CLINICAL STUDY PROTOCOL

CLINICAL TRIAL NUMBER (CTN): 05DF2007

CCI

TITLE PAGE

A Prospective Clinical Study to Evaluate Safety and Effectiveness of *Restylane® Kysse* for Lip Augmentation in Chinese Subjects

Study Product:	Restylane® Kysse
Clinical Trial Number (CTN):	05DF2007
SPONSOR:	Q-Med AB Seminariegatan 21 SE-752 28 Uppsala, Sweden Telephone: +46 18 474 90 00

Statements of compliance

The study should be conducted in compliance with the clinical trial agreement, the clinical investigational plan, good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2020 should be followed. The International Conference on Harmonization (ICH) guideline for GCP (E6 (R2)) should be followed as applicable for medical device. The study should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki[1].

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

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

SPONSOR CONTACT:

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Phone:	+1 817 961 5000

Name:	Galderma Research and Development, China
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CCI [redacted]

SAFETY:

For safety questions, please contact the Safety email or Medical Monitor using the details below:

Safety email CCI [redacted]

Serious adverse events (SAEs) and pregnancy report forms should be submitted as described in Sections 7.1.2.1 and 7.1.6.

MEDICAL MONITOR:

For any medical questions related to the clinical study protocol, please contact the Medical Monitor:

PPD

Further details on all participating investigators and the complete administrative structure of the study are found in the study files.

SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL

CTN: 05DF2007

Title: A Prospective Clinical Study to Evaluate Safety and Effectiveness of *Restylane Kysse* for Lip Augmentation in Chinese Subjects

I, the undersigned, have read and understand the clinical study protocol (CSP) specified above, and agree on the contents. The CSP, the clinical trial agreement (CTA) and the additional information given in the Instructions for Use (IFU) will serve as a basis for co-operation in this study.

Principal Investigator:

Printed name	Signature	Date

Study site

SYNOPSIS

Clinical Study Title:	A Prospective Clinical Study to Evaluate Safety and Effectiveness of *Restylane Kysse* for Lip Augmentation in Chinese Subjects
CTN:	05DF2007
Indication:	*Restylane Kysse* is indicated for injection into the lips for lip augmentation and the correction of upper perioral rhytids.
Study Population:	Chinese adult men and women meeting the inclusion/exclusion criteria.
Countries Involved:	United Stated (US) CCI
Planned Number of Study Centers:	Approximately 5 sites; 4 sites in the US and CCI
Total Number of Subjects (planned):	Approximately 50 subjects will be enrolled.
Clinical Study Design:	This is a prospective, open-label, multi-center study to evaluate the safety and effectiveness of *Restylane Kysse* for lip augmentation and correction of perioral rhytids, if applicable, in subjects with both biological parents of full Chinese descent. Approximately 50 subjects with a score of 1 (Very Thin) or 2 (Thin) on the Medicis Lip Fullness Scale (MLFS) will be enrolled. The upper lip and lower lip scores do not have to be equal as long as each score is either 1 or 2 at baseline. Following the informed consent and screening process, eligible subjects will be injected in the lips by the investigator at baseline. The method of injection is at the discretion of the investigator and will be recorded. Sufficient amount of product should be injected to achieve optimal aesthetic improvement as determined by the investigator and subject. Optimal aesthetic improvement is defined as at least 1-point improvement from baseline using the MLFS and the best correction that can be achieved as agreed by the investigator and the subject. Subjects in the US meeting the Wrinkle Severity Assessment (WAS) inclusion criteria may also receive optional treatment with *Restylane Kysse* in the perioral rhytids at baseline. Treatment of the upper perioral lines, vermillion border, philtral columns, Cupid's bow, and/or oral commissures may be performed to obtain optimal aesthetic improvement, as agreed by the investigator and subject. Touch-up treatment of the lips and perioral area, if treated at baseline, may be administered 4 weeks after baseline treatment if deemed necessary to obtain optimal aesthetic improvement; this decision should be agreed upon by the investigator and the subject. Touch-up treatment will not be performed if the subject has a disease or condition described in the exclusion criteria or is experiencing an ongoing treatment-related AE that, in the opinion of the investigator, would be worsened by touch-up treatment. The recommended maximum injected volume per subject per treatment visit is 6 mL (i.e. 1.5 mL for the upper lip, 1.5 mL for the lower lip, and 3 mL for perioral area, if treated). Treatment will be performed according to the approved Instructions for Use (IFU) in the US CCI

	Subjects will have in-clinic follow up visits at 2, 4, 8, 16, 24, 32, 40, and 48 weeks after the last injection. If a touch-up is deemed necessary and performed at 4 weeks post-baseline, a second 2-week and 4-week follow-up visits should be scheduled. See flowchart (Figure 1).
Safety Objective and Endpoints:	To evaluate the safety of *Restylane Kysse* for lip augmentation in Chinese subjects via assessment of: • Adverse event (AE) at all study visits. CCI Safety endpoints include: • Incidence, intensity, duration, and onset of related AEs collected during the entirety of the study. CCI
Effectiveness Objective and Endpoints:	1. To evaluate the effectiveness of *Restylane Kysse* for lip augmentation as assessed by the investigator using the MLFS for the upper and lower lips.

	Endpoints: a. Change from baseline at 8, 16, 24, 32, 40, and 48 weeks after last injection. b. Response rates (defined as at least 1-point improvement from baseline) at 8, 16, 24, 32, 40, and 48 weeks after last injection. 2. For subjects in the US: To evaluate the aesthetic improvement of the upper perioral rhytids and oral commissures after treatment with *Restylane Kysse* as assessed by the investigator using the WAS. *Note: After baseline, WAS will only be assessed for subjects who have been treated in the upper perioral rhytids or the oral commissures.* Endpoints: a. Change from baseline at 8, 16, 24, 32, 40, and 48 weeks after last injection. b. Response rates (defined as at least 1-point improvement from baseline) at 8, 16, 24, 32, 40, and 48 weeks after last injection. 3. To evaluate the aesthetic improvement (overall appearance) of the upper and lower lips after treatment with *Restylane Kysse* as assessed by the subject and the investigator, independently, using the Global Aesthetic Improvement Scale (GAIS). Endpoint: a. Response rates (defined as at least "Improved") at 8, 16, 24, 32, 40, and 48 weeks after last injection. CCI [redacted]
Subgroup Analyses:	All study subjects in the MITT population will be divided into two subgroups according to country (US CCI [redacted]
Duration of Subject Participation:	Clinical study participation for each subject is approximately 14 months, including 30 days screening period through the final follow-up visit. End of Study is defined as the time point when the last subject has completed the last study visit. One month is defined as 4 weeks in the study.
Inclusion Criteria:	1. Willing to comply with the requirements of the study and provide a signed written informed consent. 2. Ability to adequately understand the verbal explanations and the written subject information provided in English for subjects in the US and CCI [redacted]

	3. Males or non-pregnant, non-breastfeeding females, 22 years of age or older with both biological parents of full Chinese descent. 4. Subjects seeking augmentation therapy for the lips. CCI
Exclusion Criteria:	1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins. CCI 6. Previous use of any permanent (non-biodegradable) or semipermanent (e.g., calcium hydroxylapatite or poly-L-lactic acid) facial tissue augmentation therapy, lifting threads, permanent implants or autologous fat below the level of the lower orbital rim. 7. Previous use of any HA-based or collagen-based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months prior to the baseline visit.

