CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 43USCH2208

TITLE PAGE

A randomized, evaluator-blinded, parallel group, comparator-controlled, multicenter study to evaluate the safety and effectiveness of *Restylane Lyft with Lidocaine* for augmentation of the chin region to improve the chin profile

Clinical Trial Number (CTN): 43USCH2208

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[1] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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Details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a Clinical Study Protocol (CSP) amendment.

SYNOPSIS

Clinical Study Title:	A randomized, evaluator-blinded, parallel group, comparator-controlled, multicenter study to evaluate the safety and effectiveness of *Restylane Lyft with Lidocaine* for augmentation of the chin region to improve the chin profile.
Clinical Trial Number:	43USCH2208
Country Involved and Planned Number of Study Centers:	Country: USA No of Study Centers: Approximately 12
Target Indication:	Restylane Lyft with Lidocaine is an injectable implant, intended to be used for augmentation of the chin region to improve the chin profile, in patients over the age of 21 years.
Total Number of Subjects (Planned):	Approximately 174 subjects in will be enrolled. At least 35 subjects will be Fitzpatrick skin type (FST) IV through VI, this includes at least 18 subjects with FST V – VI, where at least 9 subjects will be FST V and at least 9 subjects will be FST VI.
Clinical Study Design:	This is a prospective, randomized, evaluator-blinded, parallel group, comparator-controlled, multicenter study in the US. Approximately 174 subjects will be randomized 2:1 to treatment with either *Restylane Lyft with Lidocaine* (Investigational Group) or comparator, *Juvéderm® Voluma™ XC* (Comparator Group). Injection technique is at the Treating Investigator's discretion with needle only or a combination of needle and cannula. *Restylane Lyft with Lidocaine* and the comparator-control will be administered by needle in the pogonion. The mentum and pre-jowl sulci may be injected by needle or cannula. After providing informed consent, eligible subjects randomized to receive either *Restylane Lyft with Lidocaine* or a comparator-control will be injected by the Treating Investigator at Baseline (Day 1). A follow-up telephone call should be made 72 hours after treatment and a follow-up visit should be scheduled after 14 days. Optional touch-up treatment may be administered 1 month (4 weeks) after initial treatment, if deemed necessary by the Treating Investigator and the subject to obtain optimal aesthetic improvement. If optional touch-up is performed, a 72-hour follow-up telephone call, a follow-up visit at 14 days and a follow-up visit at 1 month should be scheduled. Investigator blinding will be accomplished by using a Treating Investigator to administer the treatments and a Blinded Evaluator, to whom randomization and treatment are concealed, to conduct the blinded assessments. Safety assessments will be performed by non-blinded personnel. Effectiveness and safety data will be collected for up to 12 months (48 weeks) after last treatment including physical follow-up visits at 1, 3, 6, 9 and 12 months as well as 14 days after each treatment. A

	subject will be involved in the study for up to 13 months, including a 21-day screening period. The study visits are illustrated in the study flow chart and the schedule of events. Before study start, a randomization list will be prepared under the supervision of a designated biostatistician from the Sponsor. **General study safety stopping rule:** Enrollment and treatment in the study will be temporarily halted if a serious adverse event (SAE) occurs for the following: • any unanticipated SAE which is possibly related to the study device or procedure including but not limited to a vascular embolic event that leads to skin necrosis, vision loss or stroke, damage to facial nerves which may result in facial paralysis or injury to internal facial structures. The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE: • was unanticipated, • directly related to the study product or device injection procedure, • and presents an unreasonable risk to study subjects, the study will be terminated, and the Investigators will be notified. The institutional review board (IRB) and regulatory authority (RA) will also be notified if the study is prematurely terminated due to safety concerns. If the SAE does not meet the above criteria, then enrollment in the study will continue.
Primary Effectiveness Objective and Endpoint:	The primary objective of the study is to demonstrate non-inferiority of *Restylane Lyft with Lidocaine* versus a comparator-control for augmentation of the chin region to improve the chin profile by comparing change from baseline in the Blinded Evaluator live assessment of the Galderma Chin Retrusion Scale (GCRS) at 3 months after last treatment. Primary Endpoint: Change from baseline in the Blinded Evaluators' live assessment using the GCRS at 3 months after last treatment.
Secondary Effectiveness Objective and Endpoints	To evaluate the effectiveness of *Restylane Lyft with Lidocaine* versus a comparator-control for augmentation of the chin region to improve the chin profile, for the defined endpoints: 1. Responder rate based on the Blinded Evaluators' live assessment using the GCRS at 3, 6, 9 and 12 months after last treatment. A responder is defined as a subject with at least 1 grade improvement from baseline on the GCRS. CCI

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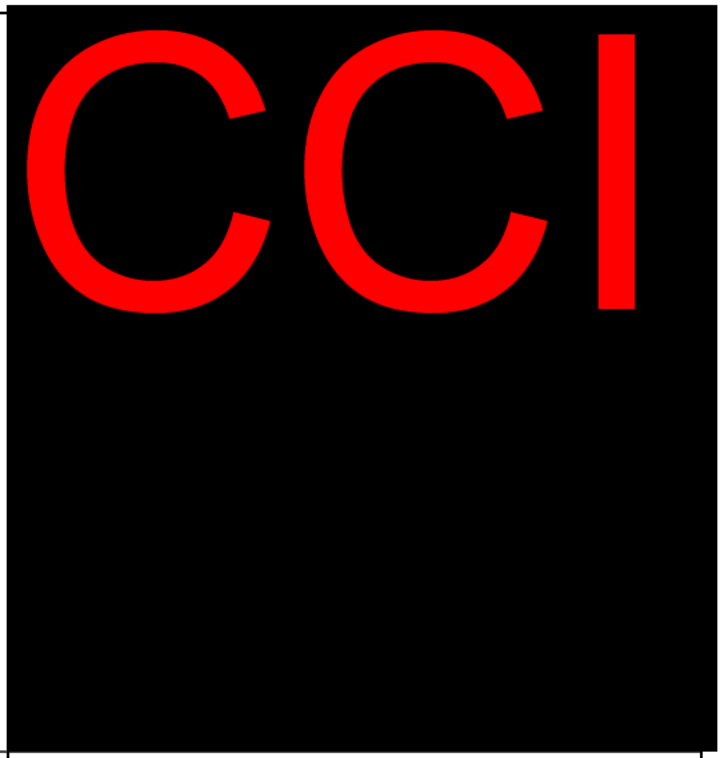
Subgroup Analyses	To evaluate the consistency of the primary analysis results across different subgroups, specifically: • Injection with needle • Combination needle and cannula • Study center

	• Fitzpatrick Skin Type (I–III and IV–VI) • Race • Ethnicity • Sex at birth • Age (≤ median age, and > median age) • Injection volume (≤ median total injection volume, and > median total injection volume) To evaluate the consistency of AE data across different subgroups, specifically: • Injection with needle • Combination needle and cannula • Study center • Fitzpatrick Skin Type (I–III and IV–VI) • Race • Ethnicity • Sex at birth • Age (≤ median age, and > median age) • Injection volumes (≤ median total injection volume, and > median total injection volume)
Clinical Study Duration:	First subject first visit (FSFV) to last subject last visit (LSLV): estimated to approximately 18 months including 4 months enrollment period. Duration for each Subject will be up to 14 months, including: • Up to 21 days screening • Treatment at Baseline (Day 1) and optional touch-up at 1 month. • Data collection and safety follow-up visits at 1, 3, 6, 9and 12 months after last treatment as well as 14 days after each treatment. One month is defined as 4 weeks in the study and 4 weeks is defined as 28 days.
Inclusion Criteria:	**The subjects must meet all the following criteria to be eligible for the study:** CCI 2. Males or non-pregnant, non-breastfeeding females, 22 years of age or older. CCI 4. Intent to receive treatment for augmentation and correction of retrusion in the chin region. CCI

	
Exclusion Criteria:	**The presence of any of the following exclusion criteria excludes a subject from enrollment in the study:** 1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins. 2. Known/previous allergy or hypersensitivity to local anesthetics, e.g., lidocaine or other amide-type anesthetics. 3. Previous or present multiple severe allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of angioedema. 4. Previous facial surgery (including facial aesthetic surgery and liposuction) below the level of the horizontal line from the subnasale. 5. Any previous aesthetic procedures or implants: 

- Previous mechanical (e.g., dermabrasion, needling) or chemical aesthetic procedures (e.g., medical chemical peel, mesotherapy) below the level of the horizontal line from subnasale within 6 months.
- Previous cryolipolysis treatment below the level of the horizontal line from subnasale within 6 months.
- Oral surgery (e.g., tooth extractions, orthodontia, or implantation) within 6 months

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7. Presence of any disease or lesions near or on the area to be treated, e.g.,
   - Inflammation, active or chronic infection (e.g., in mouth, dentals, head and neck region).
   - Facial psoriasis, eczema, acne (defined as active inflammatory reaction), rosacea, perioral dermatitis, herpes simplex or herpes zoster.
   - Scars or deformities.
   - Cancer, or precancer such as actinic keratosis or actinic cheilitis

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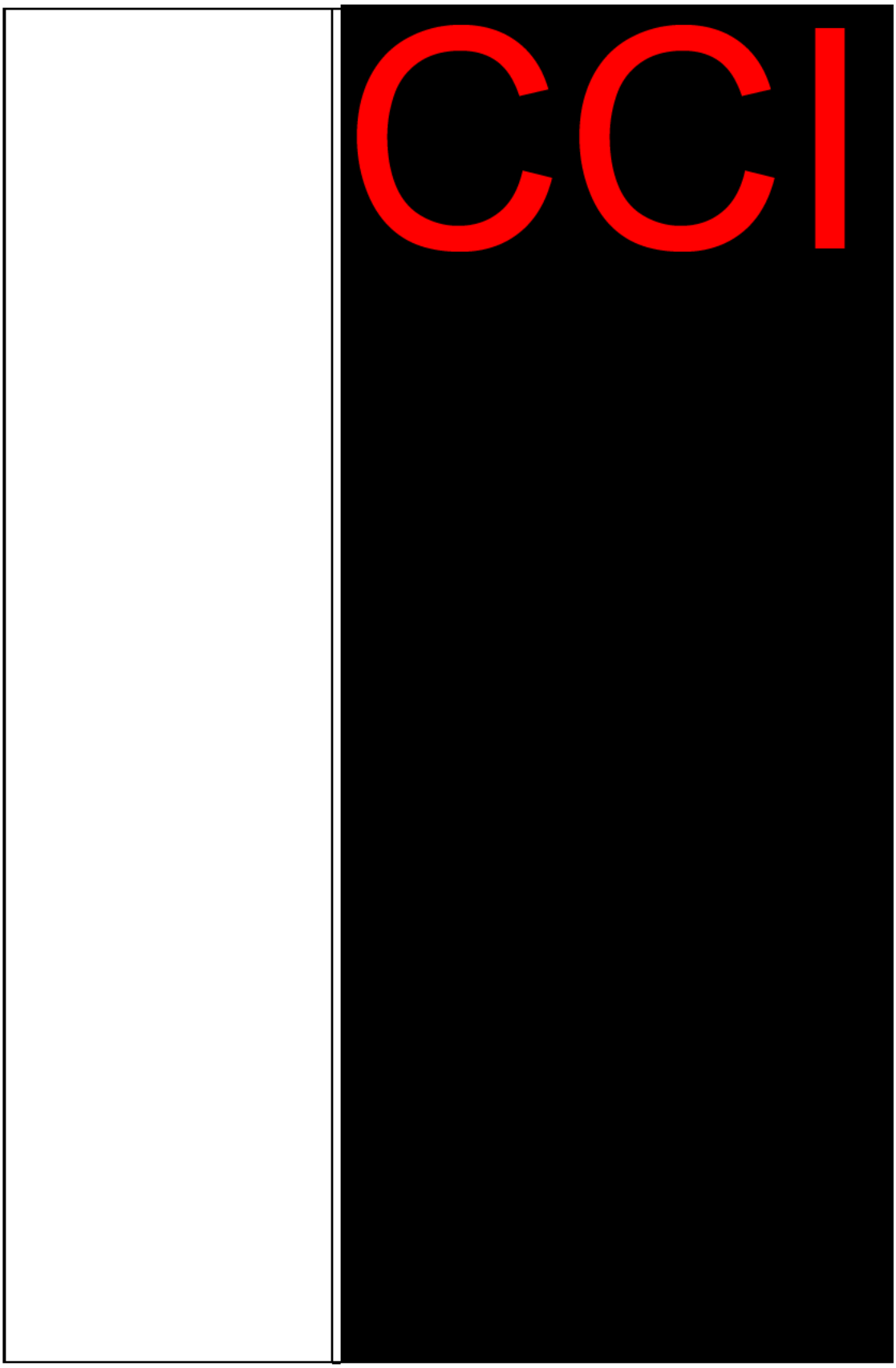

Investigational Product:	*Restylane Lyft with Lidocaine* is a sterile gel of HA generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine.
Comparator/Placebo Product:	*Juvéderm Voluma XC* is a sterile gel of HA produced by the *Streptococcus* species of bacteria, which is crosslinked with BDDE. It is formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.
Treatment area:	The treatment area includes the chin and surrounding regions: pogonion, mentum and pre-jowl sulci. Subjects will be treated to optimal chin retrusion correction, which is defined as at least 1 GCRS grade improvement from Baseline and best correction that can be achieved as agreed upon by the Treating Investigator and the subject.
Treatment regimen:	Subjects in the treatment group will receive injection in the chin and surrounding regions with either *Restylane Lyft with Lidocaine* or a comparator-control at Baseline (initial treatment) with optional touch-up treatment 1 month (4 weeks) after initial treatment, if deemed necessary by Treating Investigator and subject to obtain optimal aesthetic improvement.
Mode of administration:	Injection technique is at the Treating Investigator´s discretion (with needle only or a combination of needle and cannula). Injection should be in the deep subcutaneous tissue or supraperiosteal plane, as per Investigator's discretion. Appropriate injection volume for the chin area will be determined by the Treating Investigator but is not to exceed a maximum total volume of 4.0 mL for initial and touch-up treatments combined. Injection in the pogonion is only permitted with a needle; a cannula is permitted for injection in the other treatment areas. Depending on the location, serial puncture and linear threading among other techniques can be used to safely and effectively enhance the contour, shape and definition of this aesthetic region. The injection method and depth of injection, number of syringes used, and the volume of study product injected during each injection session will be recorded in the electronic Case Report Form (eCRF). Aspiration is recommended prior to each injection. Slow injection is recommended, and overcorrection should be avoided.
Statistical Method:	In general, all effectiveness, safety and baseline characteristics variables will be presented using descriptive statistics and graphs as appropriate. Continuous endpoints will be summarized using descriptive statistics, e.g., mean, median, standard deviation, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level. The primary effectiveness analysis is test of non-inferiority of *Restylane Lyft with Lidocaine* to a comparator-control *Juvéderm Voluma XC* in the Intention to treat (ITT) and Per Protocol (PP) analysis sets, using the confidence interval (CI) approach and non-inferiority margin of 0.5 units. The change from baseline in GCRS, as assessed by the Blinded Evaluator, will be analyzed using a mixed effect model with treatment as fixed effect and subject as random factor. The change from baseline at Month 3, after last treatment, will be the response variable. Non-inferiority will be established if the upper limit of the confidence interval (CI) is below

	the non-inferiority margin of 0.5 units. Superiority will be declared if the upper limit is below 0. This decision criterion is consistent with a gate-keeping strategy (testing for superiority following the test for non-inferiority) to maintain the overall type I error rate at 2.5%. <u>Secondary analyses</u> For the GCRS, a responder will be defined as a subject with at least 1 point improvement from baseline based on the GCRS. For a significant result, the two-sided p-value of the comparison of responder rates between the treatment groups at Month 3, 6, 9 and 12 using the Fisher's exact test. The estimates of the responder rate in each treatment group will be presented with corresponding CIs. CCI

