Section 12.1 and Section 12.4.1:** updated to clarify the definition of UADEs and to specify investigator and sponsor responsibilities for reporting UADEs **Sponsor related contact details** Update of Croma-Pharma Clinical Project Manager Update of Croma-Pharma Global Director Clinical Development
5.0	**10.12.2019**	In the synopsis under Outcome measures (Secondary outcome measures and additional outcome measure and in 7.3.1.2 and 7.3.1.3 the following has been added: "Responder is defined as having at least one grade improvement over Baseline, on the 5-point NLF-SRS" **Section 12.3.1:** Correction in first sentence: **medical** device (instead of medicinal device) **Addition in Section 12.3.1** Clarification of process in case of disagreement between Investigator and Sponsor was added Addition in 12.4 Any details about AE reporting and casuality assessement are described in the current valid version of device safety management plan.

		Section 12.4.1: deletion of 'working' in the sentence: For the purpose of submission, any incidence of visual disturbance will be considered a reportable event within 10 ~~working~~ days. Required reporting details of visual disturbances are specified **Sponsor related contact details** Update of Croma-Pharma Clinical Project Manager
4.0	**03.10.2019**	**The retreatment procedure has been changed in a way that subjects are offered Princess Filler Lidocaine in both nasolabial folds at week 36/week 48, and no comparator product is used for retreatment. The visit schedule for subjects being retreated at week 36/48, and for subjects without retreatment has been explained in more detail. Throughout the document, slight modifications for clarification purposes have been implemented.** **The following Sections have been changed:** **2. Clinical Investigation Synopsis** **7.1 Description of the Clinical Investigation** **7.3 Outcome measures** **7.6 Randomization and Blinding** **8.6 Medical Device Accountability** **9.4 Subject Enrollment, Number and Duration of Subject's participation** **10.1 Nasolabial Folds Severity Rating Scale (NLF-SRS)** **10.8 Other Assessments** **10.10 Schedule of the Clinical Investigation** **12.4 Adverse Event Monitoring and Assessment** **12.6. Device Deficiencies**

3.0	04.01.2019	As per FDA request, the CIP has been updated: the follow up visit after optional repeat treatment has been increased from one to three months to allow for the collection of valuable safety and efficacy data following repeat-treatment. In addition, CIP was updated to eliminate smaller, but important errors. The Schedule of Clinical Investigation Procedures and Assessments as well as the Clinical Investigation Procedures and Assessments-Section have been updated to eliminate inconsistencies. Description of the Medical Device-Section has been updated to add the possibility to use cannulas. The Safety section has been updated in order to clarify Adverse events of special interest and the SAE/Device deficiency reporting procedure has been updated The following Sections have been updated: 2. Clinical Investigation Synopsis 2.1 Schedule of Investigation procedures and Assessments 4.3 Description of the IMD 7. Design description revised 10. Clinical Investigation Procedures and Assessments 12. Assessment of Safety
2.0	24.09.2018	As per FDA request, the CIP has been updated: visual examinations have been added in order to ensure that adverse events related to vision changes are fully evaluated. Additionally, clinical investigation stopping rules for vascular occlusion have been introduced. Moreover, the content of the subject diary has been extended to reflect the above changes, as well as the “Precautions for use” and “Warnings” sections. Following sections have been therefore updated: 2. Clinical Investigation Synopsis 5. Clinical Investigation Purpose and Objectives 6. Risks and Benefits of the Investigational Device and Clinical Investigation 7. Outcome Measures 8. IMDs 10. Clinical Investigation Procedures and Assessments 12. Assessment of Safety:

		18. Suspension or Premature Termination of the Clinical Investigation: 20. References 21. Revision History
1.8	13.07.2018	CIP updated to accurately reflect wrinkle severity scores for the inclusion criteria.
1.7	22.06.2018	Deletion of investigational sites located in Europe, and therefore deletion of any mention to European Ethics committees or competent authorities. Updated timelines in the "Planned Clinical Investigation Period" part of the synopsis. Clarification of indication wording to distinguish between the study and the indications as placed on the current EU label of the device.
1.6	09.04.2018	As per FDA request and because of the availability of new information, additional changes were performed and are resulting in the update of the following sections: **2. Clinical Investigation Synopsis:** inclusion of European clinical investigational site(s) within the twelve planned sites **3. Investigators and Administrative Structure of the Clinical Investigation:** inclusion of European clinical investigation site(s) within the twelve planned sites and change of CRO name (only name but no organization change) **4. Background Information Regarding Dermal Fillers:** • intended use definition completed with medical indications • addition of pyrogenicity testing results • addition of results of one clinical investigation with Princess® FILLER (CPH-401-201259, medical indications) • update of state-of-the-art literature • update of Post-Market Surveillance data **6. Risks and Benefits of the Investigational Device and Clinical Investigation:** update of Post-Market Surveillance data **7. Outcome Measures:** same definition of responders used for all outcome measures (primary, secondary and additional). Detailed definition of the "improvement" term added **9. Subject Enrolment, Number and Duration of Subject's Participation:** addition of European clinical investigational site(s)

		12. Assessment of Safety: change of name and contact data of the medical monitor **15. Data Handling and Record Keeping:** • deletion of any sentences concerning paper CRF, since eCRF will be used • changes in the retention period of clinical investigation documentation, following the addition of European clinical investigational site(s) **16. Regulatory and Ethical Considerations:** addition of ethics committees (EC) for additional European clinical investigation site(s) **18. Suspension or Premature Termination of the Clinical Investigation:** addition of ethics committees (EC) and competent authorities (CA) for additional European clinical investigation site(s)
1.5	14.04.2017	Update of the following sections as per FDA request: **14. Statistical considerations:** update of site poolability testing with additional information
1.4	13.04.2017	Update of the following sections as per FDA request: **14. Statistical considerations:** update of site poolability testing
1.3	11.04.2017	Update of the following sections as per FDA request: **2. Clinical investigational synopsis:** updated according to the changes performed in CIP (described below) **5. Clinical Investigation Purpose and Objectives:** the order of the secondary objectives has been changed **7. Design of the Clinical Investigation**: the order of the secondary outcome measures has been changed
1.2	10.04.2017	Update of the following sections as per FDA request: **2. Clinical investigational synopsis:** updated according to the changes performed in CIP (described below) **5. Clinical Investigation Purpose and Objectives:** the hierarchy of one objective has been changed from additional to secondary objective **7. Design of the Clinical Investigation:** the hierarchy of one outcome measure has been changed from additional to secondary outcome measure **9. Subject Selection, Withdrawal and Discontinuation:** update of exclusion criteria **14. Statistical considerations:** additional hierarchical testing