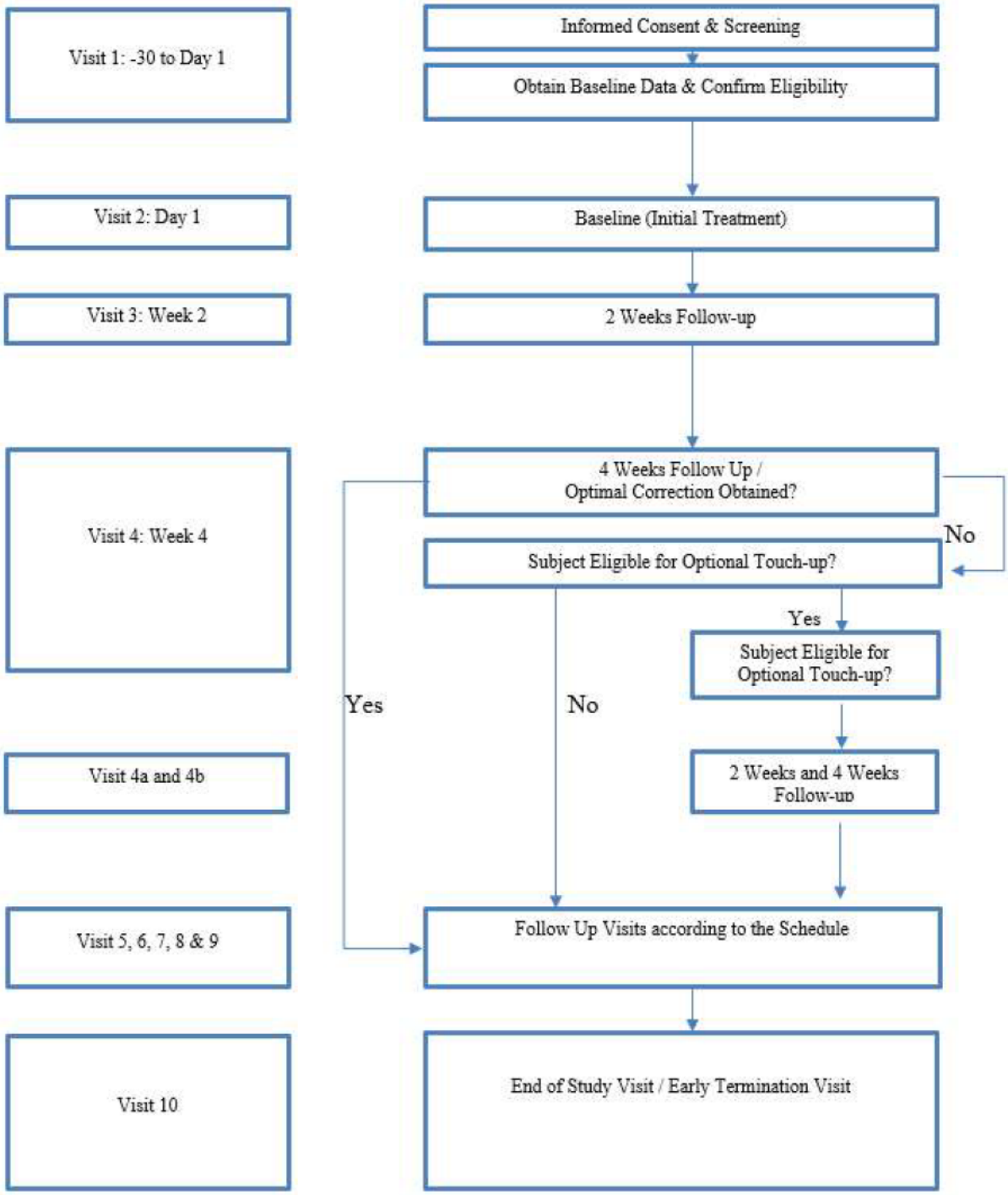
	8. History of other facial treatment/procedure in the previous 6 months below the level of the lower orbital rim that, in the investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, CCI
	9. Previous surgery to the upper or lower lip, lip piercing or tattoo, or history of facial trauma. CCI

	CCI 19. Participation in any interventional clinical study within 30 days of screening. CCI
Study Product:	*Restylane Kysse*
Reference Product:	N/A
Treatment Details:	Treatment Area for subjects in the US: Upper and lower lips, and optional treatment of the perioral area. CCI Mode of Administration: For lip augmentation, *Restylane Kysse* should be injected into the submucosal layer of the lip. Care should be taken to avoid intramuscular injection. For correction of the perioral rhytids, *Restylane Kysse* should be injected into the mid-dermis to the subcutaneous layer. Injection Needle Size: 30G x ½" Ultra-thin Wall needles (Terumo) should be used for injection. Injection Technique: The injection technique may vary based on the subject's treatment needs, and the investigator's experience and preference. Injection techniques may include: linear antegrade, linear retrograde, serial puncture, fern pattern, and/or fan technique. Treatment Regimen: All enrolled subjects will receive treatment with *Restylane Kysse* in the upper and lower lips at baseline. Subjects may receive optional touch-up treatment at Week 4 in order to achieve optimal aesthetic improvement. For subjects in the US that qualify for treatment in the perioral area, treatment may be performed at baseline and Week 4 at the discretion of the investigator and subject. Subjects will be treated to achieve optimal aesthetic improvement. Dose: The recommended maximum injected volume per subject and treatment visit is 6 mL (i.e.,3 mL for lips [1.5 mL upper lip, 1.5 mL lower lip] and 3 mL for perioral area). At each injection session and injection site, the maximum dose is at the discretion of the investigator based on clinical judgment and the subject's anatomy.

Effectiveness Assessments:	• MLFS • WAS CCI • Subject GAIS • Investigator GAIS
Safety Assessments:	• AEs CCI • Device Deficiencies • UPT for Females of Childbearing Potential
Statistical Method:	The sample size of approximately 50 subjects is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of the studied endpoints by using descriptive statistics. In general 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.
Sample Size:	Approximately 50 subjects.
Interim Analysis:	N/A

CLINICAL STUDY FLOW CHART

Figure 1: Study Flow Chart



SCHEDULE OF EVENTS

Table 1: Schedule of Events

PROCEDURE	Visit 1 *Day -30 to Day 1* Screening	Visit 2 *Day 1* Baseline / Tx	Visit 3 *Week 2 (± 3 Days)* Follow-up	Visit 4 *Week 4 (+3 Days)* Follow-up / Touch-up	Visit 4a *2 Weeks after touch-up (± 3 Days)* Follow-up	Visit 4b *4 Weeks after touch-up (+3 Days)* Follow-up	Visits 5-9 *Weeks 8-40 after baseline OR touch-up (± 5 Days)* Follow-up	Visit 10 or ET *Week 48 after baseline OR touch-up (± 5 Days)* Follow-up
Informed consent	X							
Medical history	X	X[1,2]						
Demographics	X							
Inclusion/exclusion	X	X[1,2]		X[2,4]				
Urine pregnancy test[5]	X	X[1,2]		X[2,4]				
Treatment or touch-up		X		X[4,6]				
MLFS (investigator)	X	X[1,2]		X[2]			X	X
WAS upper perioral lines & oral commissures (investigator) if applicable[7]	X	X[1,2]		X[2]			X	X
GAIS (subject and investigator)							X	X
[redacted]								
Evaluate device deficiencies		X[3]		X[3,4]				
[redacted]								
Photography		X[2]	X	X[2]	X	X	X	X
Concomitant meds/procedures	X	X[1,2,3]	X	X[2,3]	X	X	X	X
Assessment of AEs	X	X[1,2,3]	X	X[2,3]	X	X	X	X

Abbreviations: GAIS, Global Aesthetic Improvement Scale; MLFS, Medicis Lip Fullness Scale; WAS, Wrinkle Assessment Scale

[1] Omit if the screening and baseline visits occur on Day 1
[2] Prior to treatment
[3] Post treatment
[4] Omit if touch-up was not performed
[5] For females of childbearing potential
[6] Optional touch-up at Visit 4 to obtain optimal aesthetic improvement.
If a touch-up is performed, a 2wk and 4wk follow-up visits are scheduled (Visits 4a & 4b)
[7] Subjects who are not treated in the upper perioral area or the right & left oral commissures at baseline (i.e. treated in the upper and lower lips only) are not required to have WAS assessed beyond

ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
°C	Degrees Celsius
°F	Degrees Fahrenheit
AE	Adverse event
BDDE	1,4-butanediol diglycidyl ether
CRO	Contract research organization
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CSP	Clinical study protocol
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labelling)
DMP	Data management plan
eCRF	Electronic case report form
ET	Early termination
FDA	Food and Drug Administration
FSFV	First subject's first visit
FSLV	First Subject Last Visit
FST	Fitzpatrick Skin Type
G	Gauge
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
GDPR	General Data Protection Regulation
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
IDE	Investigational device exemption
IEC	Independent Ethics Committee

Abbreviation	Definition
IFU	Instructions for Use
Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.
Investigator	The principal investigator (PI) or other qualified person, i.e. sub-investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log.
ICF	Informed Consent Form
Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the investigator.
IUD	Intra Uterine Device
IPL	Intense pulsed light
IRB	Instructional Review Board
ISO	International Organization for Standardization
LSLV	Last subject's last visit
MLFS	Medicis Lip Fullness Scale
MedDRA	Medical dictionary for regulatory activities
mg	milligram
mL	milliliter
N/A	Not applicable
NSAID	Non-steroidal anti-inflammatory drugs
O_2	Oxygen
OTC	Over the counter
PI	Principal investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
SAE	Serious adverse event
SDV	Source data verification
SOC	System organ class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the sponsor.