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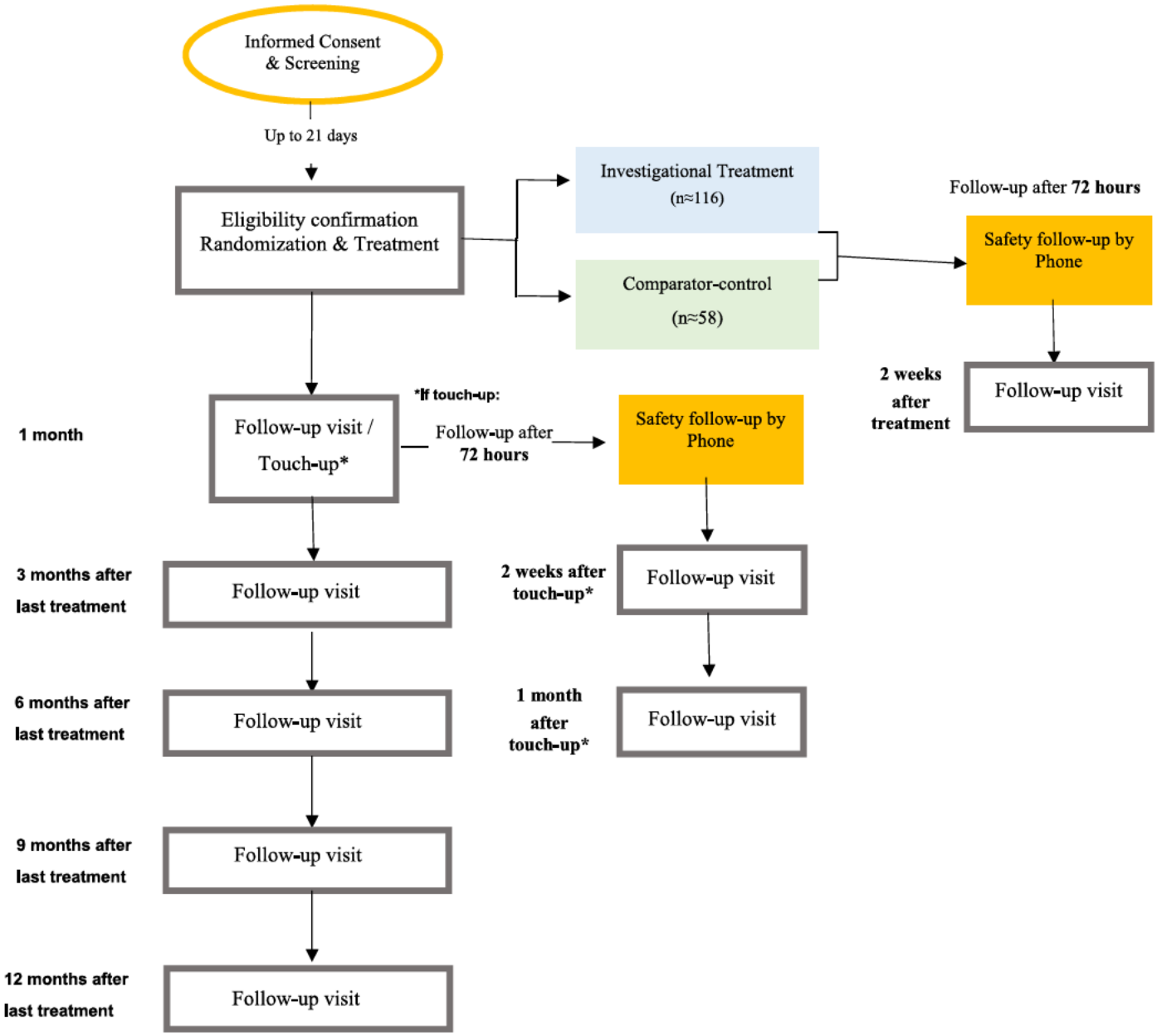
Sample Size:	Approximately 174 subjects in will be treated in the study, randomized in a 2:1 ratio (116 with *Restylane Lyft with Lidocaine*: 58 with *Juvéderm Voluma XC*). For sample size calculation of 174, it was assumed that the true effectiveness of *Restylane Lyft with Lidocaine* compared to control treatment assessed by the GCRS is approximately 0.1 point lower. A common standard deviation of 0.7 point was assumed for the treatments. Based on the non-inferiority margin of 0.5, a total sample size of 147 evaluable subjects is then required to show non-inferiority of *Restylane Lyft with Lidocaine* to the control treatment with a power of 90%, using a two-sided 95% CI for the difference between treatment means. Accounting for approximately 15% dropouts and non-evaluable subjects due to protocol deviations at 3 months, a total of approximately 174 subjects will be randomized in the study.
Interim Analysis:	No interim analysis is planned.
Effectiveness Assessments	• Blinded Evaluator GCRS • Treating Investigator GCRS CCI
Safety Assessments	1. Adverse Event reporting: AEs will be obtained from signs and symptoms reported by the Subject or detected during each examination. Any ongoing AEs related to product or injection procedure will be followed until resolved or chronic/stable through end of study participation. 2. A subject diary will be dispensed to all subjects for daily completion over the first 28 days after each treatment to record the following pre-identified symptoms: bruising, redness, tenderness, swelling, pain, lumps/bumps, itching, and other. Subjects will be specifically asked to record any of the following symptoms in the other section; changes in vision (i.e., loss of vision, blurriness, double vision, pain in

	or around your eye, blindness, blind spots, problems moving your eyes), skin changing color around the eyelids, crusty or scabby skin around the eyelids, pain, headache, fever, dizziness, confusion, weakness or numbness in the arms or legs, changes to consciousness or alertness, difficulty speaking/speech impairment and face droop, changes in ability to chew and drink, sensitivity to hot and cold or subject discomfort. Information from the diary will be presented separately from other AEs. • Contact the study doctor immediately if they experience severe pain, headache, fever, skin changing color near the injection site, or crusty or scabby skin near the injection site. • Contact an eye doctor (retinal specialist or ophthalmologist) if they experience changes in vision (i.e., vision loss, blurriness, double vision, pain in or around eye, blindness, blind spots, problems moving your eyes), change in skin color, or crusty/scabby skin around the eyelids. • Call 911 and seek immediate medical attention if signs of stroke or subject experience dizziness, confusion, weakness, or numbness in face, arms or legs, changes to consciousness or alertness, difficulty speaking/speech impairment, or face droop. 3. Visual function assessments (i.e., Snellen visual acuity test, extraocular muscle function test, and confrontation visual field test) at baseline and at all following physical visits. At treatment visits, the assessments will be performed both prior to and post injection of the study product. 4. Subject pain assessment before (prior to application of any anesthetic) and immediately after (before any post-injection therapy is provided, e.g., ice packs) treatment, using an 11-point Numeric Pain Scale (NPS). 5. Changes in hair growth (e.g., loss or growth) in the treated area, at each physical follow-up visit after baseline. 6. Lower lip movement, chin and lip function and sensation, according to pre-defined methods, at baseline and at each physical follow-up visit. 7. Palpation tests according to pre-defined methods, at screening, baseline and at each physical follow-up visit. 8. Device deficiencies will be assessed at treatment visits.

GALDERMA	Title 43USCH2208, Clinical Investigation Plan R Lyft Chin US	Doc id MA-52558

CLINICAL STUDY FLOW CHART

Figure 1 Study Flow Chart



GALDERMA EST. 1981	Title **43USCH2208, Clinical Investigation Plan R Lyft Chin US**	Doc id **MA-52558**

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AESI	Adverse event of special interest
BDDE	1,4-butanediol diglycidylether
BOCF	Baseline observation carried forward
CFR	Code of Federal Regulations
CI	Confidence interval
CMC	Chemistry, manufacturing and control
COX-2	Cyclooxygenase-2
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
CTN	Clinical Trial Number
CV	Curriculum vitae
DMP	Data Management Plan
eCRF	Electronic case report form
EOS	End of study
FDA	Food and Drug Administration
FSFV	First subject first visit
FST	Fitzpatrick Skin Type
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GCP	Good Clinical Practice
GCRS	Galderma Chin Retrusion Scale
GDPR	General Data Protection Regulation
GLP	Good laboratory practice
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFU	Instructions for Use
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IRB	Institutional review board
ITT	Intention to treat
IUD	Intra uterine device
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Medical Devices Regulation
MI	Multiple imputation
n	Number of subjects
NPS	Numeric Pain Scale
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator
PP	Per protocol
PMS	Post market surveillance
PT	Preferred term
RA	Regulatory Authority
ROPI	Report of prior investigations

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDV	Source Data Verification
SOC	System organ class
CCI	[redacted]
TC	Telephone call
Tx	Treatment
UADE	Unanticipated adverse device effect
UPT	Urine pregnancy test
UTW	Ultra-thin wall
WHO	World Health Organization

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1. BACKGROUND INFORMATION

1.1 Medical background, indication, and population description

The safety and effectiveness of *Restylane*® fillers are well known; the number of treatments performed with the *Restylane* range of products since first marketing approval has been estimated to over 55 million worldwide. *Restylane* was first approved for use on the US market in 2003, and other members of the *Restylane* family of products have been approved on the US market since then.

The Restylane family of products are transparent, viscous and sterile gels of hyaluronic acid (HA) generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE (1,4-butanediol diglycidylether) and suspended in phosphate buffered saline (pH of 7) solution at a concentration of 20 mg/mL HA. Some of the products contain 0.3% lidocaine.

In 2010, *Restylane Lyft with Lidocaine* received US marketing approval. Currently, *Restylane Lyft with Lidocaine* is approved in the US for the following indications:

- Implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.
- Subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21.
- Injection into the subcutaneous plane in the dorsal hand to correct volume deficit in patients over the age of 21.

Restylane Lyft with Lidocaine is branded *Restylane Lyft Lidocaine* outside the US, e.g., in EU and is approved for facial tissue augmentation. It is recommended to be used for shaping the contours of the face, the correction of folds and for lip enhancement.

This randomized and controlled study is planned to collect safety and effectiveness data to support the use of *Restylane Lyft with Lidocaine* into the chin region to improve the chin profile in subjects over the age of 21, with the aim to expand the currently approved US indication. *Restylane Lyft with Lidocaine* will be administered by needle and cannula injections in the chin area.

1.2 Relevant previous data

1.2.1 Non-clinical documentation

The currently marketed *Restylane Lyft with Lidocaine* will be used as the study product. This clinical investigation is aiming to support approval of a new indication for subcutaneous and/or supraperiosteal injection for augmentation of the chin region to improve the chin profile in adults over the age of 21. There are no changes in product manufacture, specifications, or shelf-life, therefore, no additional animal or laboratory testing has been conducted.

1.2.2 Clinical documentation

Please refer to the Report of Prior Investigations (ROPI) for a description of clinical studies completed in facial indications including the chin area with *Restylane* products, post-market reporting of the *Restylane* products in total as well as separately in the chin area, and available clinical data from publications with HA fillers in the chin area.

Please also refer to the study specific Instructions for Use (IFU) for *Restylane Lyft with Lidocaine* that summarizes the expected AEs for this product along with precautions that can minimize these potential complications.

For intravascular complications or embolic event, the treating physician should provide prompt medical attention and follow relevant clinical practice guidelines[1] for handling these symptoms. The treating physician should also review the Intravascular Treatment Protocol[2] provided separately in the Investigator file, as a support tool.

1.3 Risks and benefits

The benefit of using HA-fillers for chin injections has been documented in clinical studies.[3,4,5,6,7,10] Clinical data from literature confirm the overall picture from these studies, i.e., treatment was well tolerated, and satisfactory results were obtained. Both needles and cannulas have been used effectively as injection devices.

Medical complaints received from post marketing surveillance are few and the most common medical complaints received from post marketing surveillance after treatment with *Restylane* NASHA fillers in the chin are swelling, mass/induration and pain/tenderness. Serious adverse events are rarely reported (reporting frequency <0.001% based on post-market surveillance data) following treatment with *Restylane Lyft with Lidocaine* in any indication. Among the few case reports assessed as serious and related to treatment, with *Restylane Lyft with Lidocaine*, events of infection/abscess, swelling and ischemia/necrosis were most commonly reported. Serious adverse events following treatment in the chin region showed a similar reporting pattern as that for treatment with *Restylane Lyft with Lidocaine* in any treatment area.

Potential hazards related to treatment with *Restylane Lyft with Lidocaine* including the chin region are continuously assessed, evaluated, and managed in accordance with requirements in the ISO 14971 standard and in-house established risk management procedures. To date, no unacceptable risks have been identified for *Restylane Lyft with Lidocaine* treatment. Any potential concerns related to the clinical study have been assessed and the remaining risks are disclosed in the study specific IFU.

Based on clinical studies sponsored by the company as well as published literature and spontaneously reported adverse events from the market, it is concluded that there is reasonable assurance from a safety perspective for conducting an IDE clinical trial in the US, using *Restylane Lyft with Lidocaine* for injection into the chin region, to improve the chin profile, in subjects over the age of 21.

2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESIS

2.1 Study objectives

2.1.1 Primary objective and endpoint

The primary objective of the study is to demonstrate non-inferiority of *Restylane Lyft with Lidocaine* versus *Juvéderm® Voluma™ XC* for augmentation of the chin region to improve the chin profile by comparing change from baseline in the Blinded Evaluator live assessment of the Galderma Chin Retrusion Scale (GCRS) at 3 months after last treatment.

Primary Endpoint:

Change from baseline in the Blinded Evaluators' live assessment using the GCRS at 3 months after last treatment.

2.1.2 Secondary objectives and endpoints

To evaluate the effectiveness of *Restylane Lyft with Lidocaine* versus a comparator-control for augmentation of the chin region to improve the chin profile, for the defined endpoints:

1. Responder rate based on the Blinded Evaluators' live assessment using the GCRS at 3, 6, 9 and 12 months after last treatment.

A responder is defined as a subject with at least 1 grade improvement from baseline on the GCRS.