		procedure for secondary outcome measures 2; removing timing of analysis
1.1	30.03.2017	Update of the following sections as per FDA recommendations: **1. Abbreviations and definition of terms:** missing abbreviations added **2. Clinical investigational synopsis:** updated according to the changes performed in CIP (described below) **4. Background Information and Scientific Rationale:** data updated accordingly to Post Market Surveillance report 2016; justification of comparator choice **5. Clinical Investigation Purpose and Objectives:** the hierarchy of the objectives has been changed in secondary and additional objectives **6. Risks and Benefits of the Investigational Device and Clinical Investigation:** addition of risk mitigation strategies **7. Design of the Clinical Investigation:** the hierarchy of the outcome measures has been changed in secondary and additional outcome measures; better description of the subject allocation to both randomization groups; description of emergency blinding **8. Investigational Medical Devices:** additional description of touch-up treatment and of the applied volume of the device; Section "Precautions, Prohibited Medications/Treatments and Restrictions" has been moved from Section 7 to Section 8; Section "Medical Device Accountability" has been moved from Section 7 to Section 8 **9. Subject Selection, Withdrawal and Discontinuation:** update of exclusion criteria; additional enrolment cap per study site **10.Clinical investigation Procedures and Assessments:** better description of the procedures and assessments **12. Assessment of Safety***:* better description of assessment of causality and adverse event outcome **14. Statistical considerations:** additional poolability analysis; additional analysis of missing data; additional hierarchical testing procedure of the primary outcome measure, as well as the secondary outcome measures; additional timing of analysis **15. Data Handling and Record Keeping:** additional description of data cleaning process **20. References:** addition of missing references

[a.] Version 6.0 (Draft) of the Clinical Investigation Plan was submitted to the FDA; further changes were required following FDA review, and the additional changes were made under Clinical Investigation Plan Version 7.0

22 Appendices

22.1 Appendix 1: FACE-Q Questionnaires

SATISFACTION WITH OUTCOME

We would like to know how you feel about your most recent procedure. For each statement, circle only one answer. Please indicate how much you agree or disagree with each statement.

[redacted]

APPRAISAL OF NASOLABIAL FOLDS

[redacted]

22.2 **Appendix 2:** Princess® FILLER Lidocaine Instructions for Use

Princess® FILLER Lidocaine — EN

Instructions for use

Composition:

[illegible]

Description:

[illegible]

Indications:

[illegible]

Exclusion criteria:

[illegible]

Precautions for use:

[illegible]

Undesired side effects:

[illegible]

Methods of use:

[illegible]

Princess® FILLER Lidocaine — FR

Mode d'emploi

[illegible]

Princess® FILLER Lidocaine — DE

Gebrauchsanleitung

[illegible]

Princess® FILLER Lidocaine — NL

Gebruiksaanwijzing

[illegible]

Princess® FILLER Lidocaine — DA

Brugsanvisning

[illegible]

Princess® FILLER Lidocaine — SV

Bruksanvisning

[illegible]

Princess® FILLER Lidocaine — FI

Käyttöohjeet

[illegible]

Princess® FILLER Lidocaine — NO

Bruksanvisning

[illegible]

Istruzioni per l'uso

Composizione:

Descrizione:

Indicazioni:

Criteri di esclusione:

Precauzioni per l'uso:

Effetti indesiderati:

Metodi d'uso:

Avvertenze:

Conservazione:

使用说明

成分：

描述：

适应症：

排除标准：

使用注意事项：

不良副作用：

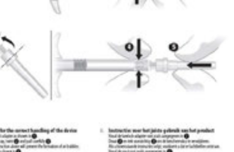
使用方法：

警告：

保存：

Használati utasítás

Upute za upotrebu



Instructions for the correct handling of the device

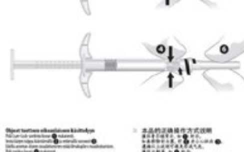
Instructies voor het juiste gebruik van het product

Instructions concernant la manipulation correcte du dispositif

Instruktioner til korrekt håndtering af produktet

Anleitung für die korrekte Handhabung des Produkts

Instruktioner för korrekt hantering av enheten



Ohjeet tuotteen oikeanlaiseen käsittelyyn

本品的正确操作方式说明

Instruksjoner for korrekt håndtering av enheten

Az eszköz helyes kezelésére vonatkozó utasítások

Istruzioni per il corretto uso del prodotto

Upute za pravilno rukovanje proizvodom

Explanation of international symbols | Explication des symboles internationaux | Erklärung der internationalen Symbole | ... | 国际通用符号说明 | A nemzetközi szimbólumok magyarázata | Objašnjenje međunarodnih simbola

Last revised | Dernière mise à jour | Letzte Überarbeitung | ...

2016-08

22.3 Appendix 3: Juvéderm® Ultra XC Instructions for Use

Juvéderm® ULTRA XC

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION

JUVÉDERM® Ultra XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of cross-linked hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, formulated to a concentration of 24 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

2. INTENDED USE/INDICATIONS

- JUVÉDERM® Ultra XC injectable gel is indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
- JUVÉDERM® Ultra XC is indicated for injection into the lips and perioral area for lip augmentation in adults over the age of 21.

3. CONTRAINDICATIONS

- JUVÉDERM® Ultra XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- JUVÉDERM® Ultra XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- JUVÉDERM® Ultra XC contains lidocaine and is contraindicated for patients with a history of allergies to such material.

4. WARNINGS

- The product must not be injected into blood vessels. Introduction of JUVÉDERM® Ultra XC into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft-tissue fillers, for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary. Rare, but serious, adverse events associated with the intravascular injection of soft-tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care professional specialist should an intravascular injection occur (see Health Care Professional Instructions #13).
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled.
- Injection site reactions consist mainly of short-term inflammatory symptoms starting early after treatment and lasting ≤ 7 days in facial wrinkles and folds, and typically last ≤ 14 days in the lips. Refer to the ADVERSE EVENTS section for details.

5. PRECAUTIONS

- JUVÉDERM® Ultra XC is packaged for single-patient use. Do not resterilize. Do not use if package is opened or damaged.
- In order to minimize the risks of potential complications, this product should only be used by Health Care professionals who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- Health Care professionals are encouraged to discuss all potential risks of soft-tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- Based on preclinical studies, patients should be limited to 20 mL of any JUVÉDERM® injectable gel per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- The safety and effectiveness for the treatment of anatomic regions other than facial wrinkles and folds, lips, and perioral area have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- JUVÉDERM® Ultra XC is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product and it can therefore no longer be assured.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 18 years has not been established.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- JUVÉDERM® Ultra XC should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at injection sites.
- After use, treatment syringes and needles may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.
- JUVÉDERM® Ultra XC injectable gel is a clear, colorless gel without visible particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; notify Allergan Product Support at 1-877-345-5372.
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with JUVÉDERM® Ultra XC, there is a possible risk of eliciting an inflammatory reaction at the implant site. An inflammatory reaction is also possible if the product is administered before the skin has healed completely after such a procedure.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the LUER-LOK® and needle hub connection.