Abbreviation	Definition
Study files	The investigator file and the sponsor file
Study product	Medical device being assessed for safety or performance in a study.
Study site	Institution or site where the study is carried out.
Touch-up	Repeated injection to be performed after treatment, if necessary, to achieve optimal aesthetic improvement
TW	Thin wall
U	Units
U-HCG	Urinary human chorionic gonadotropin
UPT	Urine Pregnancy Test
US	United States
UTW	Ultra-thin wall
WAS	Wrinkle Assessment Scale
WHO	World Health Organization

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1. BACKGROUND INFORMATION

1.1 Indication and Population Description

Restylane Kysse is indicated for injection into the lips for lip augmentation. In the US, Restylane Kysse is also indicated for correction of upper perioral rhytids.

The study population consists of Chinese adult men and women meeting the inclusion/exclusion criteria.

1.2 Study Product Profile

The study product, *Restylane Kysse,* is described in Section 5.1.

1.3 Relevant Previous Data

Please refer to the study *Restylane Kysse* Instructions for Use (IFU) for the US[2] CCI respectively. The study specific IFU summarizes the adverse effects experienced with hyaluronic acid (HA) injections along with precautions that can minimize these potential complications.

1.4 Study Rationale

Restylane Kysse has been evaluated in non-clinical and clinical studies and was approved for use by the United States Food and Drug Administration (US FDA) in 2020 CCI CCI The intended use in this post-market study will be in accordance with the approved IFU.

The rationale for performing this study is to obtain evidence of safety and effectiveness of *Restylane Kysse* in Chinese subjects to support a future marketing application in China.

1.5 Risks and Benefits

As the lip appearance is an essential feature in determining the attractiveness of a face, and thus, plays a key role in human social interactions.[4] The primary potential benefit of the study product is a perceived improvement in the visual appearance of lip fullness.

For subjects in the US, another potential benefit is the correction of the upper perioral rhytids, philtral columns and oral commissures.

Injection site reactions (e.g. swelling, erythema, tenderness, pain, bruising, itching, lumps/ bumps, and discoloration) experienced with HA fillers have been observed as consisting mainly of short-term minor or moderate symptoms starting early after treatment that generally resolve spontaneously within one to two weeks after injection. According to published literature, the most common complications related to HA injections in the lips include these injection site reactions.

The most common adverse events (AE) reported in both post-marketing surveillance data and clinical trial data for the *Restylane*® family of products (utilizing the XpresHAn/OBT Technology) injected in the lips are swelling, mass/induration, papules/nodules, pain/tenderness, and bruising/bleeding.

Although most AEs occur within days to weeks following the implant procedure, some AEs, such as swelling and mass, have been reported several weeks to months after the injection. Inflammation, infection, and damage to body structures such as nerves or blood vessels at the injection site, have also been reported. Rare but serious AEs associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures.

Additional information about reported AEs and anticipated risks are included in the product-specific IFU.

To mitigate these risks, only study investigators qualified by education and experience, and who are skilled in the use of dermal fillers from their clinical practice and involvement in clinical research, and with a firm knowledge of the vascular anatomy and understanding of the depth and plane of injection as well as knowledge of the signs and symptoms and management of potential complications will be chosen in order to assure proper device implantation and management of study risk.

Given the anticipated low level of transient and acceptable AEs in connection with the injection, the protocol required safety assessments, and the training being provided on the injection technique, it was determined the risk-benefit assessment for use of *Restylane Kysse* for lip augmentation and correction of the upper perioral rhytids, vermillion border, philtral columns, Cupid's bow, and oral commissures appears to offer a clinical benefit at reasonable risk.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives and Endpoints

2.1.1 Safety Objective and Endpoints

The safety objective of the study is to evaluate the safety of *Restylane Kysse* for lip augmentation in Chinese subjects via assessment of:

- AEs at all study visits.

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Safety endpoints include:

- Incidence, intensity, duration, and onset of related AEs collected during the entirety of the study.

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2.1.2 Effectiveness Objectives and Endpoints

The effectiveness objectives and endpoints are:

1. To evaluate the effectiveness of *Restylane Kysse* for lip augmentation as assessed by the investigator using the Medicis Lip Fullness Scale (MLFS) for the upper and lower lips.

   Endpoints:

   a. Change from baseline at 8, 16, 24, 32, 40, and 48 weeks after last injection.

   b. Response rates (defined as at least 1-point improvement from baseline) at 8, 16, 24, 32, 40, and 48 weeks after last injection.

2. For subjects in the US: To evaluate the aesthetic improvement of the upper perioral rhytids and oral commissures after treatment with *Restylane Kysse* as assessed by the investigator using the Wrinkle Assessment Scale (WAS). *Note: After baseline, WAS will only be assessed for subjects who have been treated in the perioral area.*

   Endpoints:

   a. Change from baseline at 8, 16, 24, 32, 40, and 48 weeks after last injection.

b. Response rates (defined as at least 1-point improvement from baseline) at 8, 16, 24, 32, 40, and 48 weeks after last injection.

3. To evaluate the aesthetic improvement (overall appearance) of the upper and lower lips after treatment with *Restylane Kysse* as assessed by the subject and the investigator, independently, using the Global Aesthetic Improvement Scale (GAIS).

   Endpoint:

   a. Response rates (defined as at least "Improved") at 8, 16, 24, 32, 40, and 48 weeks after last injection.

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2.2 Appropriateness of Measurements

The effectiveness and safety measurements used in this study are considered standard measurements, and are generally recognized as reliable, accurate, and relevant. The MLFS is a validated photograph-based outcome instrument that is designed specifically for quantifying lip fullness.[5] The WAS is a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds.[6] CCI
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3. STUDY DESIGN

3.1 Overall Design

This is a prospective, open-label, multi-center study to evaluate the safety and effectiveness of *Restylane Kysse* for lip augmentation and correction of perioral rhytids, if applicable, in subjects with both biological parents of full Chinese descent.

Approximately 50 subjects with a score of 1 (Very Thin) or 2 (Thin) on the MLFS will be enrolled. The upper lip and lower lip scores do not have to be equal as long as each score is either 1 or 2 at baseline.

Following the informed consent and screening process, eligible subjects will be injected in the lips by the investigator at baseline. The method of injection is at the discretion of the investigator and will be recorded. Sufficient amount of product should be injected to achieve optimal aesthetic improvement as determined by the investigator and subject. Optimal aesthetic improvement is defined as at least 1-

point improvement from baseline using the MLFS and the best correction that can be achieved as agreed by the investigator and the subject.

Subjects in the US meeting the WAS inclusion criteria may also receive optional treatment with *Restylane Kysse* in the perioral rhytids at baseline. Treatment of the upper perioral lines, vermillion border, philtral columns, Cupid's bow, and/or oral commissures may be performed to obtain optimal aesthetic improvement, as agreed by the investigator and subject.

Touch-up treatment of the lips and perioral area, if treated at baseline, may be administered 4 weeks after baseline treatment if deemed necessary to obtain optimal aesthetic improvement; this decision should be agreed upon by the investigator and the subject. Touch-up treatment will not be performed if the subject has a disease or condition described in the exclusion criteria or is experiencing an ongoing treatment-related AE that, in the opinion of the investigator, would be worsened by touch-up treatment.

The recommended maximum injected volume per subject per treatment visit is 6 mL (i.e. 1.5 mL for the upper lip, 1.5 mL for the lower lip, and 3 mL for perioral area). Treatment will be performed according to the approved IFU.