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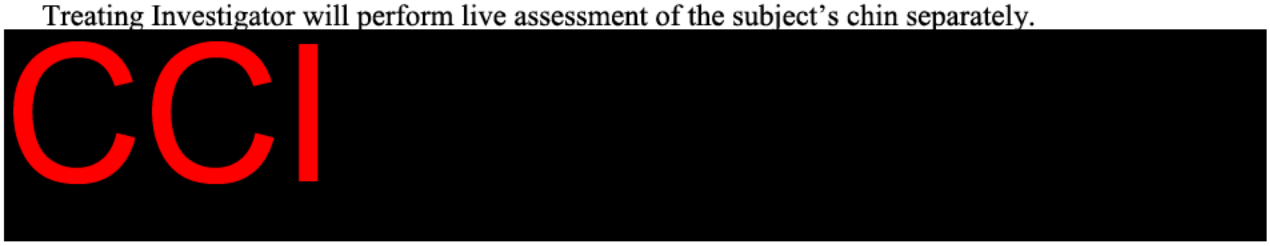
2.2 Appropriateness of measurements

The aim of the study is to evaluate the safety and effectiveness of *Restylane Lyft with Lidocaine* of the chin region to improve the chin profile.

Primary effectiveness will be evaluated by comparing the change from baseline in the Blinded Evaluators' live assessment at 3 months (12 weeks) after last treatment, using the GCRS.

The GCRS is a validated 4 grade scale for assessment of Chin retrusion (Appendix 1). Each score in the GCRS is exemplified by Photographic images of the scale. The Blinded Evaluator and Treating Investigator will perform live assessment of the subject's chin separately.



Effectiveness evaluation in dermal filler clinical studies includes a combination of clinician-and subject-reported outcomes. As these are aesthetic devices and elective procedures, the incorporation of the subject perspective is critical to the study benefits associated with dermal fillers.

2.3 Clinical hypothesis

This study has been designed to show non-inferiority of *Restylane Lyft with Lidocaine* to *Juvéderm Voluma XC* for augmentation of chin region to improve the chin profile.

The primary objective of the study is to demonstrate non-inferiority of Restylane Lyft with Lidocaine versus a comparator-control for augmentation of the chin region to improve the chin profile by comparing change from baseline in the Blinded Evaluator live assessment of the GCRS at 3 months after last treatment.

3. Study design

3.1 Overall design

This is a prospective, randomized, evaluator-blinded, parallel group, comparator-controlled, multicenter study in the US to evaluate the safety and effectiveness of *Restylane Lyft with Lidocaine* for augmentation of the chin region to improve the chin profile. The chin region is comprised of the anatomical areas of the pogonion, menton, and pre-jowl sulcus.

Before study start, a randomization list will be prepared under the supervision of a designated biostatistician from the Sponsor.

Approximately 174 subjects will be randomized (2:1) to treatment with either *Restylane Lyft with Lidocaine* (Treatment Group) or *Juvéderm Voluma XC* (Control Group).

Injection technique is at the Treating Investigator's discretion with needle only or a combination of needle and cannula. *Restylane Lyft with Lidocaine* and the comparator-control will be administered by needle in the pogonion. The mentum and pre-jowl sulci may be injected by needle or cannula.

At least 35 subjects will be Fitzpatrick skin type (FST) IV through VI, this includes at least 18 subjects with FST V – VI, where at least 9 subjects will be FST V and at least 9 subjects will be FST VI.

After providing informed consent, eligible subjects randomized to receive either *Restylane Lyft with Lidocaine* or a comparator-control will be injected by the Treating Investigator at Baseline (Day 1). A follow-up telephone call should be made 72 hours after treatment and a follow-up visit should be scheduled after 14 days.

Optional touch-up treatment may be administered 1 month (4 weeks) after initial treatment, if deemed necessary by the Treating Investigator and the subject to obtain optimal aesthetic improvement. If optional touch-up is performed, a 72-hour follow-up telephone call, a follow-up visit at 14 days and a follow-up visit at 1 month should be scheduled.

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

Effectiveness and safety data will be collected for up to 12 months (48 weeks) after last treatment including physical follow-up visits at 1, 3, 6, 9 and 12 months as well as 14 days after each treatment. A subject will be involved in the study for up to 14 months, including a 21-day screening period.

The study visits are illustrated in the study flow chart (Figure 1) and the schedule of events (Table 1).

3.2 Study rationale and justification for design

The rationale of performing this study is to obtain evidence of safety and effectiveness of *Restylane Lyft with Lidocaine* for use in augmentation of chin region to improve the chin profile.

This is a comparator-controlled study. The commercially available *Juvéderm Voluma XC* has been chosen as comparator and is approved in the US for deep (subcutaneous and/or supraperiosteal)

injection for augmentation of the chin region to improve the chin profile in adults over the age of 21.

A study of the safety and effectiveness of *Restylane Lyft with Lidocaine* in the treatment of chin region will establish whether augmentation of the chin region can be successfully achieved, with an acceptable safety profile.

By using a validated evaluation tool, the GCRS assessed by the Blinded Evaluator and Investigator, the results of the augmentation of the chin region can be confirmed by accurate measurements. Objective evaluation of chin region augmentation will enable Blinded Evaluator and Investigators to determine the degree to which treatment has improved the appearance of the chin compared to the comparator group.

3.3 Number of subjects and investigational sites

A total of 174 subjects is planned to be included at up to 12 study centers in the US.

To minimize potential bias in the study results, 35 subjects will be the maximum allowed to be enrolled at any one study center.

3.4 Study duration

The total duration of the study is approximately 17 months. This includes approximately 4 months recruitment time and approximately 13 months for data collection.

The screening visit and baseline visit can be combined and performed on the same day if no drug washout is needed.

One month is defined as 4 weeks in the study; 4 weeks is defined as 28 days.

End of Study is when enrollment has reached the target number of subjects and all ongoing subjects have completed their last study visit.

3.5 Procedures/reasons for subject discontinuation

An investigator may decide to discontinue a subject from the clinical study for safety reasons.

Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, a subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and, when appropriate, a subject may be treated with other conventional therapy as clinically indicated.

When a subject does not complete the clinical study, s/he will be fully assessed, if such assessment is possible. The procedures designated for the Early Termination (ET) visit should be completed for

all subjects discontinuing the clinical study and the appropriate electronic Case Report Form (eCRF) should be completed.

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the Study Exit form in the eCRF.

For discontinuation due to an AE, the Adverse Event form is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

A subject who has been randomized cannot be replaced by another subject if s/he discontinues the clinical study for any reason.

Pregnancies occurring during the screening period are considered screening failures; they should be recorded as such in the eCRF and no pregnancy form is to be completed.

In case of a pregnancy occurring after the baseline visit, the Investigator should follow the procedures described in section 7.13.5. The subject may remain in the study, but no invasive procedure should be conducted.

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

Potential reasons for discontinuation are defined below:

The withdrawal criteria are:

- **Medical Reasons:** If the subject suffers from a medical condition and/or Adverse Event(s) that, in the judgment of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons should document the specific condition for withdrawing the subject.
- **Withdrawal by Subject:** Includes consent withdrawal, subject relocation, schedule conflicts. A subject can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorized representative at any time for any reason.
- **Lost to follow-up:** If a subject does not return for a scheduled visit, reasonable effort shall be made to contact that subject, i.e., confirmed with three documented phone calls and a certified letter (delivery receipt requested) without answer before declaring the subject lost to follow-up.
- **Other:** This category is to be used for a subject who discontinues due to a reason other than as specified in the pre-defined categories above. Explain the reason for discontinuation.

If reason for discontinuation is "withdrawal by subject" or "other," the subject will be followed up to rule out the possibility of an AE. If an AE led to discontinuation, then "Medical reason" should be chosen as the reason for discontinuation, rather than "withdrawal by subject" or "other."

If an AE, which, according to the Investigator's assessment, is related to the use of any of the study products and is still ongoing at the time of the withdrawal, the Investigator shall follow-up with the subject until the AE resolves, is assessed by the Investigator to be "chronic", "stable" or subject is lost to follow up. Follow-up information shall be reported on the AE follow-up form.

3.6 Suspension or premature termination

The Sponsor will suspend or terminate the study when so instructed by the institutional review board (IRB) or regulatory authorities (RA), or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons, or for business reasons. The sponsor shall submit a Clinical Study Report within three months of an early termination or temporary halt.

The Sponsor may also decide to close a single study center due to unsatisfactory subject enrollment or non-compliance with the CSP, GCP, or applicable regulatory requirements.

In the event of premature termination, the Sponsor will provide information on the handling of currently enrolled subjects who have not completed the study.

4. STUDY POPULATION

A total of 174 adult male and female subjects over the age of 21 years with the intent to undergo treatment for augmentation of the chin region, is planned to be included in this study.

4.1 Clinical study population characteristics

4.1.1 Inclusion criteria

The subjects must meet all the following criteria to be eligible for the study:

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2. Males or non-pregnant, non-breastfeeding females, 22 years of age or older.

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4. Intent to receive treatment for augmentation and correction of retrusion in the chin region.

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4.1.2 Exclusion criteria

The presence of any of the following exclusion criteria excluded a subject from enrollment in the study:

1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins.
2. Known/previous allergy or hypersensitivity to local anesthetics, e.g., lidocaine or other amide-type anesthetics.
3. Previous or present multiple severe allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of angioedema.
4. Previous facial surgery (including facial aesthetic surgery and liposuction) below the level of the horizontal line from the subnasale.
5. Any previous aesthetic procedures or implants:

[redacted]

7. Presence of any disease or lesions near or on the area to be treated, e.g.,

[redacted]

4.2 Medical history

History of relevant surgical events and medical conditions should be documented (including any prior dermatological procedures or implants) in the electronic eCRF using medical terminology.

4.3 Previous and concomitant therapies

4.3.1 Definition

Prior therapies are defined as therapies that have been used within 30 days preceding the Screening visit or within the timelines specified in the Inclusion/Exclusion criteria, and then stopped prior to the Screening visit.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the Screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the study, or
- any new therapies received by the subject since the Screening visit.

4.3.2 Categories

Previous and concomitant therapies are to be recorded on the appropriate form in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis or dose modification for a chronic condition.

4.3.3 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (section 4.3.4), all therapies are authorized.

4.3.4 Prohibited concomitant therapies

The following therapies are prohibited during the study because they may interfere with the effectiveness and/or safety assessment of the study product and/or injection procedure:

- Medications that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g., warfarin, clopidogrel, aspirin, NSAIDs), Omega 3 or Vitamin E should not be used within 2 weeks (i.e., 14 days) before any treatment to avoid increased bruising or bleeding at injection sites.

  Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation. COX-2 inhibitors are allowed.
- The study product contains lidocaine, but additional local anesthesia may be used. Lidocaine should, however, be used with caution in subjects receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g., certain antiarrhythmics, as the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., immunosuppressive monoclonal antibodies, antiviral treatment for hepatitis) is prohibited.
- Systemic steroids (except intranasal/inhaled steroids) or prescription topical steroids (below the level of the horizontal line from subnasale).
- Topical (facial) prescription retinoids below the level of the horizontal line from subnasale including the neck, or systemic retinoids.
- Energy-based aesthetic procedures (e.g., laser, intense pulsed light, radiofrequency and ultrasound) below the level of the horizontal line from subnasale.
- Mechanical (e.g., dermabrasion, needling) or chemical aesthetic procedures (e.g., chemical peel) below the level of the horizontal line from subnasale.
- Treatment with cryotherapy below the level of the horizontal line from subnasale including the neck.
- Lipolytic injections below the level of the horizontal line from subnasale.
- Neurotoxin treatment below the level of the horizontal line from subnasale including the neck.

- Treatments below the level of the horizontal line from subnasale including the neck with absorbable or temporary dermal fillers (e.g., collagen, HA products, Calcium Hydroxylapatite, poly L-lactic acid products, etc.).
- Treatments with any permanent filler or implant, lifting threads, or autologous fat in the face.
- Tattoo or piercing interfering with the study injections and/or study assessments.
- Planned aesthetic facial plastic surgery (e.g., surgery to either the upper or lower lip, facelift, rhinoplasty, facial liposuction etc.) or oral surgery including dental implants, tooth extractions, orthodontia are prohibited.
- Participation in any other clinical study during this study is prohibited.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, the Sponsor Medical Expert should be notified, time permitting, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical study, the Sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical study.

4.3.5 Documentation and recording instructions

4.4 Subject identification number

Prior to any study procedures being conducted, the subject must sign the informed consent form (ICF). Each subject who has signed the ICF will be assigned a subject number that will be allocated in ascending order within each center.

A screen failure is a subject who signed the informed consent but never enrolled (i.e., was randomized and/or received treatment) in the study. For screen failures, the subject source documents should indicate which assessments have been made and the reason why the subject was determined to be a screen failure. A screen failure should not be re-entered in the study. A subject is considered enrolled when they have signed the ICF and are randomized and/or treated.

For the duration of the clinical study, each subject will be identified using the subject number for all documentation and discussion. A subject identification log is required to be kept in the Investigator file.

5. STUDY INTERVENTION

5.1 Description of the investigational device

5.1.1 Investigational device

The investigational device is *Restylane Lyft with Lidocaine,* manufactured by Q-Med AB, part of the Galderma group, located in Uppsala, Sweden.

Restylane Lyft with Lidocaine is a sterile gel of HA generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine.

During manufacturing, cross-links are introduced into the HA molecule by use of BDDE. This is to obtain the desired physical form; a gel network, that gives the gel its residence time in the body. *Restylane Lyft with Lidocaine* is produced using the NASHA® Technology.

Lidocaine is included in the formulation to reduce local pain associated with the injection. The addition of lidocaine has been shown to substantially reduce pain experienced by subjects in clinical trials.[8]

The study products are reserved for use by Treating Investigators who are experienced in chin area injection procedures.

5.1.2 Reference product

The commercially available product *Juvéderm Voluma XC* will be used as comparator in the study.

Juvéderm Voluma XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of HA produced by *Streptococcus* species of bacteria, which is crosslinked with BDDE. It is formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer. The volume in each syringe is as stated on the syringe label and on the carton.

In this study, *Juvéderm Voluma XC* is to be injected with a sterile needle 27G x ½" or a sterile cannula 25G x 1½" Steriglide from TSK that are approved for use in the US for chin augmentation. The product is for single use only.

Juvéderm Voluma XC will be obtained by the study centers. The Sponsor will provide labels to identify the product as study inventory. The product should be stored according to the specifications provided in the commercially available IFU provided by the manufacturer.

5.1.3 Additional products and materials

Topical or local anesthesia may be used at the discretion of the treating Investigator before the treatment. If used, the anesthesia shall be supplied by the study center. Type of anesthesia, administration route, product name, and quantity used must be recorded in the eCRF.

The product is supplied by the Sponsor in a sealed blister package containing a syringe with 1 mL sterile gel and two 27G Thin Wall (TW) x ½" needles.

Alternatively, commercially available 29G TW x ½" sterile needle and sterile blunt cannula 25-27G x 1.5 or 2" that are approved for use in the US for midface correction can be used in the study and will be obtained by study centers.

In addition, the Sponsor will provide cotton wisps and monofilaments for sensory tests (see Section 7.2) and Snellen eye charts, and eye occluders for visual acuity test (see Section 7.6), to each study center.

Urine pregnancy tests (UPT) will also be provided to each study center for testing of all females of childbearing potential, at screening, baseline, and prior to optional touch-up.