6. ADVERSE EVENTS

A. Clinical Evaluation of JUVÉDERM® Ultra XC in the Nasolabial Folds (NLFs)

A 2-week, randomized, controlled U.S. clinical study for JUVÉDERM® Ultra XC compared with JUVÉDERM® Ultra without lidocaine showed a similar safety profile in all subjects (N = 36), with the exception of fewer reports of pain/tenderness with the product containing lidocaine. Common treatment site responses by severity and duration, are presented in Tables 1 and 2. Aside from injection site responses, there were no adverse events related to the device, procedure, or anesthesia.

- The most common injection site responses for JUVÉDERM® Ultra XC were redness, swelling, tenderness, firmness, lumps/bumps, discoloration, and bruising.

Table 1. Injection Site Responses by Maximum Severity (Number/% of Subject NLFs)

Injection Site Responses	TOTALS		JUVÉDERM® Ultra XC (N^a = 36 NLFs)			JUVÉDERM® Ultra (N^a = 36 NLFs)		
	JUVÉDERM® Ultra XC n^c %	JUVÉDERM® Ultra n^c %	Mild n^c %	Mod[b] n^c %	Severe n^c %	Mild n^c %	Mod[b] n^c %	Severe n^c %
Redness	29 81%	30 83%	22 61%	7 19%	0 0%	21 58%	9 25%	0 0%
Pain	17 47%	22 61%	12 33%	5 14%	0 0%	16 44%	5 14%	1 3%
Tenderness	22 61%	29 81%	18 50%	3 8%	1 3%	22 61%	6 17%	1 3%
Firmness	32 89%	33 92%	22 61%	8 22%	2 6%	24 67%	9 25%	0 0%
Swelling	30 83%	29 81%	23 64%	6 17%	1 3%	17 47%	12 33%	0 0%
Lumps/Bumps	20 56%	22 61%	13 36%	6 17%	1 3%	17 47%	4 11%	1 3%
Bruising	27 75%	24 67%	16 44%	8 22%	3 8%	15 42%	6 17%	3 8%
Itching	12 33%	11 31%	12 33%	0 0%	0 0%	10 28%	1 3%	0 0%
Discoloration	22 61%	21 58%	17 47%	2 6%	3 8%	16 44%	3 8%	2 6%

[a] Number of subject NLFs treated with the respective device
[b] Mod = Moderate
[c] Number of NLFs with any occurrence of a particular ISR (or severity for the overall percentages)

Table 2. Duration of Injection Site Responses (Number/% of Subject NLFs)

Injection Site Responses	JUVÉDERM® Ultra XC (N^a = 36 NLFs) n^b %				JUVÉDERM® Ultra (N^a = 36 NLFs) n^b %			
Duration[c]	1-3 Days	4-7 Days	8-14 Days	> 14 Days	1-3 Days	4-7 Days	8-14 Days	> 14 Days
Redness	22 61%	4 11%	1 3%	2 6%	22 61%	4 11%	2 6%	2 6%
Pain	15 42%	0 0%	1 3%	1 3%	18 50%	3 8%	0 0%	1 3%
Tenderness	14 39%	3 8%	3 8%	2 6%	23 64%	5 14%	0 0%	1 3%
Firmness	15 42%	7 19%	5 14%	5 14%	15 42%	7 19%	8 22%	3 8%
Swelling	19 53%	7 19%	2 6%	2 6%	17 47%	7 19%	3 8%	2 6%
Lumps/Bumps	10 28%	4 11%	2 6%	4 11%	11 31%	5 14%	3 8%	3 8%
Bruising	12 33%	8 22%	4 11%	3 8%	7 19%	8 22%	6 17%	3 8%
Itching	8 22%	3 8%	0 0%	1 3%	9 25%	1 3%	0 0%	1 3%
Discoloration	13 36%	2 6%	4 11%	3 8%	10 28%	5 14%	4 11%	2 6%

[a] Number of subject NLFs treated with the respective device
[b] Number of subject NLFs with each specific ISR by maximum duration
[c] Duration refers to number of days from symptom onset until resolution, irrespective of date of implantation

B. Clinical Evaluation of JUVÉDERM® Ultra (Without Lidocaine) in the NLFs

In the initial randomized, controlled clinical trial to evaluate safety and effectiveness, 146 subjects were injected with JUVÉDERM® Ultra in one NLF and ZYPLAST® dermal filler in the contralateral NLF. Preprinted diary forms were used by subjects to record specific signs and symptoms experienced during each of the first 14 days (day 0 through day 13) after initial and touch-up treatments. Subjects were instructed to rate each common treatment response listed on the diary as "Mild," "Moderate," "Severe," or "None." Injection site responses reported by >5% of subjects in either treatment group are summarized in Tables 3 and 4.

Table 3. Injection Site Responses by Maximum Severity Occurring in > 5% of Treated Subjects (Number/% of Subject NLFs)

Injection Site Responses	TOTALS		JUVÉDERM® Ultra (N^a = 146 NLFs)			ZYPLAST® (N^a = 146 NLFs)		
	JUVÉDERM® Ultra n^c %	ZYPLAST® n^c %	Mild n^c %	Mod[b] n^c %	Severe n^c %	Mild n^c %	Mod[b] n^c %	Severe n^c %
Redness	136 93%	130 89%	72 49%	48 33%	16 11%	69 47%	45 31%	16 11%
Pain/ Tenderness	131 90%	128 88%	74 51%	45 31%	12 8%	87 60%	34 23%	7 5%
Firmness	129 88%	127 87%	66 45%	53 36%	10 7%	60 41%	56 38%	11 8%
Swelling	125 86%	122 84%	60 41%	54 37%	11 8%	77 53%	37 25%	8 5%
Lumps/Bumps	115 79%	122 84%	61 42%	45 31%	9 6%	66 45%	42 29%	14 10%
Bruising	86 59%	80 55%	43 29%	29 20%	14 10%	47 32%	27 18%	6 4%
Itching	52 36%	53 36%	42 29%	5 3%	5 3%	43 29%	7 5%	3 2%
Discoloration	48 33%	49 34%	31 21%	11 8%	6 4%	31 21%	15 10%	3 2%