Subjects will have in-clinic follow up visits at 2, 4, 8, 16, 24, 32, 40, and 48 weeks after the last injection. If a touch-up is deemed necessary and performed at 4 weeks post-baseline, a second 2-week and 4-week follow-up visits should be scheduled. See flowchart (Figure 1).

3.2 Number of Subjects and Investigational Sites

Subjects will be recruited from up to 5 study sites; 4 sites in the US CCI
Approximately 50 subjects of full Chinese descent will be included in the study.

3.3 Study Duration

A subject may be involved in the study for approximately 14 months from screening to the final follow-up visit.

End of Study (EOS) is defined as the time point when the last subject has completed the last study visit.

3.4 Description of Study Visits

All study visits and assessments are outlined in the Table 1.

3.4.1 Visit 1: Screening (Day -30 to Day 1)

The screening visit and baseline visit (Day 1/Treatment) may be performed on the same day.

The following activities and screening assessments will be performed within 30 days prior to baseline.

- Obtain informed consent prior to conducting any study specific procedure.

- Record the subject's medical history (including any prior dermatological procedures or implants).
- Record the subject's prior and concomitant medications/procedures.
- Obtain demographic data: date of birth, height, weight, gender, ethnicity, race, and Fitzpatrick Skin Type (FST). For determination of the FST, see Table 2 below.
- Perform UPT for females of childbearing potential.
- Investigator assessment of lip fullness using the MLFS.
- For subjects in the US: Investigator assessment of perioral rhytid wrinkle severity using the WAS.

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- Evaluate the subject for pre-treatment AEs.
- Assess eligibility (inclusion and exclusion criteria), including confirmation that subject is of full Chinese descent.
- Schedule the baseline visit (Day 1/Treatment), if performed on a different day than the screening visit.

Table 2: Fitzpatrick Skin Type

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

FST is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet light.[8]

3.4.2 Visit 2: Baseline/Day 1 (Treatment)

If the screening and baseline visits are not performed on the same day, the following procedures should be repeated:

- Record the subject's medical history (including any prior dermatological procedures or implants).
- Record the subject's prior and concomitant medications/procedures.
- Perform UPT for females of childbearing potential.
- Investigator assessment of lip fullness using the MLFS.
- For subjects in the US: Investigator assessment of perioral rhytid wrinkle severity using the WAS.

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- Interview and assess for pre-treatment AEs.
- Re-confirm eligibility.

The following procedures should be performed at the baseline visit only:

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- Obtain pre-treatment photography.
- Investigator to treat the subject with *Restylane Kysse* (upper and lower lips, and perioral rhytids, if eligible and agreed upon by the investigator and subject).
- Evaluate the subject for post-treatment AEs.
- Record post-treatment concomitant medications/procedures
- Evaluate for device deficiencies.

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- Schedule the Week 2 visit (Visit 3).

3.4.3 Visit 3: Week 2 (±3 days)

- Interview and assess for AEs.
- Interview for concomitant medications/procedures.

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- Obtain photography.
- Schedule the Week 4 visit (Visit 4).

3.4.4 Visit 4: Week 4 (+3 days)

- Interview and assess for AEs.
- Interview for concomitant medications/procedures.

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- Obtain photography (if an optional touch up will be performed, ensure photos are taken prior to treatment).

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- Investigator assessment of lip fullness using the MLFS.
- For subjects in the US: Investigator assessment of perioral rhytid wrinkle severity using the WAS.
- Assess whether optimal aesthetic improvement has been obtained (as agreed by the investigator and subject). If touch-up is to be performed, confirm eligibility criteria. No touch-up should be given if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the investigator would be worsened by touch-up treatment. If needed, re-schedule for touch-up treatment within the visit window.
- If subject does not receive touch-up treatment, schedule the Week 8 visit (Visit 5).

The following procedures should be completed if touch-up treatment is performed:

- Perform UPT for females of childbearing potential.
- Investigator to perform optional touch-up treatment with *Restylane Kysse* (upper and lower lips, and perioral rhytids, if treated at baseline).
- Evaluate the subject for post-treatment AEs.
- Record post-treatment concomitant medications/procedures
- Evaluate for device deficiencies.

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- Schedule the 2 weeks after touch-up visit (Visit 4a).

3.4.5 Visit 4a: 2 Weeks After Touch-up (±3 days)

This visit should only be conducted for subjects who received a touch-up treatment at Visit 4.

- Interview and assess for AEs.
- Interview for concomitant medications/procedures.

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- Obtain photography.
- Schedule the 4 weeks after touch-up visit (Visit 4b).

3.4.6 Visit 4b: 4 Weeks After Touch-up (+3 days)

This visit should only be conducted for subjects who received a touch-up treatment at Visit 4.

- Interview and assess for AEs.
- Interview for concomitant medications/procedures.

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- Obtain photography.

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- Schedule the Week 8 visit (Visit 5).

3.4.7 Visit 5: Week 8 (± 5 days after baseline or touch-up)

- Interview and assess for AEs.
- Interview for concomitant medications/procedures.

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- Obtain photography.
- Subject assessment of global aesthetic improvement of the lips using the GAIS.

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- Investigator assessment of lip fullness using the MLFS.
- For subjects in the US: Investigator assessment of perioral rhytid wrinkle severity using the WAS.
- Investigator assessment of global aesthetic improvement of the lips using the GAIS.
- Schedule the Week 16 visit (Visit 6).

3.4.8 Visits 6-9: Weeks 16, 24, 32, and 40 (± 5 days after baseline or touch-up)

- Interview and assess for AEs.
- Interview for concomitant medications/procedures.

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- Obtain photography.
- Subject assessment of global aesthetic improvement of the lips using the GAIS.

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- Investigator assessment of lip fullness using the MLFS.
- For subjects in the US: Investigator assessment of perioral rhytid wrinkle severity using the WAS.
- Investigator assessment of global aesthetic improvement of the lips using the GAIS.
- Schedule the next visit.

3.4.9 Visit 10: Week 48 (± 5 days after baseline or touch-up)

- Interview and assess for AEs.
- Interview for concomitant medications/procedures.

CCI

- Obtain photography.
- Subject assessment of global aesthetic improvement of the lips using the GAIS.

CCI

- Investigator assessment of lip fullness using the MLFS.
- For subjects in the US: Investigator assessment of perioral rhytid wrinkle severity using the WAS.
- Investigator assessment of global aesthetic improvement of the lips using the GAIS.
- Exit the subject from the study.

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, any 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 when clinically indicated.

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the closest upcoming study visit should be completed for a subject discontinuing the clinical study and the appropriate eCRF should be completed.

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

For discontinuation due to and AE, the AE form is to be completed. The investigator should also ensure that the subject receives suitable therapy for the AE.

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

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

In case of a pregnancy occurring after the baseline visit, follow the procedures described in Section 7.1.6. 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 Events 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, confirm 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 questioned to rule out the possibility of an AE. If the AE led to discontinuation then "adverse event" 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 the subject until the AE resolves, is assessed by the investigator to be "chronic" or "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/ Independent Ethics Committee (IRB/IEC), 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 may also decide to close a single study site due to unsatisfactory subject enrollment or non-compliance with the Clinical Study Protocol (CSP), good clinical practice (GCP), or applicable regulatory requirements.

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

4. STUDY POPULATION

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:

1. Willing to comply with the requirements of the study and provide a signed written informed consent.
2. Ability to adequately understand the verbal explanations and the written subject information provided in English for subjects in the US CCI
3. Males or non-pregnant, non-breastfeeding females, 22 years of age or older with both biological parents of full Chinese descent.
4. Subjects seeking augmentation therapy for the lips.

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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 HA gel or to gram positive bacterial proteins.

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6. Previous use of any permanent (non-biodegradable) or semipermanent (e.g., calcium hydroxylapatite or poly-L-lactic acid) facial tissue augmentation therapy, lifting threads, permanent implants or autologous fat below the level of the lower orbital rim.

7. Previous use of any HA-based or collagen-based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months prior to the baseline visit.

8. History of other facial treatment/procedure in the previous 6 months below the level of the lower orbital rim that, in the investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, e.g.,

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9. Previous surgery to the upper or lower lip, lip piercing or tattoo, or history of facial trauma.