5.2 Packaging and labelling

Restylane Lyft with Lidocaine is supplied in a sealed blister package containing a syringe with 1 mL sterile gel and co-packed with two sterilized needles 27G Thin Wall (TW) x ½" as indicated on the carton.

Juvéderm Voluma XC is supplied in a sealed blister package containing 2 pre-filled disposable syringes each containing 1 mL of hyaluronic acid gel implant.

Labelling will be performed according to United States Code of Federal Regulations (CFR) 21 CFR 812.5: Labelling of investigational devices. The carton will be labeled with the lot number as well as expiration date and the Clinical Trial Number (CTN) and the following:

"CAUTION - Investigational Device. Limited by US Law to Investigational Use."

5.3 Instructions for use and administration

The study product is reserved for use by Treating Investigators who are experienced in chin area procedures. Treating Investigators should be aware of important neurovascular and anatomical structures near the injection site. The Treating Investigator must be trained on, and have at hand, the relevant clinical practice guidelines[1] and the actions to be taken if visual disturbances occur. The Treating Investigator should also have reviewed the Intravascular Treatment Protocol supportive tool provided separately in the Investigator file.

Detailed information regarding the injection procedure, pre- and post-treatment care and subjects' instructions are provided in the respective IFUs for *Restylane Lyft with Lidocaine* (study specific IFU) and *Juvéderm Voluma XC* (commercially available IFU).

Please also refer to the ROPI for *Restylane Lyft with Lidocaine* for a description of performed clinical studies, PMS data on reported AEs, and published data related to injections of HA in the chin area.

5.3.1 Pre-treatment procedure

Before treatment, the subject will be informed about expected post-treatment events that should be recorded in the Subject Diary, if experienced, potential risks involved with the treatment, and when to contact the Investigator in case of emerging symptoms.

It is necessary to counsel the subject and discuss the appropriate indication, risks, benefits, and expected responses to the *Restylane Lyft with Lidocaine* and *Juvéderm Voluma XC* treatment.

- Advise the subject of the necessary precautions before commencing the procedure.

Prior to treatment, the subject's medical history should be obtained, and the s/he should be fully appraised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Subjects also should be advised that supplemental touch-up implantations may be required to achieve and maintain the desired level of correction.

Prohibited concomitant medication use should be checked before any treatment is given (see Section 4.3.4).

For subjects who have experienced medically important AEs during initial treatment, a decision for touch-up should take into consideration the cause and severity of previous reactions.

Subjects need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block should be assessed. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period. Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.

5.3.2 Treatment regimen (dose and interval)

Restylane Lyft with Lidocaine and *Juvéderm Voluma XC* will be administered by needle or cannula injections in the chin area. Needle or cannula will be used for supraperiosteal or subcutaneous injections.

The treatment area includes the chin and surrounding regions: Pogonion, mentum and pre-jowl sulci.

Subjects randomized will be administered at baseline (Day 1) and, if deemed necessary, at optional touch-up after 1 month (4 weeks).

Injection technique is at the Treating Investigator's discretion (with needle only or a combination of needle and cannula). Injection should be in the deep subcutaneous tissue or supraperiosteal plane, as per Investigator's discretion.

Appropriate injection volume for the chin area will be determined by the Treating Investigator but is not to exceed a maximum total volume of 4.0 mL for initial and touch-up treatments combined. Injection in the pogonion is only permitted with a needle. Both needle and cannula are permitted for injection in the other treatment areas.

Depending on the location, serial puncture and linear threading among other techniques can be used to safely and effectively enhance the contour, shape and definition of this aesthetic region. The injection method and depth of injection, number of syringes used, and the volume of study product injected during each injection session will be recorded in the eCRF.

Aspiration is recommended prior to each injection. Slow injection is recommended, and overcorrection should be avoided.

5.3.3 Post-treatment care

When the injection is completed, the treated area may be gently molded or massaged to avoid any irregularities.

Brisk molding or massaging should be avoided in order to prevent undue swelling of the region.

Post treatment procedures with ice pack is allowed as per investigator normal procedure. Ice pack can be applied for a short period if the treated area is swollen.

After the injection, some common injection-related reactions might occur. These reactions include redness, swelling, pain, itching, bruising or tenderness at the implant site. Typically, resolution is spontaneous within two to four weeks after injection into the skin.

Any medication or therapy used by the subject must be recorded in the eCRF.

Subjects will be asked to:

- Avoid heat (sunbathing, sauna, steam baths, etc.) or extreme temperatures until any signs of local inflammation have disappeared.

- Avoid touching or shaving the treated area and not to apply any creams or cosmetics in the treated area before the skin has healed completely in order to prevent infections or elicit an inflammatory reaction.
- Abstain from prohibited medications, treatments and procedures (see Section 4.3.4).
- Contact the study center if common injection-related reactions such as bruising, redness, pain, tenderness, lumps/bumps, itching, swelling at the injection site, have not diminished within two weeks or if they get worse.
- Contact the study center if they have signs of infection and/or inflammation such as pain, tenderness, heat, redness, swelling, small lumps that contain pus or yellowish fluid, and fever. These symptoms can occur within days or several weeks after treatment.

Subjects treated with the comparator *Juvéderm Voluma XC*, should also avoid strenuous exercise within the first 24 hours of treatment. Please refer to post-treatment recommendation in the IFU provided with the product.

5.3.4 Recording instructions

The following information for the injection should be recorded in the eCRF:

- Date and time of completed injection
- Lot number
- Number of syringes used
- Volume of study product used
- Needle or cannula used for supraperiosteal or subcutaneous injections
- Injection method and depth of injection
- Additional local or topical anesthesia used

5.4 Supplies management

5.4.1 Product accountability

Restylane Lyft with Lidocaine will be released to the Investigator or his/her authorized designee after study approvals have been received from the US Food and Drug Administration (FDA) and IRB and the Clinical Trial Agreement (CTA) has been signed by all parties.

The Investigator must ensure that the study products are kept in a secure location (separated from commercial inventory) with access limited to those authorized by the Investigator.

The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the Investigator maintain accurate product accountability records, i.e., documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the Investigator, and documentation of administration of product to the subject.

Any malfunctioning study products should be reported as described in section 7.13.4.

Products deliberately or accidentally destroyed during shipment or at a study center should be accounted for and documented. Used syringes, needles, cannulas and any unused material must be discarded immediately after the treatment session and must not be reused due to risk for

contamination of the unused material and the associated risks including infections according to standard procedures at the study center. Disposal of hazardous material, i.e., syringes, needles and cannulas must conform to applicable laws and regulations. The study products must not be used outside the study.

5.4.2 Storage of study product

The *Restylane Lyft with Lidocaine* syringes should be stored in their original packaging at a temperature up to 25°C (77°F), protected from sunlight and freezing. Detailed product information is provided in the study specific IFU.

Juvéderm Voluma XC should be stored according to the specifications in the commercially approved IFU, provided by the manufacturer.

5.4.3 Dispensing and return

The treatment will be administered by the Treating Investigator at the study center and be documented in the accountability records.

When the study is completed, all unused or expired study products at each study center should be returned to the Sponsor representative for destruction, or to be destroyed locally at the study center if documented as agreed with Sponsor.

5.4.4 Treatment compliance

The study products will be administered by the Treating Investigator at the investigational study centers and recorded in the eCRF.

5.5 Randomization

Approximately 174 subjects will be randomized in a 2:1 ratio to treatment with either *Restylane Lyft with Lidocaine* (Investigational Group) or *Juvéderm Voluma XC* (Comparator Group).

Before starting the study, a computer-generated randomization list will be prepared under the supervision of a designated biostatistician from the Sponsor. The randomization will be stratified by FST (I-III, IV or V-VI). Subjects in the FST I-III stratum will be further stratified by study center; subjects in the FST IV, or FST V-VI strata will not be further stratified by study center due to the smaller sample size in these groups.

Randomization will be performed using an Interactive Response System by assigning each subject to treatment with *Restylane Lyft with Lidocaine* or *Juvéderm Voluma XC* according to the randomization list. Randomization numbers will be allocated in ascending sequential order to each subject.

5.6 Blinding

The Treating Investigator will not be blinded to study treatments.

A Blinded Evaluator, to whom randomization and treatment are concealed, will conduct the blinded assessments. As much as possible, the same Blinding Evaluator should assess a particular subject throughout the study.

The Blinded Evaluator is not allowed to be present during the injections or to discuss treatments with the Treating Investigator or subjects. All documents with information regarding study products

and randomization assignment should be kept in a separate binder not available to the Blinded Evaluator.

Safety assessments will be performed by non-blinded personnel.

5.6.1 Verification of blinding

Not applicable as the Treating Investigator is not blinded to treatment.

The Blinded Evaluator is not allowed to be present during the injections or to discuss treatments with the Treating Investigator or subjects. All documents with information regarding study products and randomization assignment should be kept in a separate binder not available to the Blinded Evaluator.

5.6.2 Emergency unblinding

Not applicable as the Treating Investigator is not blinded to treatment.

5.7 Post-trial provisions

In time, the study product will be degraded in the body and additional treatments will be necessary to maintain the aesthetic result.

After the final study visit the Sponsor will not supply any additional treatments to the subjects, even if the result does not persist.

6. EFFECTIVENESS ASSESSMENTS

The methods for collecting effectiveness data are described in the following sections.

To minimize inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations.

Assessments should be performed according to the time points indicated in the schedule of events (Table 1) and recorded in the eCRF.

6.1 Photography

Photographs will be taken prior to the first injection of the study product, before treatments, and at every physical follow-up visit in order to document treatment effect. Photographs may also be taken to document AEs at the Investigator's discretion. Baseline photographs may be used as a reference in the CCI assessment. Site personnel will be thoroughly trained on the photographic equipment and techniques before study start.

Camera equipment will be provided by the Sponsor or their designee, and standardized photographs shall be achieved. Further details regarding photography procedure will be specified in a separate user guide.

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6.3 Galderma Chin Retrusion Scale (GCRS)

The GCRS is a validated 4 grade scale for assessment of Chin retrusion (Appendix 1). Each score in the GCRS is exemplified by photographic images of the scale. The Blinded Evaluator and Treating Investigator will perform live assessment of the subject's chin separately.

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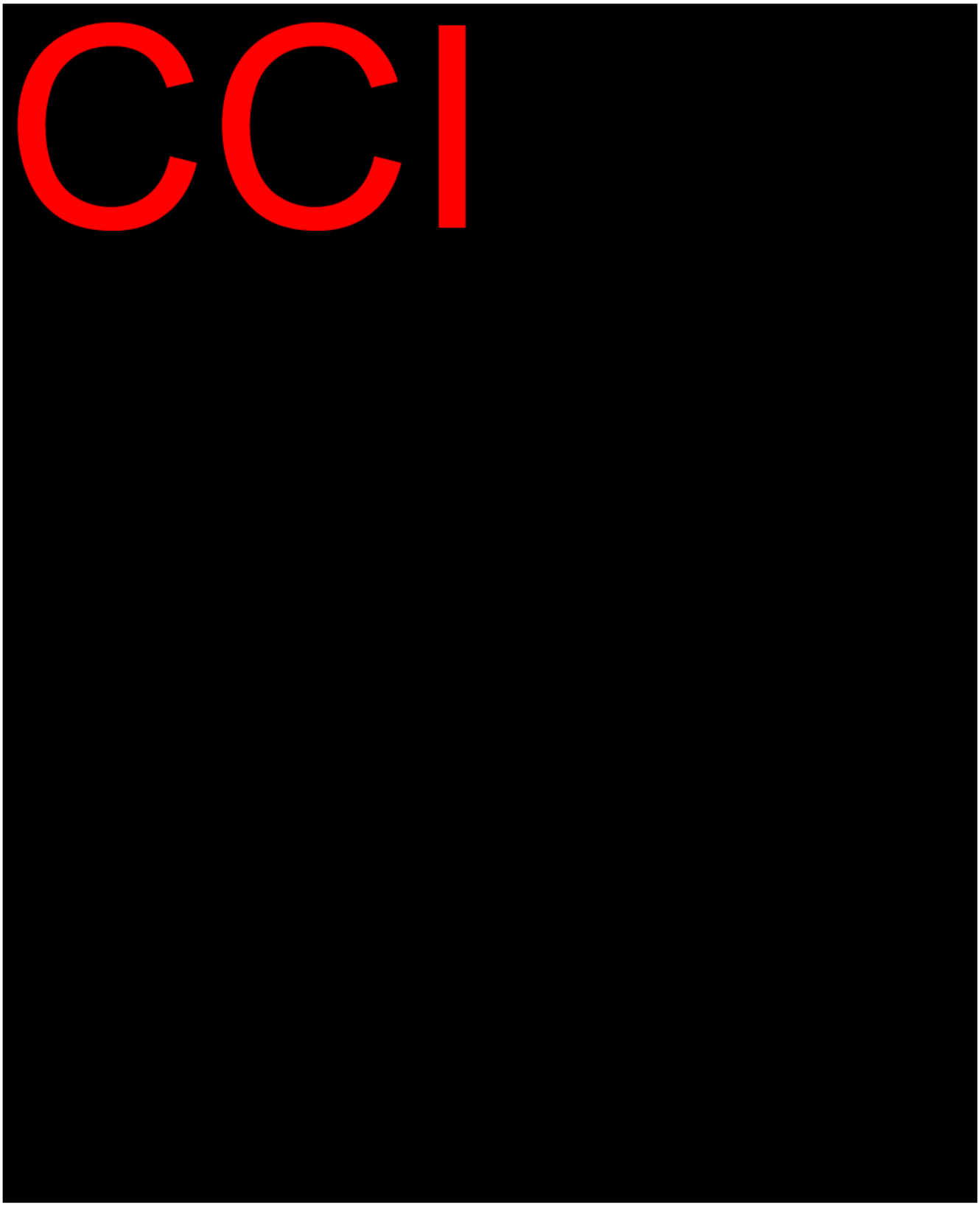
GALDERMA	Title **43USCH2208, Clinical Investigation Plan R Lyft Chin US**	Doc id **MA-52558**