[a] Number of subject NLFs treated with the respective device
[b] Mod = Moderate
[c] Number of subject NLFs with each specific ISR

Table 4. Duration of Injection Site Responses Occurring in > 5% of Treated Subjects (Number/% of Subject NLFs)

Injection Site Responses	JUVÉDERM® Ultra (N^a = 146 NLFs) n^b %				ZYPLAST® (N^a = 146 NLFs) n^b %			
Duration[c]	≤ 3 Days	4-7 Days	8-14 Days	> 14 Days	≤ 3 Days	4-7 Days	8-14 Days	> 14 Days
Redness	60 41%	50 34%	8 5%	18 12%	46 32%	46 32%	10 7%	28 19%
Pain/ Tenderness	61 42%	46 32%	18 12%	6 4%	49 34%	53 36%	14 10%	12 8%
Firmness	29 20%	34 23%	20 14%	46 32%	25 17%	28 19%	20 14%	54 37%
Swelling	38 26%	48 33%	22 15%	17 12%	54 37%	38 26%	20 14%	10 7%
Lumps/Bumps	26 18%	32 22%	18 12%	39 27%	16 11%	18 12%	19 13%	69 47%
Bruising	29 20%	28 19%	24 16%	5 3%	35 24%	27 18%	10 7%	8 5%
Itching	25 17%	15 10%	7 5%	5 3%	21 14%	17 12%	4 3%	11 8%
Discoloration	22 15%	12 8%	4 3%	10 7%	26 18%	9 6%	3 2%	11 8%

[a] Number of subject NLFs treated with the respective device
[b] Number of subject NLFs with each specific ISR by maximum duration
[c] Duration refers to number of days from symptom onset until resolution, irrespective of date of implantation

Local injection site responses were recorded in subjects' diaries one or more times for 99% of JUVÉDERM® Ultra treated NLFs and 98% of ZYPLAST® treated NLFs. Subjects' scores for both products were predominantly Mild or Moderate in intensity, and their duration was short lasting (7 days or less). JUVÉDERM® Ultra injection site responses reported by greater than 1% of subjects and not noted in the above tables were skin dryness and peeling. No clinically meaningful differences in the safety profiles of JUVÉDERM® Ultra and ZYPLAST® were found during the study.

C. Clinical Evaluation of JUVÉDERM® Ultra XC for Lip Augmentation

In a randomized, controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM® Ultra XC for lip augmentation, 213 subjects were randomized to treatment and received injections in the lips and perioral area (N = 157), or to delayed-treatment control, and had treatment delayed 3 months (N = 56).

Preprinted diary forms were used by subjects to record specific signs and symptoms of ISRs experienced during the 30 days (Day 1 through Day 30) following initial treatment, touch-up treatment (if performed), and repeat treatment. Subjects were instructed to rate each ISR listed on the diary as Mild, Moderate, Severe, or None.

- Mild ISRs were defined as having little, if any discomfort and having no effect on daily activities.
- Moderate ISRs were defined as causing some discomfort and having some effect on daily activities.

- Severe ISRs were defined as causing great discomfort and events that would compromise performance of daily activities.

ISRs reported by > 5% of the 193 subjects who completed post-treatment diary forms after initial treatment are summarized in Table 5. The majority of ISRs were Mild or Moderate in intensity, and their duration was short lasting (14 days or less). ISRs reported after touch-up treatment and repeat treatment were similar to those reported after initial treatment.

Table 5. Injection Site Responses after Initial Treatment Occurring in > 5% of Treated Subjects after Lip Augmentation by Severity and Duration

Injection Site Responses	Severity[a]			Duration[b]				Subjects N = 193[c]
	Mild	Moderate	Severe	< 3 Days	4-7 Days	8-14 Days	15-30 Days	
	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %
Swelling	45 24%	94 51%	46 25%	51 28%	63 34%	51 28%	20 11%	185 96%
Bruising	35 19%	84 47%	61 34%	31 17%	91 51%	46 26%	12 7%	180 93%
Firmness	53 31%	91 53%	29 17%	38 22%	43 25%	55 32%	37 21%	173 90%
Lumps/Bumps	59 35%	81 48%	29 17%	41 24%	32 19%	44 26%	52 31%	169 88%
Tenderness	75 46%	64 39%	26 16%	56 34%	41 25%	53 32%	15 9%	165 86%
Redness	55 36%	69 46%	27 18%	69 46%	49 33%	27 18%	6 4%	151 78%
Pain	70 49%	60 42%	13 9%	93 65%	28 20%	19 13%	3 2%	143 74%
Discoloration	36 51%	25 36%	9 13%	37 53%	8 11%	21 30%	4 6%	70 36%
Itching	34 61%	18 32%	4 7%	37 66%	11 20%	6 11%	2 4%	56 29%
Peeling	5 39%	7 54%	1 8%	9 69%	1 8%	3 23%	0 0%	13 7%

[a] Maximum reported severity
[b] Maximum reported successive occurrence of treatment response
[c] Number of subjects who completed the diary
[d] Percentage based on number of subjects reporting each specific ISR

ISRs that lasted beyond the 30-day diaries were considered adverse events. Adverse events were also reported by the Treating Investigator at follow-up visits. After initial treatment (or touch-up treatment if performed), a total of 168 treatment-related adverse events were reported in 29% of subjects (60/208). In general, AEs were mild (77%, 130/168) or moderate (16%, 27/168), resolved without sequelae (93%, 156/168), and required no action (91%, 153/168). AEs typically resolved within 3 months. Treatment-related adverse events that occurred in > 1% of subjects were injection site mass 16% (33/208), induration 10% (21/208), discoloration 5% (10/208), pain 4% (9/208), bruising 3% (7/208), swelling 3% (7/208), erythema 2% (4/208), and reaction 2% (4/208). Similar AEs were reported after repeat treatment.

In the clinical study, 11 severe treatment-related adverse events occurred in 4 subjects. These adverse events include angioedema and injection site mass, pain, bruising, swelling, erythema, and hypertrophy. All of these events resolved without sequelae, and all except the angioedema required no action. One subject experienced angioedema in the upper lip following topical anesthetic application of 25% lidocaine/7% tetracaine and injection of JUVÉDERM® Ultra XC, which resolved following administration of oral antihistamine, hyaluronidase injection, and oral anti-inflammatory medication.

Functional features of the lips, including lip sensitivity, sensation, and speech were assessed before treatment and at follow-up visits after treatment. Minimal changes were noted in subject self-assessments of the function and sensation of the lips and mouth area, Treating Investigator assessments of other functional features of the lips and mouth area, Evaluating Investigator assessments of subjects' lip sensitivity, and speech and language pathologist assessments of subjects' speech and articulation at scheduled timepoints following treatment, thus demonstrating that lip function and sensation were unaffected by treatment with JUVÉDERM® Ultra XC.