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19. Participation in any interventional clinical study within 30 days of screening.

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4.2 Medical history

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

4.3 Prior 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 course of the study, and/or
- any new therapies received by the subject since the screening visit.

4.3.2 Categories

The following two categories are to be considered for prior and concomitant therapies:

- Drugs/therapies including but not limited to prescription, over the counter (OTC), birth control pills/patches/hormonal devices, vitamins, herbal medicines/supplements, and homeopathic preparations.

- Medical and surgical procedures including, but not limited to plastic surgery (surgery to the either the upper or lower lip, facelift, rhinoplasty, facial liposuction etc.), facial tissue augmentation therapy or cosmetic procedures (e.g. lifting threads, tissue augmentation therapy, contouring or revitalization with permanent or non-permanent implants, silicone, fat, fillers, Botulinum toxin injections, deoxycholic acid injections, mesotherapy, laser, photo modulation, IPL, radio frequency, ultrasound, cryotherapy, dermabrasion, needling, chemical peeling, or other ablative/non-ablative procedures).

4.3.3 Recording

Prior 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, dose modification for a chronic condition.

4.3.4 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (Section 4.3.5) all therapies are authorized.

4.3.5 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(s) and/or injection procedure:

- Anticoagulants or inhibitors of platelet aggregation (e.g. aspirin, NSAIDs), Omega-3 or Vitamin E should not be used within 2 weeks 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.

- 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. monoclonal antibodies, antiviral treatment for HIV or Hepatitis) is prohibited.

- Systemic steroids (except intranasal/inhaled steroids) or prescription topical steroids (below the level of the lower orbital rim).
- Topical (facial) prescription retinoids below the level of the lower orbital rim or systemic retinoids.
- Energy based aesthetic procedures (e.g. laser, IPL, radiofrequency and ultrasound) in the face.
- Mechanical (e.g. dermabrasion, needling) or chemical aesthetic procedures (e.g. chemical peel) in the face.
- Treatment with cryotherapy in the face.
- Lipolytic injections in the face.
- Neurotoxin treatment below the level of the lower orbital rim.
- Facial treatment 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 assessment
- Planned aesthetic facial plastic surgery (e.g. facelift, rhinoplasty, facial liposuction etc.), sinus surgery 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.

4.4 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 screening number. Upon enrollment, each subject 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. 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 been 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 Study Product

Restylane Kysse is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless, flexible and homogeneous gel composed of HA of bacterial origin, with a moderate lifting capacity. *Restylane Kysse* is crosslinked with BDDE (1,4-butanediol diglycidylether). The product has a sodium hyaluronate concentration of 20 mg/mL in phosphate buffered saline at pH 7 and contains 3 mg/mL lidocaine hydrochloride.

Table 3: Description of Study Product

	Study Product
Trade name or equivalent:	*Restylane Kysse*
Name of treatment substance:	Hyaluronic acid
Pharmaceutical form:	Injectable gel
Concentration:	20 mg/mL HA and 3 mg/mL lidocaine hydrochloride
Packaging:	Single-use sterile syringe, 1 mL 1 syringe/2 needles per carton
Storage conditions:	Store at room temperature (up to 25°C). Protect from sunlight and freezing.
Recommended maximum volume per subject per treatment visit:	6.0 mL (i.e.,3 mL for lips [1.5 mL upper lip, 1.5 mL lower lip] and for US 3 mL for perioral area).
Frequency:	Initial treatment and optional touch-up treatment after 4 weeks.
Injection needle size:	30 G ½" ultra-thin wall (UTW) Terumo needle
Location of treated area:	Lips and for the US perioral area

Abbreviations: G, Gauge; HA, Hyaluronic acid; UTW, Ultra-thin wall.

5.2 Reference Product

N/A

5.3 Additional Products and Materials

The Sponsor will provide cotton wisps, monofilaments, and straws to each study site. UPT (urinary human chorionic gonadotropin [U-HCG]) will also be provided to each site for testing of all females of childbearing potential, at screening, baseline, and prior to treatment. The sponsor will provide pregnancy tests.

5.4 Packaging and Labelling

Restylane Kysse is supplied sterile, filled in a plastic syringe with a luer-lock fitting packaged in a blister with 2 disposable, sterile 30 G x ½" UTW Terumo needles, and an outer carton. The product is for single use only.

Labelling for the US will be performed according to US Code of Federal Regulations (CFR) 21 CFR 812.5: Labelling of investigational devices. CCI CCI An IFU leaflet is delivered with each study product.

Detailed product information is provided in the IFU (co-packed with product).

5.5 Instructions for Use and Administration

5.5.1 Pre-treatment Procedure

Any make up in the midface should be removed. It is important to thoroughly cleanse the face with an antiseptic preparation that extends below and beside the midface.

The study product contains lidocaine hydrochloride to reduce pain, but additional topical or local anesthesia or ice pack may be used at the discretion of the investigator to enhance the experience of the subject. Any additional topical or local anesthesia used should be recorded in the source documentation and on the eCRFs.

5.5.2 Treatment Procedure

Before treatment the subject will be informed about the expected post-treatment events that should be recorded in the CCI and potential risks involved with the treatment and when to contact the investigator in case of emerging symptoms.

Detailed information regarding the injection procedure, pre- and post-treatment care and patients´ instructions are provided in the IFU. Investigators will be trained on the use of the study products.

5.5.3 Treatment Regimen

Subjects will receive injection in the lips with *Restylane Kysse* at baseline (Day 1) with optional treatments at the 4 week follow-up visit. Subjects will be treated to optimal aesthetic improvement which is defined as at least 1-point improvement from baseline using the MLFS and the best correction that can be achieved as agreed by the investigator and the subject.

Subjects in the US meeting the WAS inclusion criteria may also receive optional treatment with *Restylane Kysse* in the perioral rhytids at baseline. Treatment of the upper perioral lines, vermillion border, philtral columns, Cupid's bow, and/or oral commissures may be performed to obtain optimal aesthetic improvement, as agreed by the investigator and subject.

Touch-up treatment of the lips and perioral area, if treated at baseline, may be administered 4 weeks after baseline treatment if deemed necessary to obtain optimal aesthetic improvement. A touch-up with the product will be offered provided that:

- The decision is agreed upon by the investigator and subject;
- The subject has no disease or condition described in the exclusion criteria; and

- The subject has no ongoing treatment-related AE that in the opinion of the investigator would be worsened by a touch-up injection.

If the ongoing AE, disease or condition is expected to resolve within the visit window, rescheduling for touch-up treatment may be done. Treatment procedures will be the same as at the initial treatment.

The recommended maximum injected volume per subject per treatment visit is 6 mL (i.e. 1.5 mL for the upper lip, 1.5 mL for the lower lip, and 3 mL for perioral area). Treatment will be performed according to the approved IFU.

Care should be taken to avoid excess deposition of material into individual areas. Lips should not be "overcorrected." If an overcorrection should occur, the area should be firmly massaged between fingers to obtain optimal aesthetic improvement.

5.5.4 Injection Procedures

The following injection procedures are recommended for injecting the lips, upper perioral rhytids, vermillion border, philtral columns, Cupid's bow, and/or oral commissures.

General Recommendations:

- To avoid breakage of the needle, no attempt to bend or otherwise manipulate the needle before or during treatment is recommended.
- Before injecting, remove the air by pressing the rod carefully until a small droplet is visible at the tip of the needle.
- Lip injections should be placed in the submucosal layer. Care should be taken to avoid intramuscular injection.
- For correction of the upper perioral rhytids and oral commissures, injections should be placed in mid-dermis to the subcutaneous layer.
- If the study products are injected too superficially this may result in visible lumps and/or bluish discoloration. Injection should stop just before the needle is pulled out from the skin to prevent material from leaking out or ending up too superficially in the skin.
- Excessive pressure must not be applied at any time during injection. If resistance is encountered the needle should be partially withdrawn and repositioned or fully withdrawn and checked for function.