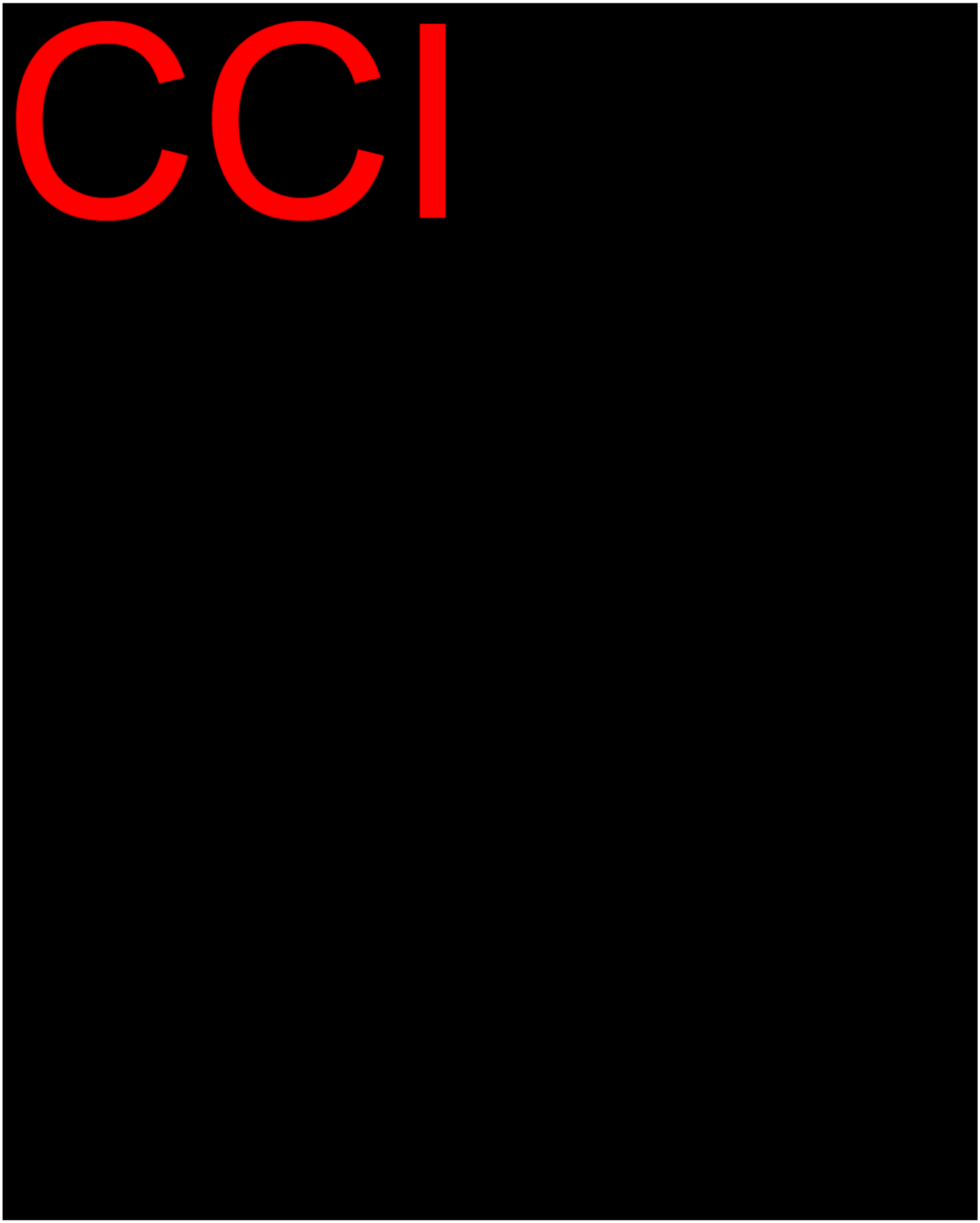


GALDERMA	Title **43USCH2208, Clinical Investigation Plan R Lyft Chin US**	Doc id **MA-52558**

Effective date: 2023-05-24 22:48

Effective

Version: 4.0



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7.3 Functionality tests

The functionality tests will be performed at screening to confirm eligibility.

7.3.1 Lip Movement

A baseline value of lip movement will be obtained, and new assessments will be done at all physical visits thereafter. A study staff member who is qualified by training and experience to perform safety assessments will score lip movement and function as "Normal" or "Abnormal." After receiving treatment, any subject with abnormal ratings should be assessed by the Investigator for confirmation of any potential AE.

Lip Movement: The subject's ability to effectively pronounce a series of 10 pre-selected words will be assessed. Each word pronounced correctly will score one point. A score of 8 words or more; pronounced correctly; will be considered a normal finding.

7.3.2 Lip and Chin Function

A baseline value of lip and chin function will be obtained, and new assessments will be done at all physical visits thereafter. A study staff member who is qualified by training and experience to perform safety assessments will score lip and chin function as "Normal" or "Abnormal." After receiving treatment, any subject with abnormal ratings should be assessed by the Investigator for confirmation of any potential AE.

Lip Function: The subject's ability to effectively suck water through a straw will be assessed. Inability to suck water through a straw (inadequate lip seal to prevent leakage of fluid or to control the direction of fluid flow) will be considered abnormal.

Chin Function: Chin movement will be tested at all on-site study visits. Subjects will be asked to open and close their mouth.

7.4 Assessment of palpability

Palpability will be assessed at screening, baseline and at each physical follow-up visit, prior to treatment. A study staff member who is qualified, by training and experience, to perform safety assessments will palpate the chin for detection of any unexpected feel such as lumpiness, mass, non-uniform density, or unexpected aggregation of product.

The study products are generally palpable (i.e., can be felt under the skin) and have uniform density. Any unexpected feel of the study product upon palpation of the chin will be assessed as "Abnormal". Any abnormality should be assessed by the investigator for confirmation of anu potential AE, including a description of the localization, feel and approximate size.

7.5 Changes in hair growth

The Treating Investigator will ask if the subject has noticed any changes in hair growth (e.g., loss or growth) in the treated area at physical follow-up visits after baseline. Clinically significant changes in hair growth, as determined by the Treating Investigator, will be reported as an AE.

7.6 Visual function assessment

Visual function assessments will be performed at screening, baseline and at all physical follow-up visits. At the treatment visits, the visual function assessment tests will be performed prior to and approximately 30 minutes post injection of the study product. These assessments include Snellen visual acuity, extraocular muscle function, and confrontation visual field tests.

The subject is considered to have normal or acceptable visual acuity if the Investigator can adequately measure the quality of his/her eyesight using the Snellen Eye Chart. If the subject is found to have severely impaired/absent eye function (20/50 or worse) in one or both eyes, even with the use of prescribed corrective lenses, and/or any other condition with the potential to cause a decline of visual acuity, s/he will be considered to have abnormal vision and will not be eligible for enrollment.

All worsening of vision during the study (for visual acuity compared to baseline and post injection compared to pre injection at treatment visits) should be assessed by the Investigator **as an adverse event of special interest (AESI)** per Section 7.10. If the subject experiences clinically significant changes in vision, the Investigator should consider further assessment and treatment by an eye specialist (ophthalmologist or retinal specialist). The Investigator should conduct appropriate follow-up with the subject to determine the cause, intensity, seriousness, relationship to the study product or procedures, and outcome.

7.6.1 Snellen visual acuity test

A Snellen eye chart will be used to objectively assess visual acuity for distance vision. Visual acuity will be conducted using the subject's best distance correction (e.g., contacts or eyeglasses) at a distance of 6 feet from the chart. Each eye will be measured separately by either using an occluder or having the subject cover each eye.

The subject will be asked to start reading the letters at the top of the chart working their way to the bottom. The smallest row of letters that the subject can read will indicate their visual acuity listed on the chart. Any subject requiring vision acuity correction must be assessed using the prescribed correction (e.g., contacts or eyeglasses).

Unacceptable vision for a subject to be eligible for enrollment would be an absolute score on the Snellen eye chart 20/50 or worse in one or both eyes. Worsening in visual acuity (i.e., change of one line or greater from baseline, and post injection compared to pre injection at treatment visits) on the Snellen eye chart during the course of study should be reviewed and assessed by the Investigator and reported as an AESI per Section 7.10.The Investigator will evaluate all negative one line or greater changes in visual acuity on the Snellen exam and the need to refer for an ophthalmic evaluation.

7.6.2 Extraocular muscle function test

Extraocular muscle function testing examines the function of the eye muscles. This test observes the movement of the eyes in six specific directions to evaluate weakness or other problem in the extraocular muscles. The subject will be asked to sit or stand with his/her head up and looking straight ahead. The assessor will hold a pen or other object approximately 16 inches in front of the subject's face. The assessor will then move the object in several directions and ask the subject to follow it with their eyes, without moving their head. The result shall be reported as "normal" or "abnormal" for each eye.

Changes in movement of the eyes during the course of the study should be reviewed and assessed by the Investigator and reported as an AESI as per Section 7.10. In the event of a change from baseline the Investigator should recommend the subject to receive an ophthalmic evaluation.

7.6.3 Confrontation visual field test

The confrontation visual field test will be used to assess the subject's peripheral vision. The examiner will sit facing the subject, about 3 to 4 feet away from the subject and ask the subject to fix their gaze on the examiner's eye. The examiner will hold their arms straight out to the side and bring their hands into the subject's visual field from the sides in each quadrant. The subject will signal as soon as the hand is seen. Each eye will be recorded as normal or abnormal.

Changes in the visual field of the eyes during the course of the study should be reviewed and assessed by the Investigator and reported as an AESI as per Section 7.10. In the event of a change from baseline the Investigator should recommend the subject to receive an ophthalmic evaluation.

7.8 Pregnancy testing

For all women of childbearing potential, including those currently using contraception, a UPT is required prior to receiving any study treatment (at screening, baseline, and optional touch-up). The

test result must be negative for the subject to receive any treatment with the study product. The test result will be documented in the subject's file and eCRF.

7.9 Adverse events

7.9.1 Definition of an Adverse Event

The definition of an AE (Medical Devices Regulation [MDR] article 2[57]): An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons[2], in the context of a clinical investigation, whether or not related to the Investigational device.

This definition includes:

a) events related to the investigational product or the reference product

b) events related to the procedures involved

c) events that are anticipated as well as unanticipated

The AE reporting on each subject shall start once a subject is enrolled (i.e., randomized and/or treated) in the study. All other events that occur after the subject signs the ICF but before enrollment will be recorded in the subject's medical history. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

All AEs, non-serious as well as serious AEs (SAEs), are to be reported as AE in the eCRF.

A request for additional information from the Sponsor Medical Expert(s) for non-serious AEs, should be collected and answered using the Adverse Event Clarification Form.

7.9.2 Anticipated adverse events

Information regarding anticipated AEs for *Restylane Lyft with Lidocaine* and *Juvéderm Voluma XC* are included in the IFUs respectively.

Further, the ROPI for *Restylane Lyft with Lidocaine* includes information from clinical studies in the chin area with similar HA products, spontaneously reported cumulative post-market reporting, and available clinical data from publications with HA fillers in the midface area.

7.9.3 Unanticipated adverse device effect

An unanticipated adverse device effect (UADE) means 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, intensity, or degree of incidence in the protocol/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 (see FDA regulation CFR 812.3 [s]).

7.9.4 Assessment of intensity

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

[2] For users or other persons, this definition is restricted to events related to the investigational product.

Mild: Awareness of symptoms or signs, but easily tolerated (acceptable)

Moderate: Enough discomfort to interfere with usual activity (disturbing)

Severe: Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.

7.9.5 Assessment of causality

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

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

- *"Do you consider that there is a reasonable possibility that the event may have been caused by the study product?"* and
- *"Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"*

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

In addition, each SAE will be classified by both the Investigator and Sponsor separately, according to four different levels of causality:

1. **Not related:** Relationship to the device, comparator or procedures can be excluded when:
   - the event has no temporal relationship with the use of the investigational device, or the procedures related to investigational device;
   - the 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 activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the SAE;
   - the event involves a body-site or an organ that cannot be affected by the device or procedure;
   - the 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);
   - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

   In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.
2. **Possible:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, 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.

3. **Probable:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. **Causal relationship:** the SAE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on;
   - the 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 activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
   - 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;
   - the event depends on a false result given by the investigational device used for diagnosis, when applicable.

   In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

7.9.6 Action taken

The action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn) for an AE should be recorded in the eCRF.

The study related medical care provided to the subjects during the study is the responsibility of an appropriately qualified medical doctor (i.e., the Principal Investigator [PI]) or, where appropriate any other person entitled by national law to provide the relevant subject care.

7.9.7 Follow-up of adverse events

7.9.7.1 Follow-up of unresolved events ongoing at termination of the study

All serious as well as non-serious AEs with a probable, possible, or causal relationship to the study product or treatment procedure and ongoing at study end/or ongoing when a subject terminates the study participation early/or ongoing if the study is temporarily halted, shall be followed up after the subject's participation in the study is over.

Such events shall be followed-up until resolved, assessed as chronic or stable, or subject is lost to follow-up. Final outcome after the end of the study shall be reported on the AE Follow-up form.

Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

7.9.7.2 Follow-up of events occurring after subject termination of the study

All AEs with a causal relationship to the study product or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor by email to:

safety.q-med@galderma.com

The Investigator shall follow the subject until the event is resolved.

7.9.8 Documentation and recording instructions

Investigators, or other study center personnel, shall record all AEs in the eCRF, including:

a) Event term (recorded in standard medical terminology and avoiding abbreviations)
b) Affected area
c) Start date (first day with symptoms)
d) Stop date (last day with symptoms)
e) Intensity (mild, moderate, or severe, according to definition in Section 7.9.4)
f) Seriousness (serious or not serious, according to definition in Section 7.11)
g) Relationship to study product or study product injection procedure (According to definition in Section 7.9.5)
h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
i) Outcome of the AE (ongoing, resolved, resolved with sequelae, death) at the end of the study)

The AE form/module in the eCRF must be signed and dated by the Investigator.

7.10 Adverse events of special interest

All incidences of **visual disturbances**, regardless of relationship to study product or seriousness, are considered **AESIs** and include, but are not limited to, the following:

- Loss of vision
- Blurry vision
- Double vision
- Pain in or around the eye
- Blind spot or shadow in the visual field
- Trouble moving eyes
- Any change to ocular motility, as determined by a worsening on the extraocular muscle function test (see Section 7.6.2)

- Any change to peripheral vision, as determined by a worsening on the confrontation visual field test (see Section 7.6.3)
- Any worsening in visual acuity (i.e., negative change of one line or greater on the Snellen visual acuity test, see Section 7.6.1) indicating:
    - a worsening from the baseline value
    - a worsening post injection compared to pre injection at a treatment visit

In addition, the following events are considered **AESIs**:

- **All abnormal findings** in functionality tests (see Section 7.3), assessed by the Investigator, regardless of relationship to the study product or seriousness
- **Stroke**
- **Skin necrosis**

Also see AESI reporting procedures in Section 7.13.1.

7.11 Serious adverse event

The definition of a SAE (MDR article 2[58]). A SAE is any AE that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in
    1. a life-threatening[3] illness or injury, or
    2. a permanent impairment of a body structure or body function, or
    3. hospitalization or prolonged hospitalization[4], or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    5. chronic disease

c) led to fetal distress, fetal death, or a congenital physical or mental impairment or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such. When an AE is related to a device deficiency, including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF, and the technical complaint shall be reported separately on the clinical study complaint form.

Also see SAE reporting procedures in Section 7.13.2.

[3] The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

[4] Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE (Source: ISO14155:2011).

7.12 Device deficiencies

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety[5], or performance.

Note: Device deficiencies include malfunctions, user errors or inadequate information supplied by the manufacturer.

Also see device deficiency reporting procedures in Section 7.13.4.

7.13 Safety reporting procedures and timelines

Safety evaluations for this study include an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an AE. Each subject should be questioned about AEs at each study visit following the baseline visit. An event that occurs after the subject signs the ICF but before enrollment (i.e., randomized and/or treated) will be recorded in the subject's medical history. The question about AEs should be asked: "Since your last clinical visit have you had any health problems?"