Subgroup analyses were completed to analyze ISRs and AEs in relation to Fitzpatrick skin phototype, age, investigational site, gender, volume injected, plane of injection, injection technique, and injection site. No increased safety risks were observed for any specific groups.

D. Other Safety Data

Other Clinical Studies

In 2 additional randomized US, clinical studies of other JUVÉDERM® formulations (without lidocaine) in a total of 293 subjects, the safety profile was similar to that described above for JUVÉDERM® Ultra.

Postmarket Surveillance

The following adverse events were received from postmarket surveillance for JUVÉDERM® Ultra and Ultra Plus, with and without lidocaine, with a frequency of 5 events or more and were not observed in the clinical study; this includes reports received globally from all sources including scientific journals and voluntary reports. All adverse events obtained through postmarket surveillance are listed in order of number of reports received: lack or loss of correction, inflammatory reaction, allergic reaction, infection, migration, paresthesia, vascular occlusion, necrosis, abscess, flu-like symptoms, headache, malaise, vision abnormalities, scarring, nausea, drainage, dyspnea, beading, syncope, dizziness, anxiety, deeper wrinkle, and granuloma.

In many cases, the symptoms resolved without any treatment. Reported treatments have included: antibiotics, steroids, steroidal creams, hyaluronidase, anti-inflammatories, anti-histamines, needle aspiration and drainage, ultrasound therapy, analgesics, anti-viral, excision, eye drops, hyperbaric oxygen, laser resurfacing, tissue debridement, surgical scar revision, ice, massage, and warm compress.

Vascular occlusion of vessels resulting in necrosis and vision abnormalities, have been reported following injection of JUVÉDERM® products, with and without lidocaine, with a time to onset ranging from immediate to within one week following injection. These reported events likely resulted from inadvertent arterial injection. In many of these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (see WARNINGS section). Reported treatments include: anticoagulants, epinephrine, aspirin, hyaluronidase, steroid treatment, eye drops, hyperbaric oxygen, and surgery. Outcomes have ranged from completely resolved to ongoing at the time of last contact.

Adverse reactions should be reported to Allergan Product Surveillance Department at 1-877-345-5372.

7. CLINICAL STUDIES

A. Pivotal Study for JUVÉDERM® Ultra (Without Lidocaine) for Treatment of NLFs

Pivotal Study Design

A prospective, double-blind, randomized, within-subject, controlled, multicenter, pivotal, clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® Ultra in the treatment of moderate to severe wrinkles. Subjects underwent treatment with JUVÉDERM® Ultra in one NLF and the control implant (ZYPLAST® bovine collagen) in the opposite NLF.

Up to 3 bilateral treatments (initial treatment and up to 2 touch-up treatments), approximately 2 weeks apart, were allowed. At 2 and 4 weeks after each treatment, the Independent Expert Reviewer (IER) assessed the level of correction achieved. If correction was less than optimal after the first or second treatment, the Investigator re-treated the under-corrected NLFs using the same respective treatment materials as in the initial treatment. The IER and the subject remained masked to the randomized treatment assignment.

Routine follow-up visits for safety and effectiveness occurred at days 3 and 7 and week 2 after each treatment, and at 4, 8, 12, 16, 20, and 24 weeks after the last treatment. Standardized facial photography was performed for documentation purposes. The Investigator and the IER independently evaluated the severity of the subject's NLFs using the validated 5-point (range 0 to 4) photographic Allergan NLF severity scale. The subject made independent self-assessments of NLF severity using a non-photographic 5-point grading scale.

Study Endpoints

The primary effectiveness endpoint for the study was the IER's NLF severity score over the post-treatment follow-up period. Effectiveness of device treatment was demonstrated by a lowering of the NLF severity score. Additional analyses included the subject's and the Investigator's live NLF severity assessments.

Subject Demographics

A total of 146 subjects (31 to 75 years of age) were randomized and treated, and 140 (96%) completed the 6-month follow-up period. Prior to enrollment, 87 (60%) had previous experience with other facial dermal treatments (eg, alpha hydroxyl-agents, neurotoxin, microdermabrasion, or retinoic acid).

Subject demographics and pretreatment characteristics of the JUVÉDERM® Ultra effectiveness population are presented in Table 6.

Table 6. Demographics and Pretreatment Characteristics of the Effectiveness Population (Number/% of Subjects) N = 146

Gender (Number/%)		
Female	135	92%
Male	11	8%
Ethnicity (Number/%)		
Caucasian	105	72%
African American	18	12%
Hispanic	15	10%
Asian	7	5%
Other	1	1%
Fitzpatrick Skin Phototype (Number/%)		
I	4	3%
II	34	23%
III	55	38%
IV	24	16%
V	24	16%
VI	5	3%
Mean Baseline NLF Severity Score[a]		
JUVÉDERM® Ultra NLF	2.6	
ZYPLAST® NLF	2.6	

[a] NLF severity was ranked on a 5-point scale from None (0) to Extreme (4)

Effectiveness Results

The primary effectiveness results for JUVÉDERM® Ultra based on the IER's assessment of NLF severity are presented in Table 7.

Table 7. Effectiveness Summary Independent Expert Reviewer's NLF Severity Scores

		JUVÉDERM® Ultra (N^a = 146 NLFs)		Control[b] (N^a = 146 NLFs)	
	n[c]	NLF Severity[d]	Improvement Since Baseline[d]	NLF Severity[d]	Improvement Since Baseline[d]
Baseline	146	2.6	–	2.6	–
Week 2	142	0.6	2.0	0.7	1.9
Week 12	129	0.9	1.7	1.6	0.9
Week 24	138	1.3	1.3	2.3	0.3

[a] Number of subject NLFs treated with the respective device
[b] A commercially available injectable bovine collagen implant
[c] Number of subject NLFs with data at baseline and the specified timepoint
[d] Mean score

Throughout the 24-week study period, JUVÉDERM® Ultra provided a clinically and statistically significant improvement in NLF severity. Clinical superiority was achieved at week 24 for JUVÉDERM® Ultra over ZYPLAST® with mean NLF severity of 1.3 and 2.3, respectively (P <0.0001). Additionally, subject assessments for product preference overwhelmingly favored JUVÉDERM® Ultra: 88% preferred the JUVÉDERM® Ultra treated NLF over the ZYPLAST® treated NLF.