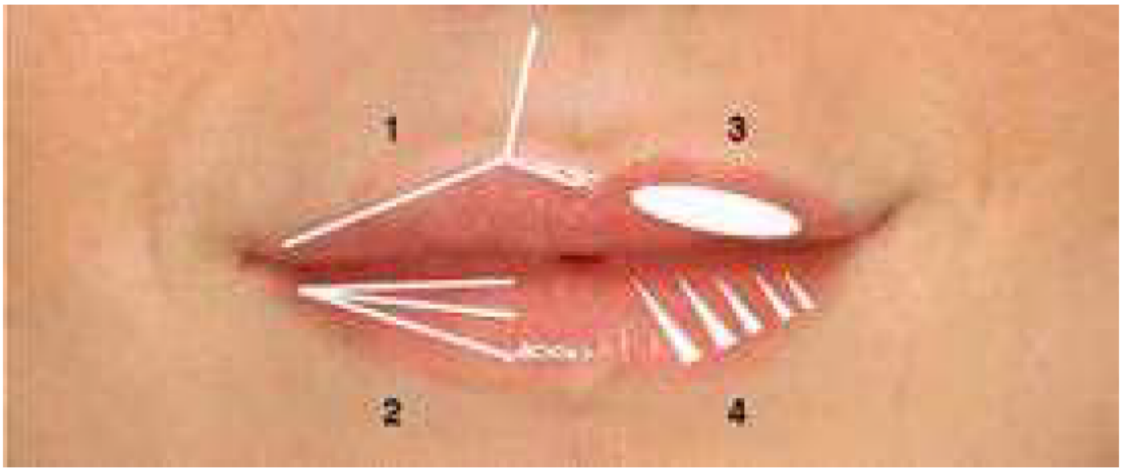
When injecting *Restylane Kysse*, the following techniques may be used in the lip (illustrated in Figure 2 below):

1. Linear threading

- Linear antegrade threading: Also called push-ahead technique as some product is pushed ahead of the needle. Once the needle is in place, the product is injected while advancing the needle.
- Linear retrograde threading: The needle is threaded into the tissue at the appropriate depth, and the product in injected as a straight line on withdrawal of the needle.

2. Fan technique: A number of linear threads to spread the product over a wider area
3. Serial puncture: Numerous small needle insertions to deliver a small bleb or bolus (e.g. depot) of the product, repeated along a line or regions of the tissues.
4. Fern pattern: Vertical or diagonal linear threads with needle entry from the center of line or the edge of vermilion border of the lip with the needle pushing into the body or vermilion of the lip and a taper-shaped pattern of product injected on withdrawal of the needle.

Figure 2: Injection Methods



1. Threading
2. Fanning
3. Depot
4. Fern pattern

When injecting the upper perioral rhytids, linear retrograde, fanning or fern pattern may be used as described above.

Of note, rapid flow or rapid injection should be avoided. Aspiration is encouraged prior to injection to verify that the needle is not intravascular.

5.5.5 Intravascular Injection Adverse Events and Recommended Treatments

For information regarding anticipated AEs for the study product, see Section 7.1.3.

5.5.5.1 *Signs of Intravascular Injections*

Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

5.5.5.2 *Signs of Orbital Pain or Visual Disturbance*

Refer the patient immediately to ophthalmology consultant. Measures to improve retinal perfusion described in the literature (albeit with limited success) include immediate ophthalmologic consultation, ocular massage, timolol eye drops, hyperbaric therapy/ oxygen (O_2), diuretics, systemic and topical corticosteroids, anticoagulation, and needle decompression of anterior chamber.[9] Also suggested in literature is retro or peribulbar injection of hyaluronidase should such an emergency arise if no ophthalmologist was immediately available.[10]

5.5.5.3 *Signs of Stroke*

Refer the patient immediately to neurology consultant.

5.5.5.4 *Signs of blanching*

As mentioned in the IFU, if so-called "blanching" is observed, i.e. the overlying skin turns a whitish color, the area should be massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, the investigator is recommended to treat in accordance with American Society for Dermatologic Surgery guidelines.[11]

5.5.5.5 *Signs of skin discoloration and/or unusual pain*

In cases of suspected intravascular injection, it is recommended to treat in accordance with American Society for Dermatologic Surgery guidelines and recent published consensus papers on management of HA filler complications,[12] which include to stop the injection immediately, and inject hyaluronidase. The minimum dose in the hyaluronidase injection is 200-300 units (U) spread over the entire area of pending necrosis. The injection should be repeated daily (minimum of 2 days) until signs of permanent necrosis or re-established blood flow reappear. A larger dose may be needed if signs and symptoms are still present. Reassess every 24 hours if signs and symptoms are present (e.g. blanching not responding to massage, unusual local pain during or shortly after injection, livedo-reticularis like appearance, well demarcated erythema, and vasculature appears compromised). After injection of hyaluronidase, apply massage (with warm compresses if appropriate) and consider hyperbaric O_2 and topical nitroglycerin paste.

5.5.6 Post-injection Care

When the injection is completed, the treated area may be gently blended/massaged, with an optional topical gel, for any irregularities. Brisk molding or massaging should be avoided in order to prevent undue swelling of the region. 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.

5.5.7 Post-treatment Care

The subject should be asked to avoid heat (sunbathing, sauna, steam baths, etc.) or extreme cold until any signs of local inflammation have disappeared. The subject should be asked not to apply any creams or cosmetics and to avoid touching or shaving the treated area before the skin has healed completely in order to prevent infections or elicit an inflammatory reaction. In addition to the post-treatment recommendations, the subject should also be reminded to abstain from prohibited medications, treatments and procedures, see Section 4.3.5. CCI the subject should be reminded to record all expected symptoms in the treated area.

5.5.8 Post-trial Provisions

In time, the implant 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 more treatments to the subjects, even if the result does not persist.

5.5.9 Treatment Documentation

The following should be recorded in the eCRF:

- Date and time of completed injection
- Lot number
- Number of syringes used and the volume of each study product
- Needle and/or cannula used per treatment area
- Injection technique used
- Injection method and depth of injection
- Additional local or topical anesthesia

5.6 Supplies Management

5.6.1 Product Accountability

The study products will be released to the principal investigator (PI) or his/her authorized designee after study approvals have been received from the IRB/IEC and the clinical trial agreement (CTA) has been signed by all parties.

The PI must ensure that the study products are kept in a secure location, with access limited to those authorized by the PI.

The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the PI maintains 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 PI, and documentation of administration of product to the subject. A shipping record shall be kept of all study products received from the sponsor; including the product name, date received, lot number, expiration date and amount received. In addition, dispensing logs shall be maintained including the product name, batch number, expiry date, dispense date, the number of syringes used, the subject receiving study product, and number of syringes left in stock at the site.

When the study is completed, all unused or expired study product at each study site shall be returned to the sponsor for destruction or destroyed locally at the site, if documented as agreed with the sponsor.

Any malfunctioning study products shall be reported as described in Section 7.4.2.

Products deliberately or accidentally destroyed during shipment or at a study site shall be accounted for and documented. Used syringes, needles and any opened 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 site. Disposal of hazardous material i.e. syringes and needles, must conform to applicable laws and regulations.

All study product(s) sent to the PI will be accounted for and no unauthorized use is permitted.

5.6.2 Storage of Study Product

The syringes should be stored in their original packaging at a temperature up to 25°C (77°F), protected from sunlight and freezing. Opened packages or partially used devices should not be reused. Detailed product information is provided in the IFUs.

5.6.3 Dispensing and Return

The treatment will be administered by the 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 site should be returned to the sponsor representative for destruction or be destroyed locally at the site if documented as agreed with the sponsor.

5.6.4 Treatment compliance

Not applicable, the treatment will be administered by the injector at the investigational site and recorded in the eCRF.

5.7 Randomization

Not applicable (N/A). This is an open-label study.

5.8 Blinding

N/A. This is an open-label study.

6. EFFECTIVENSS ASSESSMENTS

The methods for collecting efficacy 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.

6.1 Medicis Lip Fullness Scale

The MLFS is a validated photograph-based outcome instrument that is designed specifically for quantifying lip fullness.[5] Scoring of lip fullness according to Table 4 below will be based on visual live assessment by the investigator at defined time points, and not on a comparison to the baseline appearance. Change from baseline (Day 1, pre-treatment) in MLFS will be calculated for each post baseline assessment.