Information on AEs can also be obtained from signs and symptoms detected during each examination by the Investigator or designee, which should include visual inspection of the treatment area or from a laboratory test, subject diaries, or spontaneous reports from the subjects or their relatives.

The AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product. If in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and eCRF.

It is the responsibility of the Investigator to determine intensity of the AE and relatedness of the event to the study product.

7.13.1 Reporting of adverse events of special interest

Suspected AESIs (see Section 7.10) shall be reported (using the AE Clarification Form) within 24 hours of awareness to the Sponsor at the following email address:

CCI [redacted]

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted with follow-up information provided within 24 hours of awareness of the new information.

The following information should be provided when reporting an AESI:

- Subject identification (subject number and initials)
- Event description including observed symptoms
- Medical history related to the event
- Event onset date and time
- Depth of injections

[5] Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

- Interventions implemented to treat the event
- Event outcome (with resolution date and time, if applicable)
- Relatedness to study product or procedure
- Seriousness of the event
- Study treatment information (number of injections, date of injections, name of product injected, volume injected, injection tool used etc.)

If the Investigator assesses an AESI to be serious, an SAE report should be submitted as specified in Section 7.13.2.

Upon receipt of the AESI report, the Sponsor Medical Expert(s) will further evaluate and document the evaluation of the reported incident.

If any of the following events occur the Sponsor will expedite the report to FDA, within 10 days and to the IRB as applicable:

1. All incidences of visual disturbances (loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving the eyes), regardless of relationship to study product or seriousness;
2. Any worsening in visual acuity (i.e., negative change of one line or greater) related to the treatment procedure or study product;
3. Any abnormal results on extraocular muscle function test or confrontation visual field;
4. All incidences of skin necrosis or stroke
5. A medical concern that requires continued monitoring of the subject's condition in regard to an AESI or if additional examinations may be needed, as assessed by the Investigator (e.g., referral to an eye specialist).

7.13.2 Reporting of serious adverse events

The Investigator shall **report any SAE** (see Section 7.11) to the CRO **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via e-mail or submitted via the eCRF.

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- Subject identification (age, gender, initials, subject number)
- AE description
- Date when AE occurred
- Name of PI
- Name of study product

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the CRO immediately but not later than 24 hours of awareness of the new data. Complete and adequate information on each SAE is required. All attempts to obtain this information, including dates for follow-up activities, must be documented by the Investigator.

Supporting documentation to be provided with the SAE report:

- Concomitant therapies form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g., hospital notes, death certificate, autopsy reports etc.)
- Study treatment records from eCRF pages including information for: date and time of injection, lot number, number of syringes and volume used, needle or cannula used per treatment area, injection technique and depth of injection, additional local or topical anesthesia used.

E-mail for SAE reporting: CCI [redacted]

E-fax number for SAE reporting: +1 888 493 0910

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed to the Sponsor. A copy of the fully completed SAE form shall be kept at the study center. The Blinded Evaluator should perform live effectiveness assessments only and not discuss the treatment or any potential AE with the subject.

In addition, the PI shall report SAEs to the responsible IRB without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her IRB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor is responsible for reporting to the RA, if applicable and according to national regulations.

7.13.3 Reporting of all SAEs

An Investigator shall prepare and submit a complete and accurate report to the Sponsor, for contact details see Section 7.13.2, and to the reviewing IRB on a suspected SAE/UADE as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect, in accordance with FDA regulation CFR 812.150.

Upon receipt of the report, the Sponsor will review the information provided, assess the event, and, if deemed reportable, report to FDA within timelines specified in FDA regulation CFR 812.150 and 21 CFR 803.

7.13.4 Reporting of device deficiencies

When a device deficiency is discovered, Part A of the Clinical Study Complaint Form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to the study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to Sections 7.9 and Section 7.13.2). If no SAE was experienced as a result of the device deficiency the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,
- Circumstances had been less fortunate

In Part B of the Clinical Study Complaint Form the Sponsor will make the same assessment.

The Investigator shall provide the completed Clinical Study Complaint Form to the CRO.

E-mail for device deficiencies reporting: CCI [redacted]

Fax number for device deficiencies reporting: +1 888 493 0910

A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the Sponsor within 24 hours after the Investigator's awareness (for contact information, see Section 7.13.2).

If the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE, the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the IRB.

The deficient study product shall be kept by the study center until the Sponsor has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study center.

7.13.5 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period, the subject must be withdrawn from any following study treatment but should continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a Pregnancy Report Form immediately upon acknowledge and be submitted to the Sponsor according to contact details specified in Section 7.13.2. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the Exposure *in utero* Report Form to the Sponsor immediately but no later than 24 hours after the Investigator's awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported, and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

7.14 Stopping rules

Enrollment and treatment in the study will be temporarily halted if a SAE occurs for the following:

- any unanticipated SAE which is possibly related to the study device or procedure including but not limited to a vascular embolic event that leads to skin necrosis, vision loss or stroke, damage to facial nerves which may result in facial paralysis or injury to internal facial structures.

The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:

- was unanticipated,
- directly related to the investigational device or device injection procedure, and
- presents an unreasonable risk to study subjects,

the study will be terminated, and the Investigators notified. The IRB and RA will also be notified if the study is prematurely terminated due to safety concerns.

If the SAE does not meet the above criteria, then enrollment in the study will continue provided all other safety criteria have been met.

8. DESCRIPTION OF STUDY VISITS

All study visits and assessments are described in the sections below and outlined in the schedule of events in Table 1.

A written signed informed consent (incl. Health Insurance Portability and Accountability Act of 1996 [HIPAA] and photo consent) must be obtained prior to performing any study related evaluations and/or procedures. The subject must be provided with a fully completed dated and signed copy.

8.1 Screening/Visit 1a

The following activities and screening assessments will be performed within 21 days prior to the baseline[6] (Day 1) visit (Table 1):

- Obtain informed consent.
- Record the subject's medical history (including any prior dermatological procedures or implants, see Section 4.2) and previous or concomitant therapies (see Section 4.3).
- Obtain demographic data: Month and year of birth, sex at birth, gender identity, race, ethnicity, and FST. For determination of the FST, see Table 4.
- For all females of childbearing potential, obtain a UPT.
    - The test result must be negative for the subject to be eligible for study participation and prior to receiving any study treatment.
- Assessment of GCRS – Treating Investigator and Blinded Evaluator (see Section 6.3).
- Perform visual function assessments (see Section 7.6).
- Perform palpability assessments (see Section 7.4).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).
- Assess eligibility (inclusion and exclusion criteria).
- Schedule the baseline/Day 1 visit or proceed to Day 1 activities if the subject meets all eligibility criteria.

[6] The screening and baseline visits can be combined.

Table 4 Fitzpatrick Skin Type (FST)

Skin type	Skin color	Skin characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Fitzpatrick Skin Type (FST) is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet light.[9]

8.2 Baseline/Initial treatment/Visit 1b

The screening visit and the baseline visit may be performed on the same day if the subject is deemed eligible by the Treating Investigator.

If the screening and baseline visits are not performed on the same day, the following procedures should be repeated at the baseline visit (Table 1) **prior to treatment**:

- Review for changes in medical history and concomitant therapies.
- Re-confirm eligibility (inclusion and exclusion criteria).
- Perform UPT for all females of childbearing potential
    - The test result must be negative for the subject to be eligible for treatment.
- Assessment of GCRS – Treating Investigator and Blinded Evaluator (see Section 6.3).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).
- Perform palpability assessments (see Section 7.4).
- Perform visual function assessments (see Section 7.6).
    - If a subject is considered to have abnormal vision per the exclusion criteria, the subject is not eligible for the study.

Once the subject is deemed eligible for study treatment by the Treating Investigator, the following procedures should be completed:

- Record subject's height and weight.
- Randomization to treatment with *Restylane Lyft with Lidocaine* (Investigational Group) or *Juvéderm Voluma XC* (Comparator Group).
- Obtain pre-treatment/baseline photographs of the chin area.

- Obtain pre-treatment/baseline responses to the FACE-Q™ Satisfaction with chin questionnaire (see Section 6.9).
- Obtain pre-treatment/baseline responses to the FACE-Q™ Satisfaction with lower face and jawline questionnaire (see Section 6.10).
- Pre-treatment pain assessment using the NPS (prior to application of any anesthetic) (see Section 7.1).
- Subjects will be injected with either *Restylane Lyft with Lidocaine* (Investigational Group) or *Juvéderm Voluma XC* (Comparator Group) in the chin area. After injection, the following should be performed:
    - Immediately following injection, subject should complete the post-treatment pain assessment using the NPS (see Section 7.1). This should be completed before any post-injection therapies are provided.
    - Approximately 30 minutes after injection, perform visual function assessments - post-treatment (see Section 7.6).
    - Record all concomitant medications/procedures used prior, during or after the injection session.
    - Record the following injection details:
        - Date and time of completed injection
        - Lot number
        - Number of syringes used
        - Volume of study product used
        - Needle or cannula used for supraperiosteal or subcutaneous injections
        - Injection method and depth of injection
        - Additional local or topical anesthesia used
    - Evaluate for device deficiencies. If any device deficiency is noted, complete the procedures as specified in Section 7.13.4.

CCI [redacted]

    - Evaluation of post-injection AEs by Treating Investigator.
    - Schedule the follow-up telephone call (Visit 2) 72 hours (±24 hours) and the follow-up visits (Visit 2a) at 14 days (2 weeks; +7 days) and (Visit 3) 1 month (4 weeks; +7 days) after the baseline visit (Visit 1b).

8.3 Follow-up visits

8.3.1 Telephone call/Visit 2

The following should be completed at the telephone contact 72 hours (±24 hours) after the Baseline/Initial treatment/Day 1 visit (Table 1):

- Interview the subject regarding the Subject Diary completion and reported events since receiving treatment. Remind subject to complete the Subject Diary daily and bring it to the next on-site visit.
- Interview the subject regarding any concomitant therapies.
- Interview the subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the study center for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview the subject regarding when (in hours after treatment) the subject felt comfortable returning to social engagements (public/social appearances) exemplified as returning to business office or other public workplace, having dinner in a public restaurant, attending a social event/gathering such as dinner party, etc.
- Remind the subject of the next scheduled on-site visit (Visit 2a), 14 days (2 weeks; +7 days) after the baseline visit (Visit 1b).

8.3.2 Follow-up visit/Visit 2a

The following should be completed at the follow-up visit 14 days (+7 days) after the Baseline/Initial treatment/Day 1 visit (Table 1):

- Perform visual function assessments (see Section 7.6).
- Perform palpability assessments (see Section 7.4).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).
- Evaluate changes in facial hair growth in the treated area (see Section 7.5).
- Review of the Subject Diary. Remind subject to complete the Subject Diary daily and bring it to the next on-site visit.
- Obtain post-treatment photographs of the chin area.
- Interview the subject regarding any concomitant therapies.
- Interview the subject regarding any AEs that have occurred since last visit.
- Remind subject of the next scheduled on-site visit (Visit 3) 1 month (4 weeks; +7 days) after the baseline visit (Visit 1b).

8.3.3 Follow-up visit/Optional touch-up/Visit 3

The following should be completed at the follow-up visit 1 month (4 weeks; +7 days) after the Baseline/Initial treatment/Day 1 visit (Table 1):

- Assessments to be performed prior to optional touch-up if treatment will be given:
  - Assessment of GCRS – Treating Investigator (see Section 6.3).
  - Pre-treatment pain assessment using the NPS (prior to application of any anesthetic) (see Section 7.1).

- Perform visual function assessments (see Section 7.6).
- Perform palpability assessments (see Section 7.4).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).
- Evaluate changes in facial hair growth in the treated area (see Section 7.5).

CCI [redacted]

- Obtain pre-treatment photographs of the chin area.

- Interview the subject regarding any concomitant therapies.
- Interview the subject regarding any AEs that have occurred since last visit.

If touch-up is to be performed, the following should be confirmed/performed:

- Assess whether optimal aesthetic result has been achieved (as agreed by the Treating Investigator and subject) and determine whether optional touch-up is appropriate.
- Re-confirm eligibility (inclusion and exclusion criteria) – prior to treatment.
- Perform UPT for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for treatment.
- Optional touch-up treatment – subjects will be injected with the assigned study product. After injection, the following should be performed:
  - Immediately following injection, subject should complete the post-treatment pain assessment using the NPS (see Section 7.1). This should be completed before any post-injection therapies are provided.
  - Approximately 30 minutes after injection, perform visual function assessments - post-treatment (see Section 7.6).
  - Record all concomitant medications/procedures used prior, during or after the injection session.
  - Record the following injection details:
    - Date and time of completed injection
    - Lot number
    - Number of syringes used
    - Volume of study product used
    - Needle or cannula used for supraperiosteal or subcutaneous injections
    - Injection method and depth of injection
    - Additional local or topical anesthesia used
  - Evaluate for device deficiencies. If any device deficiency is noted, complete the form as specified in Section 7.13.4.

CCI [redacted]

- Evaluation of post-injection AEs by Treating Investigator.
- Schedule the 72 hours (±24 hours) follow-up telephone call (Visit 3a), the follow-up visit (Visit 3b) at 14 days (2 weeks; +7 days) after touch-up and the follow-up visit (Visit 3c) at 1 month (+7 days) after touch -up as well as (Visit 4) at 3 months (±14 days) after touch-up.

If touch-up is not to be performed:

- Schedule the next on-site visit (Visit 4), 3 months (12 weeks; ±14 days) after the Baseline/Initial treatment/Day 1 visit (Visit 1b).

8.3.4 Telephone call/Visit 3a (Subjects that received touch-up)

The following should be completed at the telephone contact 72 hours (±24 hours) after touch-up (Table 1):

- Interview the subject regarding the Subject Diary completion and reported events since receiving treatment. Remind subject to complete the Subject Diary daily and bring it to the next on-site visit.
- Interview the subject regarding any concomitant therapies.
- Interview the subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the study center for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview the subject regarding when (in hours after treatment) the subject felt comfortable returning to social engagements (public/social appearances) exemplified as returning to business office or other public workplace, having dinner in a public restaurant, attending a social event/gathering such as dinner party, etc.
- Remind the subject of the next scheduled on-site visit (Visit 3b), 14 days (2 weeks; +7 days) after the touch-up treatment (Visit 3).

8.3.5 Follow-up visit/Visit 3b (Subjects that received touch-up)

The following should be completed at the follow-up visit 14 days (+7 days) after touch-up treatment (Table 1):

- Perform visual function assessments (see Section 7.6).
- Perform palpability assessments (see Section 7.4).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).
- Evaluate changes in facial hair growth in the treated area (see Section 7.5).
- Review of the Subject Diary. Remind subject to complete the Subject Diary daily and bring it to the next on-site visit.
- Obtain post-treatment photographs of the chin area.
- Interview the subject regarding any concomitant therapies.

- Interview the subject regarding any AEs that have occurred since last visit.
- Remind the subject of the next scheduled on-site visit (Visit 3c), 1 month after the touch-up treatment (Visit 3).