B. Extended Follow-up Clinical Study

Of the 146 randomized and treated subjects, more than three-quarters (79%, 116/146) returned after completion of their 24-week follow-up in the pivotal study for complimentary repeat treatment. Demographics for the subjects receiving repeat treatment were similar to those in the overall study. The majority of subjects were Caucasian and female, with a median age of 50 years. More than one-third of subjects were of Fitzpatrick Skin Phototypes IV, V, or VI.

After completing the 24-week study, subjects returned for repeat treatment at their convenience or their Investigator's convenience. The average time elapsed between last initial treatment and repeat treatment was approximately 9 months. A statistical analysis demonstrated that those subjects who returned for repeat treatment at a later timepoint were representative of the pivotal study subjects overall. There were no significant differences between these stratified groups in terms of NLF severity at baseline or at the 24-week follow-up visit or overall initial volume injected. Before repeat treatment, live assessments of wrinkle severity were made by the Investigator and the subject. The extended follow-up effectiveness results for JUVÉDERM® Ultra based on the Investigator's assessment of NLF severity are presented in Table 8.

Table 8. Extended Follow-up Prior to Repeat Treatment Effectiveness Summary Investigator's NLF Severity Scores

		JUVÉDERM® Ultra (N^a = 116 NLFs)		
	n[b]	NLF Severity[c]	Improvement Since Baseline[c]	*P* value
Baseline[a]	116	2.6	–	N/A
Follow-up Week 24[a] (Month 6)	116	1.3	1.3	< .0001
Follow-up Weeks 25-36 (Months 6-9)	68	1.3	1.2	< .0001
Follow-up Weeks > 36 (> 9 months)	48	1.6	1.1	< .0001

[a] Data collected during pivotal study
[b] Number of subject NLFs with data at baseline and the specified timepoint
[c] Mean score

All subjects returning for repeat treatment were stratified into 2 groups based on the time elapsed between last initial treatment and repeat treatment: 25 to 36 weeks or > 36 weeks. Mean improvement since baseline was clinically significant (≥ 1 point) for both groups, with a large majority of subjects treated with JUVÉDERM® Ultra demonstrating improvement:

- 84% (57/68) at 25 to 36 weeks (6-9 months)
- 75% (36/48) beyond 36 weeks (beyond 9 months)

Follow-up After Repeat Treatment

A subset of subjects enrolled in a prospective, multicenter study for follow-up after repeat treatment. Subjects were eligible for the follow-up study if they completed the pivotal study, indicated that they preferred JUVÉDERM® Ultra over the control device, and received repeat treatment between 24 and 36 weeks after their last treatment in the pivotal study.

Subjects underwent repeat treatment with JUVÉDERM® Ultra in both NLFs. Demographics for subjects enrolled in the repeat treatment extended follow-up study were similar to those in the pivotal study. Routine follow-up visits for safety and effectiveness occurred at 4, 12, 24, 36, and 48 weeks after the repeat treatment. The Investigator evaluated each subject for signs and symptoms of serious or unanticipated adverse events. The Investigator also evaluated the severity of the subject's NLFs using the validated 5-point (range 0 to 4) photographic Allergan NLF severity scale. The subject made independent self-assessments of NLF severity using the nonphotographic 5-point grading scale.

No serious or unanticipated adverse events were reported. The effectiveness results for repeat treatment with JUVÉDERM® Ultra based on the Investigator's assessment of NLF severity after repeat treatment are presented in Table 9.

Table 9. Follow-up after Repeat Treatment Effectiveness Summary Investigator's NLF Severity Scores

		JUVÉDERM® Ultra N = 24	
	n[a]	NLF Severity[b]	Improvement Since Baseline[b]
Baseline	24	2.5	–
Pre-repeat Treatment	24	1.4	1.1
Week 12	23	0.9	1.7
Week 24	23	1.1	1.4
Week 48	9	1.3	1.3

[a] Number of subject NLFs with data at baseline and the specified time point
[b] Mean score

Throughout the 48-week follow-up period, JUVÉDERM® Ultra provided a clinically significant improvement in NLF severity (≥ 1 point mean improvement) with a large majority of subjects treated with JUVÉDERM® Ultra demonstrating improvement at 24 weeks and beyond: 87% (20/23) at 24 weeks and 78% (7/9) at 48 weeks (1 year).

C. Clinical Study for JUVÉDERM® Ultra XC for Treatment of NLFs

A prospective, double-blind, randomized, within-subject, controlled, multicenter clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® Ultra XC compared with JUVÉDERM® Ultra without lidocaine. The purpose of this study was to evaluate the level of procedural pain (pain during injection) experienced by subjects when treated with each product. The duration of the study was 2 weeks.

A total of 36 subjects received a single treatment with JUVÉDERM® Ultra XC in one NLF and JUVÉDERM® Ultra without lidocaine in the other NLF. Within 30 minutes after both NLFs were treated, the subjects rated procedural pain on an 11-point scale and a 5-point comparative scale. Both the Investigators and subjects rated NLF severity at baseline and 2 weeks after treatment using the 5-point NLF severity scale from the pivotal study. Subjects utilized an interactive voice-response-system diary to record common treatment site reactions for 14 days.

Most of the subjects were women (94%) of Caucasian descent (75%) with Fitzpatrick skin phototype II or III (58%). Persons of color (Fitzpatrick skin phototypes IV, V, or VI) comprised 36% of treated subjects. Median age at study entry was 52 years (range, 32 to 73). Subject demographics are shown in Table 10.

Table 10. Subject Demographics (Number/% of Subjects) N = 36 Subjects

Gender		
Female	34	94%
Male	2	6%
Ethnicity		
Caucasian	27	75%
African American	7	19%
Hispanic	0	0%
Asian	1	3%
Other	1	3%
Fitzpatrick Skin Type		
I	2	6%
II	16	44%
III	5	14%
IV	7	19%
V	3	8%
VI	3	8%

The pain scores for the NLFs treated with JUVÉDERM® Ultra XC were significantly lower ($P < 0.0001$) than for the NLFs treated with JUVÉDERM® Ultra without lidocaine (Table 11) based on the 11-point scale. On the comparative scale, 94% (34/36) of subjects rated the side with lidocaine as less or slightly less painful compared to the side without lidocaine (Table 12).