This study will assess the magnitude of lip fullness augmentation using the two separate 5-grade MLFS photo guides (one scale for upper lip and one scale for lower lip). The MLFS photo guides are included in Appendix 1.

Table 4: Medicis Lip Fullness Scale

Grade	Description
1	Very Thin
2	Thin
3	Medium
4	Full
5	Very Full

6.2 Wrinkle Assessment Scale

The WAS is a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds.[6] Scoring of fold severity is based on visual assessment of the length and apparent depth of the wrinkle at a certain time-point. Scoring of the upper perioral rhytids and oral commissures according to Table 5 will be based on visual live assessment by the investigator at defined time points, and not on a comparison to the baseline appearance. Change from baseline (Day 1, pre-treatment) in the WAS will be calculated for each post baseline assessment.

After the baseline visit, WAS will only be assessed for subjects who have been treated in the perioral area.

The WAS photo guides for the upper perioral rhytids and oral commissure are provided in Appendix 2.

Table 5: Wrinkle Assessment Scale for Evaluation of Upper Perioral Rhytids and Oral Commissures

Grade	Description
0	No wrinkles
1	Just perceptible wrinkle
2	Shallow wrinkles
3	Moderately deep wrinkle
4	Deep wrinkle, well-defined edges
5	Very deep wrinkle, redundant fold

6.3 Global Aesthetic Improvement Scale

The 7-graded GAIS will be used to assess the appearance of the lips (upper and lower lip combined) compared to what they looked like before treatment.

Investigator assessment: The investigator will rate, in a live assessment, the global aesthetic improvement of the lips using the following categorical scale and responding to the question:

"With respect to the appearance of the subject's lips, how would you describe the result of the lip treatment compared to the photos taken before treatment?"

The subject's photographs from pre-treatment are compared to live assessment during the present visit.

Table 6. Investigator Global Aesthetic Improvement Scale

Grade	Rating	Definition
3	Very Much Improved	Optimal aesthetic result for the implant for this subject.
2	Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
1	Improved	The appearance is improved from the initial condition.
0	No Change	The appearance is essentially the same as baseline.
-1	Worse	The appearance is worse than the initial condition.
-2	Much Worse	Marked worsening in appearance from the initial condition.

Grade	Rating	Definition
-3	Very Much Worse	Obvious worsening in appearance from the initial condition.

Subject assessment: Subjects will rate, in live assessment, the global aesthetic improvement of their lips using the following categorical scale and responding to the question:

"With respect to the appearance of your lips, how would you describe the result of the lip treatment compared to the photos taken before treatment?"

The subject's photographs from pre-treatment are compared to live assessment using a mirror during the present visit.

Table 7. Subject Global Aesthetic Improvement Scale

Grade	Rating
3	Very Much Improved
2	Much Improved
1	Improved
0	No Change
-1	Worse
-2	Much Worse
-3	Very Much Worse

CCI [redacted]

7. SAFETY ASSESSMENTS

7.1 Assessment of Adverse Events

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. 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.

When an AE is related to a device deficiency (refer to Section 7.4), 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 provided separately in the investigator file.

It is the responsibility of the investigator to determine severity of the AE and relatedness of the event to the study product.

CCI [redacted]

7.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

7.1.1.1 Reporting of Adverse Events

Adverse event reporting on each subject shall start after signing of the informed consent at screening. 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 (i.e. Visit 10/Week 48 after last injection).

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

7.1.1.2 Recording Instructions for Adverse Events

Each subject should be questioned about AEs at each study visit following signing of informed consent, for example, "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 or from a laboratory test, observations made by the study site personnel, subject diaries, or spontaneous reports from the subjects or their relatives.

Exceptions from AE reporting are normal fluctuations in pre-existing diseases. However, pre-existing illnesses that deteriorate shall be reported as AEs.

When an AE is related to a device deficiency (refer to Section 7.4), 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.

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

- Event term (recorded in standard medical terminology and avoiding abbreviations)
- Affected area
- Start date (first day with symptoms)
- Stop date (last day with symptoms)
- Intensity (mild, moderate, or severe according to definition in Section 7.1.1.2.1)
- Seriousness (serious or not serious, according to definition in Section 7.1.2)
- Causal relationship to study product or study product injection procedure (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
- Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

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

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

7.1.1.2.1 Intensity

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

- **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.

7.1.1.2.2 Causal Relationship

Each AE, serious as well as non-serious, shall be assessed by the investigator for causal relationship with the study product and its use (the injection procedure).

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.

7.1.2 Serious Adverse Event Definition

A serious adverse event (SAE) is an 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* illness or injury, or
2. a permanent impairment of a body structure or body function, or
3. in-patient or prolonged hospitalization**, or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death, or a congenital abnormality or birth defect

*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).

** 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).

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

An AE does not need to be recorded as a SAE if it only represents a relapse or an expected change or progression of the condition that was the cause of the treatment, without the development of new symptoms and signs.

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

7.1.2.1 Reporting of Serious Adverse Events

The investigator shall report any SAE to the sponsor 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)
- Adverse event 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 sponsor 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: time of injection, lot number, volume used, injection method and needle used.

E-mail for SAE reporting:	CCI

For non-urgent complementary information that is not possible to send by e-mail, please use surface mail.

CCI

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 site.

In addition, the PI shall report SAEs to the responsible IRB/IEC without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her IRB/IEC 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 according to national regulations.

7.1.3 Anticipated Adverse Events

Information regarding anticipated AEs for *Restylane Kysse* is included in the IFU (co-packed with the product).

7.1.4 Follow-up of Unresolved Events Ongoing at Termination of the Study

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure and ongoing at study end / or ongoing when subject early terminated study participation / or ongoing if 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, or for three months. 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.

7.1.5 Follow-up of Events Occurring After Subject Termination of the Study

All Adverse Events with a causal relationship to the study products 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.

7.1.6 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 acknowledgement and be submitted to the CRO according to contact details specified below. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

E-mail for pregnancy reporting:	CCI

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 fulfills 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.

CCI

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7.4 Device Deficiencies

7.4.1 Device Deficiency Definition

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

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

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

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 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 7.1.1.1 and 7.1.2.1). 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.

7.4.2 Reporting of Device Deficiencies

The investigator shall send the completed clinical study complaint form to the sponsor.

E-mail for device deficiencies reporting:	CCI

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 7.1.2.1).

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 according to national regulations, and the PI is responsible for reporting it to the IRB/IEC.

The deficient study product shall be kept by the study site 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 site.

7.5 Urine Pregnancy Test (UPT)

For all women of childbearing potential, including those currently using contraception, a UPT is required prior to receiving study treatment at baseline and optional touch-up at Week 4. **The test result must be negative for the subject to receive any treatment with study product.** The test result will be documented in the subject's file and eCRF.

8. OTHER ASSESSMENTS

8.1 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 GAIS assessment by the investigator and subject. Site personnel will be thoroughly trained in 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.

9. STATISTICAL DESIGN AND ANALYSIS

9.1 General

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a detailed and technical description regarding specific data conventions, calculations and the statistical procedures that will be used to perform the analyses that are specified in the sections below. Any changes made to the finalized SAP will be documented in the Clinical Study Report (CSR).

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system. In general 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. 95% confidence intervals will be included when appropriate.

9.2 Analysis populations

The following populations will be defined:

- Modified Intention-to-treat (MITT) — Includes all subjects treated in both lips
- Safety — Includes all subjects treated in at least one lip

MITT population will be used for all effectiveness analyses. Safety analysis will be performed based on the safety population set.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, 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 MITT population using descriptive statistics, as appropriate.

9.4 Data Transformations

Responder rate (%) regarding MLFS will be calculated as (number of subjects (or upper/lower lips) with at least one grade improvement from baseline/number of subjects reporting at the specified visit) *100.

Responder rate (%) regarding WAS will be calculated as (number of subjects (or upper/lower lips) with at least one grade improvement from baseline/number of subjects reporting at the specified visit)*100.

Responder rate (%) regarding GAIS will be calculated as (number of subjects being at least improved/number of subjects reporting at the specified visit) *100.

The outcome of the questionnaires regarding FACE-Q will be summarized and transformed to a Rasch score (0-100).

Time to onset of an AE will be derived as the start date minus the date of most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment.