8.3.6 Follow-up visit/Visit 3c (Subjects that received touch-up)

The following should be completed at the follow-up visit 1 month (+7 days) after touch-up treatment (Table 1):

- Perform visual function assessments (see Section 7.6).
- Perform palpability assessments (see Section 7.4).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).
- Evaluate changes in facial hair growth in the treated area (see Section 7.5).
- Review and collection of the Subject Diary.
- Obtain post-treatment photographs of the chin area.
- Interview the subject regarding any concomitant therapies.
- Interview the subject regarding any AEs that have occurred since receiving treatment.
- Remind the subject of the next scheduled on-site visit (Visit 4), 3 months (12 weeks) after the touch-up treatment (Visit 3).

8.3.7 Follow-up visits/Visits 4–6

The following should be completed at the follow-up visits at 3, 6 and 9 months (12, 24 and 36 weeks; ±14 days) after last treatment (Table 1):

- Assessment of GCRS – Blinded Evaluator (see Section 6.3).

- Perform visual function assessments (see Section 7.6).
- Perform palpability assessments (see Section 7.4).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).

- Evaluate changes in facial hair growth in the treated area (see Section 7.5).
- Obtain post-treatment photographs of chin area.
- Interview the subject regarding any concomitant therapies.
- Interview the subject regarding any AEs that have occurred since last visit.
- Schedule or remind the subject of the next on-site visits (as applicable); Visit 5 at 6 months (24 weeks; ±14 days), Visit 6 at 9 months (36 weeks; ±14 days) after last treatment.

8.3.8 Follow-up visit/End of study visit/Visit 7

The following should be completed at the end of study (EOS) visit at 12 months (48 weeks, +14 days) after last treatment (Table 1):

- Record subject's weight.
- Assessment of GCRS – Blinded Evaluator (see Section 6.3).

- Perform visual function assessments (see Section 7.6).
- Perform palpability assessments (see Section 7.4).
- Perform sensory tests (see Section 7.2).
- Perform functionality tests (see Section 7.3).
- Evaluate changes in facial hair growth in the treated area (see Section 7.5).
- Obtain post-treatment photographs of the chin area.
- Interview the subject regarding any concomitant therapies.
- Interview the subject regarding any AEs that have occurred since last visit.

9. STATISTICAL DESIGN AND ANALYSIS

9.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be developed before database lock.

All study data will be listed in subject data listings.

All statistical analyses, including summary tables and data listings, will be performed using SAS. Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95% unless

otherwise specified. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified.

Continuous endpoints will be summarized using descriptive statistics, e.g., number of subjects (n), mean, median, standard deviation (SD), minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

9.2 Analysis populations

The following analysis populations will be defined:

Intention to treat (ITT):

Includes all subjects who are randomized and will be analyzed according to the randomization scheme.

Per protocol (PP):

Includes all subjects in the ITT population who complete the primary endpoint assessment at 3 months after baseline or last treatment without any deviations considered to have substantial impact on the primary effectiveness.

Safety:

Includes all subjects who were treated with *Restylane Lyft with Lidocaine* or *Juvéderm Voluma XC* will be analyzed according to the as-treated principle.

The ITT population will be the primary population for all effectiveness analyses. If the PP population contains less than 90% of the subjects in the ITT, a sensitivity analysis of the primary effectiveness endpoint will be performed based on the PP population.

The safety analysis will be performed on the safety population.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, randomized, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

9.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the ITT analysis set using descriptive statistics by treatment, as appropriate.

9.4 Effectiveness analysis

9.4.1 Primary effectiveness analysis

The primary effectiveness analysis is test of non-inferiority of *Restylane Lyft with Lidocaine* to a comparator-control *Juvéderm Voluma XC* in the Intention to treat (ITT) and Per Protocol (PP) analysis sets, using the confidence interval (CI) approach.

The change from baseline in GCRS, as assessed by the Blinded Evaluator, will be analyzed using a mixed effect model with treatment as fixed effect and subject as random factor. The change from baseline at Month 3, after last treatment, will be the response variable.

Non-inferiority will be established if the upper limit of the Confidence Interval (CI) is below the non-inferiority margin of 0.5 units. Superiority will be declared if the upper limit is below 0. This

decision criterion is consistent with a gate-keeping strategy (testing for superiority following the test for non-inferiority) to maintain the overall type I error rate at 2.5%.

The null and alternative hypotheses are stated below.

Δ= the LS mean estimate of (Restylane Lyft with Lidocaine - Juvéderm Voluma XC), the statistical hypotheses to be tested are:

H_0: $\Delta \geqslant 0.5$

H_1: $\Delta < 0.5$

The primary variable is the Month 3 GCRS value minus the Baseline GCRS value. This change from Baseline measure indicates a favorable result for a subject if the value is negative. From the model a 95% confidence interval for the LS mean estimate of the treatment difference (Restylane – Control) is calculated. A negative value for the mean treatment difference is a favorable result for Restylane, and a positive value for the mean treatment difference is a favorable result for the Comparator.

9.4.2 Secondary effectiveness analysis

For the GCRS, a responder will be defined as a subject with at least 1 point improvement from baseline based on the GCRS. For a significant result, the two-sided p-value of the comparison of responder rates between the treatment groups at Month 3, 6 ,9 and 12 using the Fisher's exact test. The estimates of the responder rate in each treatment group will be presented with corresponding CIs.

9.6 Handling of missing data

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

For ITT analysis of the responder rate based on the Blinded Evaluators' live assessment of the GCRS, at 3 months after last treatment, the analysis will be performed using multiple imputation (MI) as the primary imputation method.

Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the baseline observation carried forward (BOCF) method, and the observed cases in the ITT set.

All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases in the Safety population.

9.7 Subgroup analyses

9.6.1 Effectiveness

For consistency of the results of the primary effectiveness analysis, the primary endpoint will be evaluated across different subgroups:

- Study center
- Race
- Ethnicity
- Sex at birth
- Age (≤ median age vs > median age)
- FST I-III and IV-VI
- Injection volume (≤ median total injection volume vs > median total injection volume)

9.6.2 Safety

The consistency of AE data across different subgroups will be evaluated. The following subgroup factors will be used:

- Study center
- Race
- Ethnicity
- Sex at birth
- Age (≤ median age vs > median age)
- FST I-III and IV-VI
- Injection volume (≤ median total injection volume vs > median total injection volume)

9.8 Interim analysis

No interim analysis is planned.

9.9 Independent data monitoring committee

Not applicable.

9.10 Withdrawals and deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with protocol deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to database lock. Deviations from the SAP will be documented in the Clinical Study Report (CSR).

9.11 Sample size

Approximately 174 subjects in will be treated in the study, randomized in a 2:1 ratio (116 with *Restylane Lyft with Lidocaine*: 58 with *Juvéderm Voluma XC* comparator-control).

For sample size calculation of 174, it was assumed that the true effectiveness of *Restylane Lyft with Lidocaine* compared to control treatment assessed by the GCRS is approximately 0.1 point lower. A common standard deviation of 0.7 point was assumed for the treatments. Based on the non-inferiority margin of 0.5, a total sample size of 147 evaluable subjects is then required to show non-inferiority of *Restylane Lyft with Lidocaine* to the control treatment with a power of 90%, using a two-sided 95% CI for the difference between treatment means.

Non-inferiority margin:

The GCRS scale is designed so that a complete scale step considers a meaningful clinical difference. A change of up to 0.5 points is not considered clinically important, thus, the non-inferiority margin of 0.5 is chosen. We have estimated the standard deviation from previous studies where the scale GCRS has been used.

10. ETHICS AND GENERAL CLINICAL STUDY CONDUCT

10.1 Ethical considerations

10.1.1 Statement of ethical compliance

The study shall be conducted in compliance with the CTA, the CSP, GCP, and applicable regional or national regulations.

The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study) insofar as such revisions are consistent with US treaty obligations and in accordance with US law.

The study shall follow the international standard for clinical study of medical devices for human subjects, ISO 14155:2020 or later updates as applicable for US regulations, and the International Conference on Harmonisation (ICH) guideline for GCP (E6[R2]) as applicable for medical device.

The study related medical care provided to the subjects during the study is the responsibility of an appropriately qualified medical doctor (i.e., the PI and delegated Investigators) or, where appropriate any other person entitled by national law to provide the relevant subject care.

10.1.2 Application to independent Institutional Review Boards and/or Regulatory Authorities

It is the responsibility of the PI to obtain approval of the CSP and any CSP amendment(s) from the IRB. The study shall not begin until the required favorable opinion from the IRB has been obtained. The PI shall file all correspondence with the IRB in the Investigator file and copies of IRB approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the IRB or RA shall be followed.

The study requires application for approval from the FDA. The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed. The Sponsor will provide the PI with a copy of the relevant document.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

10.2 Subject information and consent

The PI or his/her authorized designee must always use the most recently IRB-approved subject information and ICF. The ICF must not be changed without prior discussion with the Sponsor and approval from the applicable IRB.

It is the responsibility of the PI or his/her authorized designee to give each subject, prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to his/her decision to participate in the study, e.g., explain the purpose and procedures of the study, the study's duration, number of expected participants, possible risks involved, and the opinion of the IRB. The subject shall be informed that the participation is confidential and voluntary and that s/he has the right to withdraw from the study at any time, without any consequences to his/her future medical care, treatment, or benefits to which s/he is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the

subject. The subject shall be given sufficient time to read and understand the ICF and to consider participation in the study. The PI/designee should make sure the subject has understood the information. Before any study-related activities are performed, the ICF shall be personally signed and dated by the subject and the PI or his/her authorized designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries. The data will not contain any information that can be used to identify any subject.

Photographs collected during the study will be analyzed and stored in a database by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study. The subjects will be recognizable on the photographs, but their names will not be disclosed.

All signed ICFs shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated ICF and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study. The subject should be informed that a description of this study, as well as results of the study once completed and reported, will be available on http://www.ClinicalTrials.gov. This web site can be searched at any time. The web site will not include information that can identify the subject.

10.3 Personnel training

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the signature and delegation log.

The product is reserved for use by the PI or his/her authorized designee in accordance with local legislation, trained in the appropriate aseptic injection techniques and expected to follow the recommendations in the specific IFUs. Additional training for treatment with the study products in the chin will be provided by the Sponsor.

10.4 Data management and documentation

10.4.1 Data entry and collection

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens, and program will be designed in accordance with the CSP and the eCRF specification. Data validation will be performed by computerized logical checks and manual review.

Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and MedDRA dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will

be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

10.4.2 Data entry and collection

A 21 CFR Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and should be completed electronically for each screen failure as well as enrolled subjects.

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data should be entered directly from the source documents, which are to be defined at each study center before inclusion of the first subject.

Authorized study center personnel designated by the Investigator should complete data collection. Appropriate training and security measures should be completed with all authorized investigation study center personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study center as part of the Investigator file.

Any delegation of collection of data should be specified in a signature and delegation log.

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

The monitor shall review the eCRFs and evaluate them for completeness and consistency as outlined in the Monitoring plan. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her authorized designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or by its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorized designee. The appropriate study center personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study center personnel, time, and date is logged.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records shall be electronically signed by the Investigator to

document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

10.4.3 Source documentation

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These should be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the CTN and subject number. Any personal information, including name, should be removed or rendered illegible to preserve individual confidentiality.

10.4.4 Protection of personal data

The study shall include collection and processing of personal data as specified in the Regulation European Union (EU) 2016/679 (General Data Protection Regulation, GDPR) and the regulation EU 2017/745 (MDR) on the protection of individuals with regard to the processing of personal data. For the purposes of the study, Sponsor will be considered the data controller, and Institution/the Investigational site and the PI will both be considered data processors.

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution/the Investigational site and the Investigator are responsible for complying with all requirements pursuant to national legislation in which the Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the study subject should be made aware of this exception in the informed consent. The Institution/the Investigational site and Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

If a subject decides to terminate the study prematurely, data collected before withdrawal of consent will be used in the evaluation of the study, however no new data may be collected.

Authorized representatives from the Sponsor, CRO or a RA may visit the study center to perform audits/inspections, including source data verification (SDV), i.e., comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

10.4.5 Archiving / record keeping

The Investigator/Institution should permit study-related monitoring, audits, IRB review, and RA inspections and should provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e., eCRF, medical records, original signed ICFs and detailed records of study product accountability). The records should be retained by the Investigator as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records should be documented and the Sponsor should be informed in writing.

The Sponsor should verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record.

All records pertaining to the conduct of the study, including signed eCRFs, ICFs, study product accountability records, source documents, and other study documentation must be retained for as long as is specified in the CTA. Measures should be taken to prevent accidental or premature destruction of these documents (e.g., protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

It is the Investigator's responsibility to inform the Sponsor in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

10.5 Protocol deviations

The PI is not allowed to deviate from the CSP and no up-front waivers from the CSP will be issued. Any CSP deviation shall be documented appropriately, verified, discussed, and collected by the monitor and appropriate actions will be taken.

Under emergency circumstances, deviations from the CSP to protect the rights, safety, and well-being of subjects may proceed without prior approval of the Sponsor and the IRB and RA. Such deviations should be documented and reported to the IRB and RA as soon as possible. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor (within 24 hours following detection) as well as the IRB if required by national regulations.

10.6 Clinical Study Report

After completion of the study a CSR will be compiled. A summary of the study results will be published on a public database, http://www.ClinicalTrials.gov.

10.6 Quality control / quality assurance

10.6.1 Clinical Monitoring

On-site monitoring of the study will be arranged by the Sponsor according to GCP guidelines to verify that the rights and well-being of the subjects are protected, the reported data are accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved CSP, subsequent amendment(s), GCP and the applicable regulatory requirements.

Specific details about monitoring in the study will be outlined in a separate Monitoring Plan.

10.6.2 Audits / inspections

The study center may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the PI and other relevant study center personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study center team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

10.7 Protocol amendments

The PI and other study center personnel involved in the study must not implement any changes to the CSP without agreement with the Sponsor and prior review and documented approval from the IRB and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a dated and version-controlled written protocol amendment.

10.7.1 Amendments

This is the first protocol amendment.

10.7.2 Protocol amendment history

Summary of Changes in the CSP from Version 3.0 to Version 4.0.

Section in the clinical study protocol	Rational for changes	Description of changes
Synopsis and section 5.3.2.	Feedback from the FDA.	Appropriate injection volume changed not to exceed a maximum total volume of 4.0 mL, instead of 6.0 mL, for initial and touch-up treatments combined.
Synopsis and section 4.1.2	Feedback from the FDA.	Exclusion criteria 4 and 8 updated.
Subject information and informed consent form		Updates required: Yes ☐ No ☒
Investigator's Brochure (IB)/ROPI/Study Specific IFU		Updates required: Yes ☒ No ☐ (Updates are required in the study specific IFU)
Case report form (CRF)/diary		Updates required: Yes ☒ No ☐ (Updates are required in the CRF)

10.8 Financing, indemnification, and insurance

This study is fully sponsored by Galderma. The Clinical Trial Agreement (CTA) between the CRO and Investigational study centers outlines the compensation and payment terms of the study. The

CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CSP regarding certain rights and obligations, the CTA is the prevailing document.