Table 11. Subject Assessment of Procedural Pain Scores (N = 36)

	Mean Pain Score[a]
JUVÉDERM® Ultra XC	1.5
JUVÉDERM® Ultra	5.2
Mean Difference	-3.7

[a] Procedural pain score ranges from 0 to 10 where 0 = No Pain and 10 = Worst Pain Imaginable

Table 12. Subject Assessments of Comparative Procedural Pain Score

	JUVÉDERM® Ultra (N = 36 NLFs) N (%)
JUVÉDERM® Ultra XC is less painful	23 (64%)
JUVÉDERM® Ultra XC is slightly less painful	11 (31%)
No difference between products	0 (0%)
JUVÉDERM® Ultra XC is slightly more painful	2 (6%)
JUVÉDERM® Ultra XC is more painful	0 (0%)

NLF severity improvement after 2 weeks was similar for both JUVÉDERM® products (with and without lidocaine). The mean baseline score was 2.3, and a clinically significant improvement (severity reduction) to 0.7 was observed after 2 weeks for both products.

D. Pivotal Study of JUVÉDERM® Ultra XC for Lip Augmentation

A prospective, single-blind, randomized, no-treatment controlled, multicenter clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® Ultra XC for injection into the lips and perioral area (vermilion, vermilion border, philtral columns, Cupid's Bow, perioral lines, and/or oral commissures) for lip augmentation. A total of 213 subjects were randomized to either treatment with JUVÉDERM® Ultra XC (N = 157) or to delayed-treatment control (N = 56), and had treatment delayed approximately 3 months.

Treatment group subjects underwent treatment with JUVÉDERM® Ultra XC at the outset of the study, followed by an optional touch-up treatment 2-4 weeks after the initial treatment, if deemed necessary to achieve optimal correction. The primary follow-up period consisted of office visits at 1 and 3 months after the last treatment. Control subjects also completed 1 and 3 month follow-up visits. Thereafter, control subjects crossed over to initiate the study treatment and touch-up with post-treatment follow-up identical to the treatment group.

All subjects continued through an extended follow-up period, which consisted of safety and effectiveness follow-up visits at 6, 7½, 9, 10½, and 12 months after their last treatment, or until the visit at which the independent Evaluating Investigator's assessment of the subject's overall Lip Fullness score returned to or was lower than the baseline score, whichever occurred first. Subjects were then eligible for a repeat treatment, with post-treatment follow-up for up to 6 months after repeat treatment, at which time all subjects completed the study.

Study Endpoints

The primary effectiveness endpoint for the study was the blinded Evaluating Investigator's assessment of the subject's overall Lip Fullness on the validated 5-point Allergan Lip Fullness Scale (LFS). A responder was defined as a subject with ≥1 point improvement in overall lip fullness score compared with the pre-treatment score on the LFS. Effectiveness was demonstrated if at least 60% of subjects treated with JUVÉDERM® Ultra XC were observed to be responders and if the responder rate for treated subjects was statistically superior to the responder rate for the no-treatment control group at 3 months after treatment.

Secondary measures included the Evaluating Investigators' assessments of the subject's upper and lower lip fullness, the severity of the subject's perioral lines and oral commissures, as well as the subjects' assessments of whether their lip fullness goal was achieved.

Additional effectiveness measures included Evaluating Investigator assessment of the treatment area using the Other Aesthetic Features of the Lips and Mouth Area questionnaire, changes in the surface area and volume of the lips as calculated from 3D imaging, subject self-assessments of the look and feel of the lips and mouth, as well as subject assessments of willingness to undergo treatment again.

Subject Demographics

Subject demographics and pretreatment characteristics of the treatment and control group are presented in Table 13.

Table 13. Subject Demographics and Pretreatment Characteristics (N = 213)

	Treatment Group (N = 157) % (n/N)	Control Group (N = 56) % (n/N)
Gender		
Female	95.5% (150/157)	96.4% (54/56)
Male	4.5% (7/157)	3.6% (2/56)
Ethnicity		
Caucasian	84.7% (133/157)	85.7% (48/56)
Hispanic	5.1% (8/157)	3.6% (2/56)
African American	8.3% (13/157)	5.4% (3/56)
Asian	0.6% (1/157)	3.6% (2/56)
Other	1.3% (2/157)	1.8% (1/56)
Fitzpatrick Skin Phototype		
I	1.3% (2/157)	5.4% (3/56)
II	36.9% (58/157)	32.1% (18/56)
III	45.9% (72/157)	44.6% (25/56)
IV	3.8% (6/157)	7.1% (4/56)
V	10.2% (16/157)	8.9% (5/56)
VI	1.9% (3/157)	1.8% (1/56)
Baseline Overall Lip Fullness (LFS[a]) Score		
Minimal	30.6% (48/157)	33.9% (19/56)
Mild	59.9% (94/157)	53.6% (30/56)

[a] Lip Fullness was rated on the 5-point LFS from Minimal (1) to Very Marked (5)

Effectiveness Results

JUVÉDERM® Ultra XC provided a clinically and statistically significant improvement in overall lip fullness compared to the no-treatment control group at Month 3. The primary effectiveness criteria were met in that the treatment group's responder rate of 79.1% was greater than the 60% threshold, and the responder rate for the treatment group was significantly greater ($p < 0.0001$) than the responder rate for the control group (26.1%).

Throughout the extended follow-up period, JUVÉDERM® Ultra XC continued to provide a clinically significant improvement in lip fullness (≥ 1 point mean improvement on the LFS), with a majority of subjects treated with JUVÉDERM® Ultra XC demonstrating improvement through 12 months (Table 14).

Table 14. Effectiveness of JUVÉDERM® Ultra XC in the Lips Through 1 Year

	n[a]	Treatment Group (N = 157) Responder Rate % (n)
Baseline[a]	157	N/A
1 Month	139	79.9% (111)
3 Months	139	79.1% (110)
6 Months	118	80.5% (95)
9 Months	99	63.6% (63)
12 Months	101	56.4% (57)

[a] Number of subjects with data at baseline and the specified timepoint

At Month 3, improvements in upper and lower lip fullness were observed in 75.4% (104/138) and 79.9% (107/134), respectively, based on Evaluating Investigator assessments. While the responder rates for improvement in perioral lines and oral commissures at Month 3 were 47.5% (29/61) and 47.3% (114/241), respectively, demonstrating some improvement in severity of upper lip perioral lines and oral commissures, inadequate information was available regarding the clinical and statistical significance of this improvement. Thus, the treatment benefit for perioral lines and oral commissures was not determined in this lip augmentation study.

At 3 months, 81.8% (112/137) of subjects rated that their overall lip fullness goals were achieved, and 87.5% (119/136) of subjects assessed their treatment outcome as expected or better than expected. The majority of subjects (89.1%, 123/138) indicated willingness to undergo treatment again at Month 3, which remained high at the end of the extended follow-up period, with 84.7% (72/85) indicating willingness to undergo treatment again. Using the Other Aesthetic Features questionnaire, Evaluating Investigators assessed their satisfaction with the subject's lips and mouth area, with over 75% of subjects assessed as improved through Month 12.

At 3 months, 92.1% (128/139) of subjects rated an improvement in overall satisfaction with the look and feel of their lips and mouth, which lasted through Month 12 for 78.4% (58/74) of subjects. The majority of subjects also reported improvement in the softness, smoothness, and natural look and feel of their lips and mouth through 12 months.

Objective lip measurements calculated from the 3D imaging showed an increase in both lip volume and overall lip surface area. At Month 3, treatment group subjects showed a mean increase in lip volume of 0.61 cc and a 25% increase in surface area (N = 130), while control group subjects showed almost no increase in lip volume and an 8% increase in surface area (N = 44). Treatment group subjects showed an increase in these measurements at later timepoints that gradually tapered off to a mean lip volume increase of 0.54 cc and a 19% surface area increase at Month 12 (N = 54).

No differences in overall lip fullness responder rates at Month 3 were observed based on the following subgroup analyses: baseline lip fullness, gender, race, investigational site, plane of injection, injection technique, injection volume, injection site, and Fitzpatrick skin phototype.

Follow-Up After Repeat Treatment

Repeat treatment was administered to 114 subjects. The effectiveness profile after repeat treatment was similar to that after the initial treatment. At Month 3 after repeat treatment, the responder rate was similar to that after initial treatment, with 85.5% of subjects showing at least a 1-point improvement in lip fullness, based on the Evaluating Investigator assessment (Table 15).

Table 15. Effectiveness of JUVÉDERM® Ultra XC after Repeat Treatment

	n[a]	Responder Rate % (n)
Month 1	71	87.3% (62)
Month 3	76	85.5% (65)

[a] Number of subjects with data at baseline and the specified timepoint

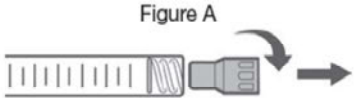
8. INSTRUCTIONS FOR USE

A. To Attach Needle to Syringe

STEP 1: Remove tip cap

Hold syringe and pull tip cap off the syringe as shown in Figure A.

Figure A



STEP 2: Insert needle

Hold the syringe body and firmly insert the hub of the needle (provided in the JUVÉDERM® package) into the LUER-LOK® end of the syringe.

STEP 3: Tighten the needle

Tighten the needle by turning it firmly in a clockwise direction (see Figure B) until it is seated in the proper position as shown in Figure C.

NOTE: If the position of the needle cap is as shown in Figure D, it is not attached correctly. Continue to tighten until the needle is seated in the proper position.

Figure B

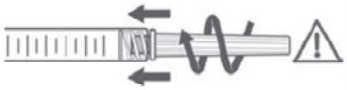


Figure C

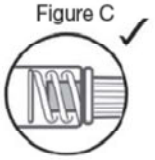


Figure D

STEP 4: Remove the needle cap

Hold the syringe body in one hand and the needle cap in the other. Without twisting, pull in opposite directions to remove the needle cap as shown in Figure E.

Figure E

B. Health Care Professional Instructions

1. JUVÉDERM® Ultra XC injectable gel is a highly crosslinked smooth gel formulation that can be injected using a fine gauge (e.g., 30-G) needle for more versatility in contouring and volumizing of facial wrinkles and folds and lips.
2. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to achieve and maintain maximum correction.
3. The patient's soft-tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Depending on the type of skin, best results are obtained when the defect is readily distensible and correction can be visualized by manual manipulation (stretching) of the skin. Pretreatment photographs are recommended.
4. Although study results showed JUVÉDERM® Ultra XC to be less painful than JUVÉDERM® Ultra, supplementary anesthesia may be used for additional pain management during and after injection.
5. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle.
6. After the first small amount of material has been injected into the patient, wait a full 3 seconds to allow the lidocaine to take effect before proceeding with the rest of the injection.
7. The injection technique for wrinkles, folds, and lips may vary with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered. A linear threading technique, serial puncture injections, fanning technique, crosshatching technique, or a combination have been used to achieve optimal results. Injecting the product too superficially may result in visible lumps and/or discoloration.
8. Inject JUVÉDERM® Ultra XC by applying even pressure on the plunger rod while slowly pulling the needle backwards. It is important that the injection be stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
9. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
10. The typical total volume to achieve optimal correction of moderate to severe nasolabial folds is 1.6 mL per treatment site. The typical volume to achieve optimal correction for repeat treatment is 0.7 mL per treatment site.
11. The typical volume injected into the lips and perioral area to achieve optimal correction for lip augmentation is approximately 2.2 mL, which may vary depending on the goals the patient wishes to achieve. Injection volumes into the lips and perioral area after repeat treatment tended to be lower, with the typical total injection volume to achieve optimal correction being approximately 1.5 mL.
12. Correct to 100% of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.
13. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.[1]
14. When injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.
15. With patients who have localized swelling, the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient to a touch-up session after 1-2 weeks.
16. Patients may have mild to moderate injection site responses, which typically resolve in a few days in the NLFs, and within 2 weeks in the lips and perioral area. If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period.

[1]Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. *Dermatol Surg.* 2008;34(suppl 1):S115-S148.

17. After the initial treatment, an additional treatment (from 1 to 4 weeks later) may be necessary to achieve the desired level of correction. If further treatment is needed, the same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as treatment goals, wrinkle severity, lip fullness, skin elasticity, and dermal thickness at the treatment site.
18. The Health Care professional should instruct the patient to promptly report to her/him any evidence of problems possibly associated with the use of JUVÉDERM® Ultra XC.

C. Patient Instructions

It is recommended that the following information be shared with patients:

- Within the first 24 hours, patients should avoid strenuous exercise, extensive sun or heat exposure, and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection sites.
- To report an adverse reaction, phone the Allergan Product Support Department, 1-877-345-5372.

9. HOW SUPPLIED

JUVÉDERM® Ultra XC injectable gel is supplied in individual treatment syringes with 30 G needles for single-patient use and ready for injection (implantation). The volume in each syringe is as stated on the syringe label and on the carton. The contents of the syringe are sterile and non-pyrogenic. Do not resterilize. Do not use if package is opened or damaged.

10. SHELF LIFE AND STORAGE

JUVÉDERM Ultra XC injectable gel must be used prior to the expiration date printed on the label.

Store at room temperature (up to 25°C/77°F). DO NOT FREEZE.

JUVÉDERM® Ultra XC injectable gel has a clear appearance. In the event that a syringe contains material that is not clear, do not use the syringe; notify Allergan Product Support immediately at 1-877-345-5372.

To place an order, contact Allergan at 1-800-377-7790.

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