The Sponsor's obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The Institution/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

10.9 Publication policy

The PI's, Institution's/Investigational site's, and Galderma Research and Development, LLC's/ Q-Med AB's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

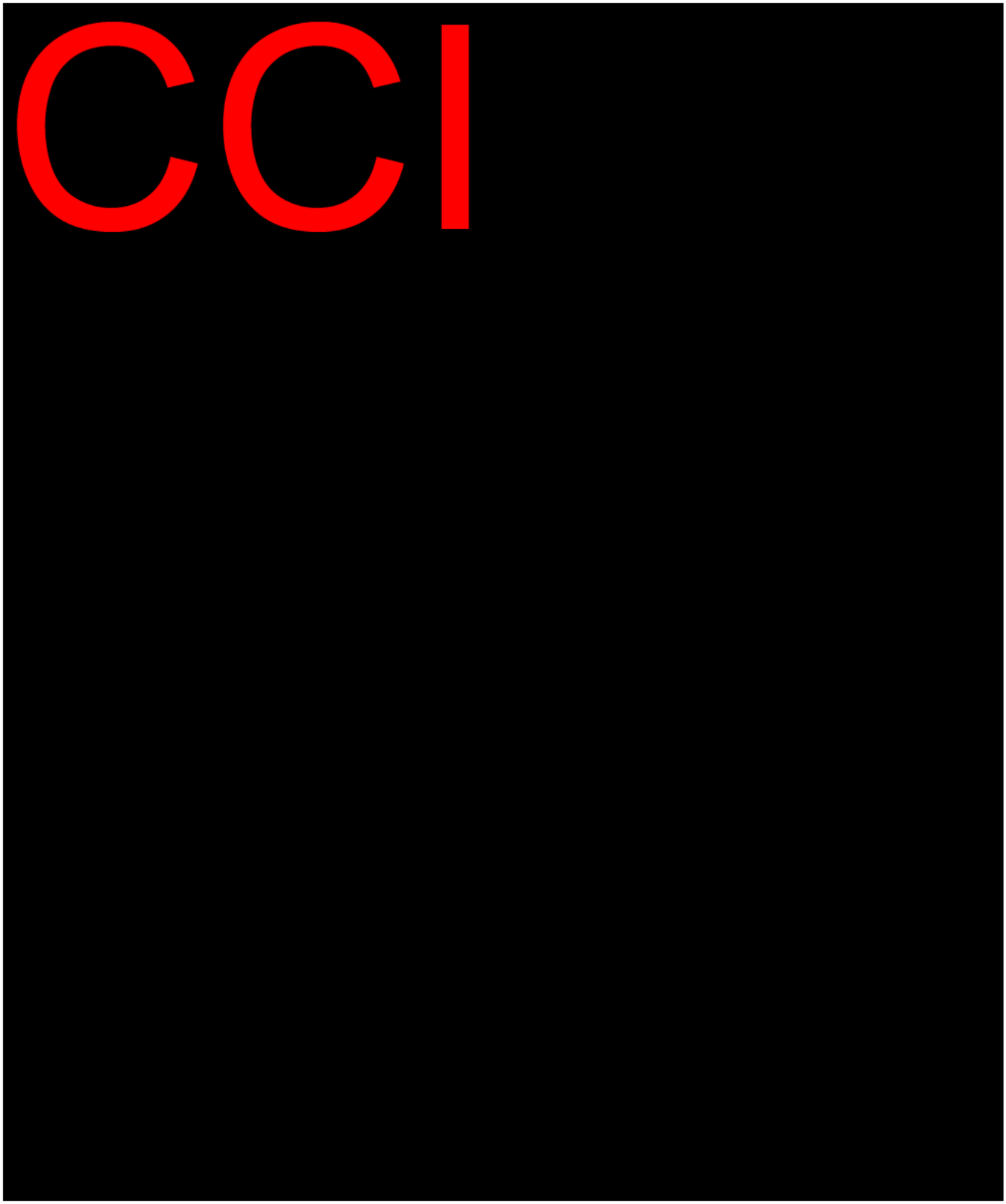
The aim is to submit the results of this study for publication in the public database www.ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved[7] Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above-mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

[7] Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org).

11. REFERENCES

1. Jones D H, Fitzgerald R, Cox S E, et al. Preventing and treating Adverse Events of Injectable Filles: Evidence-Based Recommendations from the American Society for Dermatological Surgery Multidisciplinary Task Force ASDS guidelines of care: injectable fillers. Dermatol Surg. 2021 Feb 1;47 (2):214-226. doi:10.1097/DSS.0000000000002921
2. Intravascular injection treatment protocol, internal document MA-38279
3. Huang SH and Tsai TF. Safety and Effectiveness of Hyaluronic Acid Fillers With Lidocaine for Full-Face Treatment in Asian Patients. J Drugs Dermatol 2020; 19: 836-842. 2020/10/08. DOI: 10.36849/jdd.2020.10.36849/jdd.2020.5374.
4. Molina B, David M, Jain R, et al. Patient Satisfaction and Efficacy of Full-Facial Rejuvenation Using a Combination of Botulinum Toxin Type A and Hyaluronic Acid Filler. Dermatol Surg 2015; 41 Suppl 1: S325-332. 2015/12/01. DOI: 10.1097/DSS.0000000000000548.
5. Cartier H, Hedén P, Delmar H, et al. Repeated Full-Face Aesthetic Combination Treatment With AbobotulinumtoxinA, Hyaluronic Acid Filler, and Skin-Boosting Hyaluronic Acid After Monotherapy With AbobotulinumtoxinA or Hyaluronic Acid Filler. Dermatol Surg 2020; 46: 475-482. 2019/10/09. DOI: 10.1097/dss.0000000000002165.
6. Hedén P, Hexsel D, Cartier H, et al. Effective and Safe Repeated Full-Face Treatments With AbobotulinumtoxinA, Hyaluronic Acid Filler, and Skin Boosting Hyaluronic Acid. J Drugs Dermatol 2019; 18: 682-689. 2019/07/25.
7. Farhi D, Trevidic P, Kestemont P, et al. The Emervel French survey: a prospective real-practice descriptive study of 1,822 patients treated for facial rejuvenation with a new hyaluronic acid filler. J Drugs Dermatol 2013; 12: e88-93. 2013/05/09.
8. Hedén, P., Fagrell, D., Jernbeck, J., Rylander, R., Samuelson, U., Sellman, G. and Stark, B. (2010), Injection of Stabilized Hyaluronic Acid-Based Gel of Non-Animal Origin for the Correction of Nasolabial Folds: Comparison with and without Lidocaine. Dermatologic Surgery, 36: 775-781. https://doi.org/10.1111/j.1524-4725.2010.01544.x
9. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988 Jun;124(6):869-71.
10. Restylane® Defyne, PMA P140029/S027: FDA Summary of Safety and Effectiveness Data, https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140029S027B.pdf

GALDERMA	Title **43USCH2208, Clinical Investigation Plan R Lyft Chin US**	Doc id **MA-52558**



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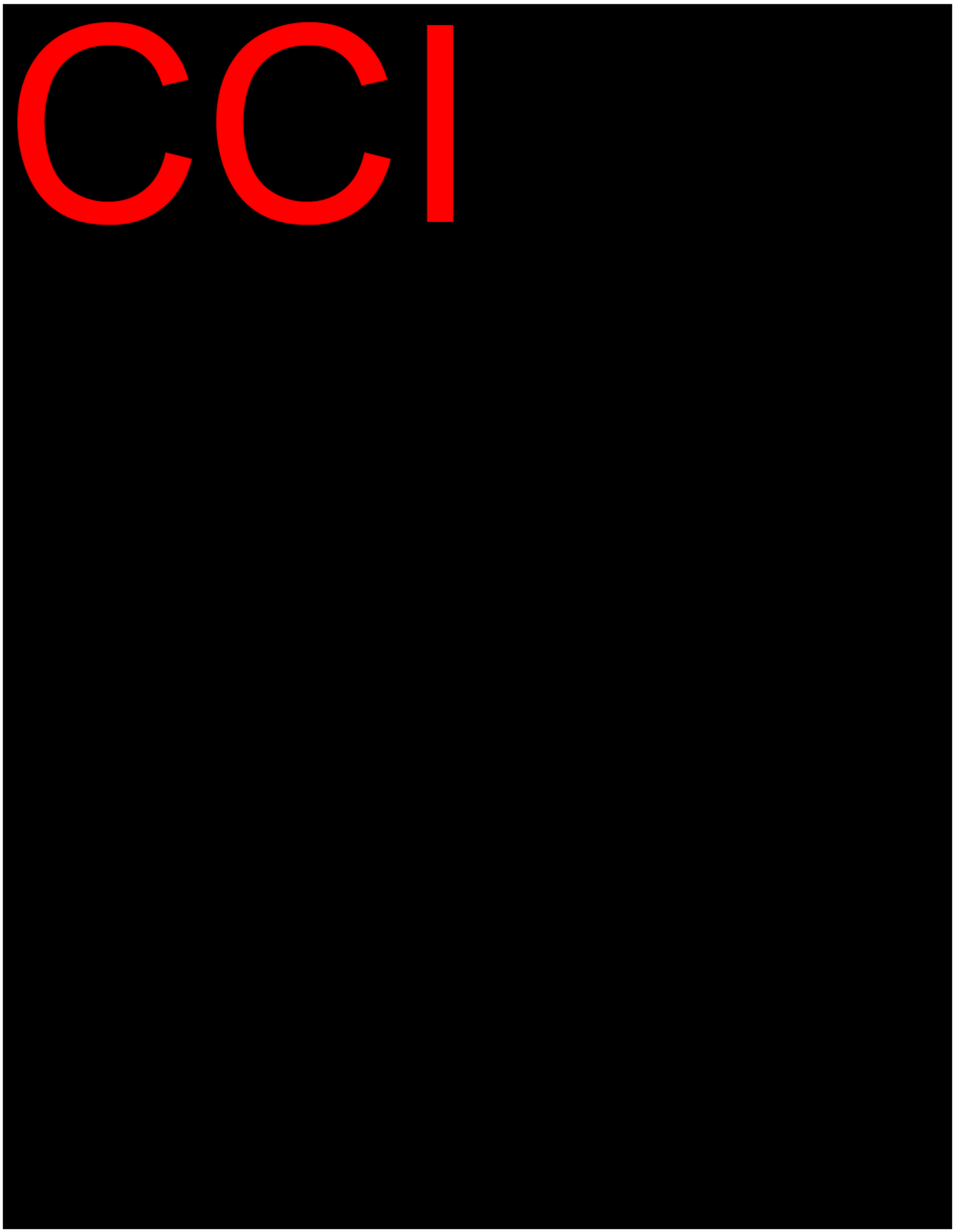

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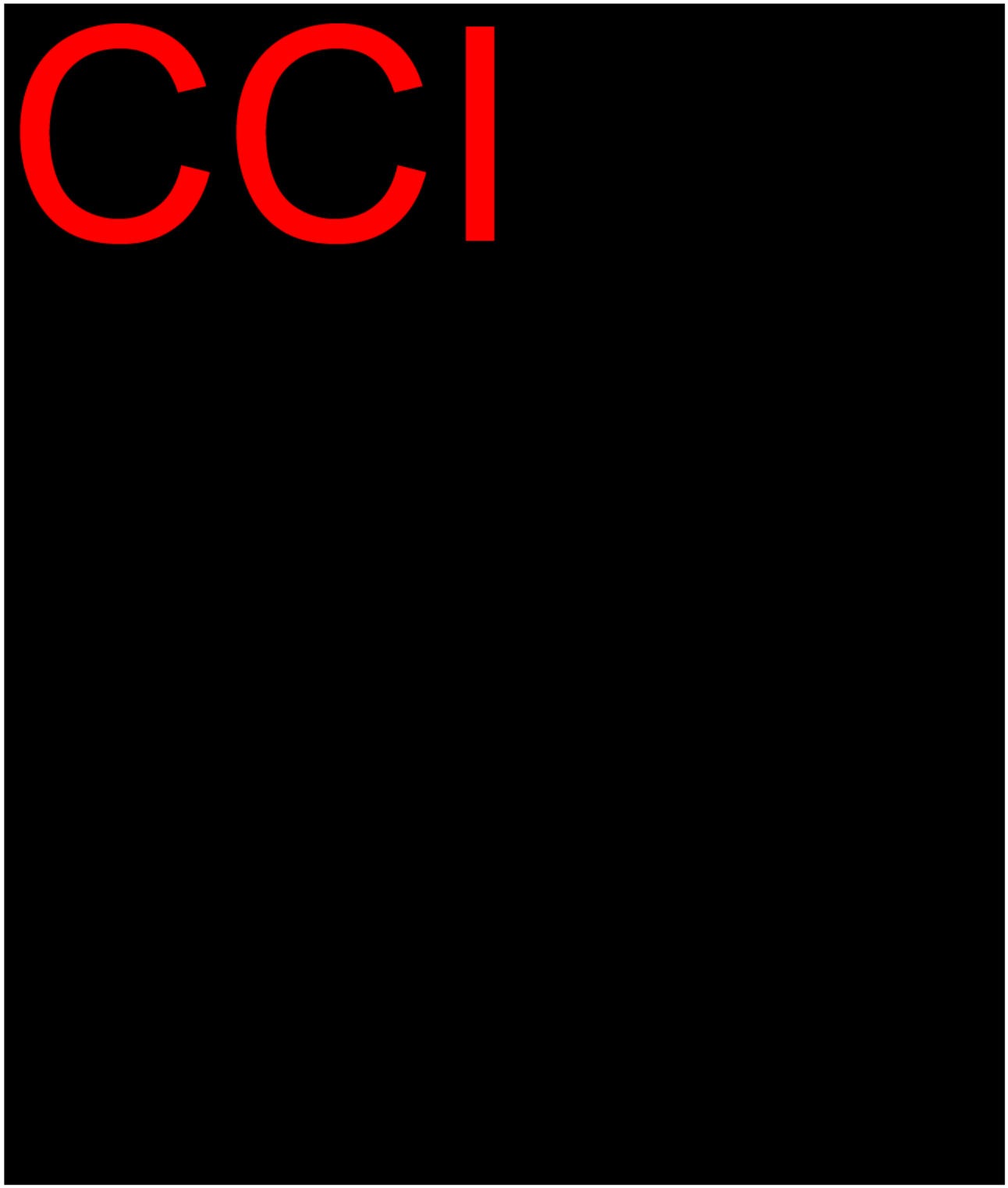

Appendix 5 **FACE-Q™ Satisfaction with Outcome**

FACE-Q™ - SATISFACTION WITH OUTCOME

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

	Definitely disagree	Somewhat disagree	Somewhat agree	Definitely agree
a. I am pleased with the result.	1	2	3	4
b. The result turned out great.	1	2	3	4
c. The result was just as I expected.	1	2	3	4
d. I am surprised at how good I look in the mirror.	1	2	3	4
e. The result is fantastic.	1	2	3	4
f. The result is miraculous.	1	2	3	4

Note to Investigators: This scale can be used independently of the other scales.

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Study center

SPONSOR SIGNATURES

The Clinical Study Protocol is electronically signed in the document management system within the Q-Med AB quality management system by the representatives listed below.

PPD

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Effective date: 2023-05-24 22:48

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SIGNATURES PAGE

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