Duration of an AE will be derived as the stop date minus the start date + 1. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment. Missing stop date will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of AEs that were ongoing at the end of the study will be given.

9.5 Effectiveness Analysis

9.5.1 Medicis Lip Fullness Scale

MLFS will be presented with number of subjects and percentage for each category of the scale. The proportion of responders based on MLFS (defined as at least 1-point improvement from baseline) as assessed by the investigator at weeks 8, 16, 24, 32, 40, and 48 after last injection will be calculated and presented with their 95% confidence intervals. Response rates will be calculated for the upper and lower lip separately as well as for both lips combined.

In addition, the change from baseline at weeks 8, 16, 24 32, 40, and 48 after last injection will be calculated for the upper and lower lip separately and presented using descriptive statistics.

9.5.2 Wrinkle Assessment Scale

WAS will be presented with number of subjects and percentage for each category of the scale. The proportion of responders based on the WAS (i.e., at least a one point improvement from the investigator baseline assessment of the upper perioral rhytids and oral commissures at weeks 8, 16, 24, 32, 40, and 48) will be calculated and presented along with their 95% confidence intervals.

In addition, the change from baseline at weeks 8, 16, 24 32, 40, and 48 after last injection will be calculated and presented using descriptive statistics.

9.5.3 Global Aesthetic Improvement Scale

GAIS will be presented with number of subjects and percentage for each category of the scale. For the GAIS, response rate is defined as a subject with a rating of at least "improved". The response rates based on the GAIS as assessed by the investigator and the subject, respectively, at Week 8, 16, 24, 32, 40, and 48 after last injection will be calculated and presented along with their 95% confidence intervals.

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9.6 Safety Analysis

AEs will be coded according to MedDRA and summarized by system organ class (SOC), preferred term (PT). The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT, and maximum intensity. In addition, for related AEs the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized. Serious AEs will be listed. Non-related AEs will be summarized by SOC, PT, and maximum intensity.

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CCI

9.7 Subgroup Analysis

All study subjects in the MITT population will be divided into two subgroups according to country (US and CCI

9.8 Handling of Missing Data

Study data will be presented based on observed cases, i.e. no imputation of missing values will be performed.

9.9 Interim Analysis

Not applicable. An interim analysis is not planned for the study.

9.10 Data Monitoring Committee

Not applicable. A data monitoring committee will not be utilized for the study.

9.11 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.

Deviations from the statistical plan will be documented.

9.12 Sample Size

The sample size of approximately 50 subjects is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of the studied endpoints by using descriptive statistics.

10. ETHICS AND GENERAL CLINICAL STUDY CONDUCT

10.1 Ethical Considerations

10.1.1 Statement of Ethical Compliance

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) or, where appropriate any other person entitled by national law to provide the relevant patient care.

10.1.2 Application to Institutional Review Board/Independent Ethics Committee

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

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 IRB/IEC-approved subject information and ICF and it must not be changed without prior discussion with the sponsor and approval from the applicable IRB/IEC.

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 the subject's decision to participate throughout the study, e.g. explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the IRB/IEC. The subject shall be informed that the participation is confidential

and voluntary and that the subject 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 the subject 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. 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 https://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 study specific IFUs. Additional training for treatment with the study products in the midface will be provided by the sponsor.

10.4 Data Management and Documentation

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 template. 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 medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety

data (SAEs and, if applicable, AEs 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.

10.4.1 Data Entry and Collection

A 21 Code of Federal Regulations Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data created in US. The international standard for clinical study of medical devices for human subjects, ISO14155:2011, CCI as well as The International Conference on Harmonization (ICH) Guideline for GCP (E6), as applicable for medical device. 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 site before inclusion of the first subject.

Authorized study site personnel designated by the investigator should complete data collection. Appropriate training and security measures should be completed with all authorized investigation site 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, 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 site 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. 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 site 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 site 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 site personnel, time, and date is logged.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. 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 user ID 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.

10.4.2 Source Documents

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.

10.4.3 Protection of Personal Data

The study shall include collection and processing of personal data as specified in the General Data Protection Regulation (GDPR) on the protection of individuals with regard to the processing of personal data and on the free movement of such data. For the purposes of the study, sponsor will be considered the data controller, and institution and investigator 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 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 US investigators understands that clinical studies conducted under an investigational device exemption (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 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. A subject who withdraws his or her consent to the processing of personal data must be considered to have withdrawn from the investigation, but the data collected until the consent was withdrawn may be used in the statistical analyses.

Authorized representatives from the sponsor may visit the investigational site to perform audits/inspections, including source data verification, i.e., comparing data in the subjects' medical records and the eCRF. Data and information will be handled with strict confidentiality.

10.5 Archiving and Record Keeping

The investigator/institution should permit study-related monitoring, audits, and IRB/IEC review, 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 informed consent forms 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 (source data verification; 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, informed consent forms, 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.

10.6 Clinical Study Report

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

10.7 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 the subjects may proceed without prior approval of the sponsor and the IRB/IEC. Such deviations should be documented and reported to the IRB/IEC 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/IEC if required by national regulations.

10.8 Quality Control and Quality Assurance

10.8.1 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.

10.8.2 Audits and Inspections

The study site may be subject to quality assurance audit by the sponsor. It is important that the PI and other relevant study site 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 site team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

10.9 Financing, Indemnification, and Insurance

This is a Galderma fully sponsored study. The CTA between sponsor and Investigational sites 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.

10.10 Publication Policy

The PI's, Institution's, and 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 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.[b] 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 fulfill the above-mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

10.11 Protocol amendments

The PI and other site 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/IEC, 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.

10.11.1 Amendments

This is the first protocol amendment.

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

10.11.2 Protocol Amendment History

Summary of Changes in the clinical study protocol from Version 1.0 to Version 2.0.

Section in the clinical study protocol	Rational for changes	Description of changes
CCI		
Section 7.2.1	Clarification	Clarification of SAE definition.
Subject information and informed consent form		Updates required: Yes ☒ No ☐
Investigator's Brochure (IB)/ROPI/Study Specific IFU		Updates required: Yes ☐ No ☒ (Not applicable for a Phase IV study)
Case report form (CRF)/CCI		Updates required: Yes ☐ No ☒

11. REFERENCES

1. World Medical Association (WMA). Declaration of Helsinki: Ethical principles for medical research involving human subjects. October 2013.

2. Restylane Kysse IFU US. Retrieved from https://www.restylaneusa.com/restylane-kysse

CCI

4. Kar M, Muluk NB, Bafaqeeh SA, Cingi C. Is it possible to define the ideal lips? Acta Otorhinolaryngol Ital. 2018;38(1):67-72. doi:10.14639/0392-100X-1511

5. Kane MA, Lorenc ZP, Lin X, Smith SR. Validation of a lip fullness scale for assessment of lip augmentation. PlastReconstrSurg. 2012;129(5):822e-8e.

6. Lemperle, G. A Classification of Facial Wrinkles. Plastic Reconstructive Surgery. 2001:1735-1750.

7. Klassen AF, Cano SJ, Schwitzer J, Baker SB, Carruthers A, Carruthers J, Chapas A, Pusic AL. Development and Psychometric Validation of the FACE-Q Skin, Lips and Facial Rhytides Appearance Scales and Adverse Effect Checklists for Cosmetic Procedures. JAMA Dermatol. 2016 Apr 1;152(4):443-51.

8. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988 Jun;124(6):869-71.

9. Signorini M, Liew S, Sundaram H, et al. Global Aesthetics Consensus Group. Global Aesthetics Consensus: Avoidance and Management of Complications from Hyaluronic Acid Fillers-Evidence- and Opinion-Based Review and Consensus Recommendations. Plast Reconstr Surg. 2016 Jun; 137(6):961e-71e.

10. Carruthers J, Fagien S, Dolman P. Retro or PeriBulbar Injection Techniques to Reverse Visual Loss After Filler Injections. Dermatol Surg. 2015 Dec; 41 Suppl 1:S354-7.

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

12. Cohen JL, Biesman BS, Dayan SH, et al. Treatment of Hyaluronic Acid Filler-Induced Impending Necrosis With Hyaluronidase: Consensus Recommendations. Aesthet Surg J. 2015 Sep; 35 (7):844-9.

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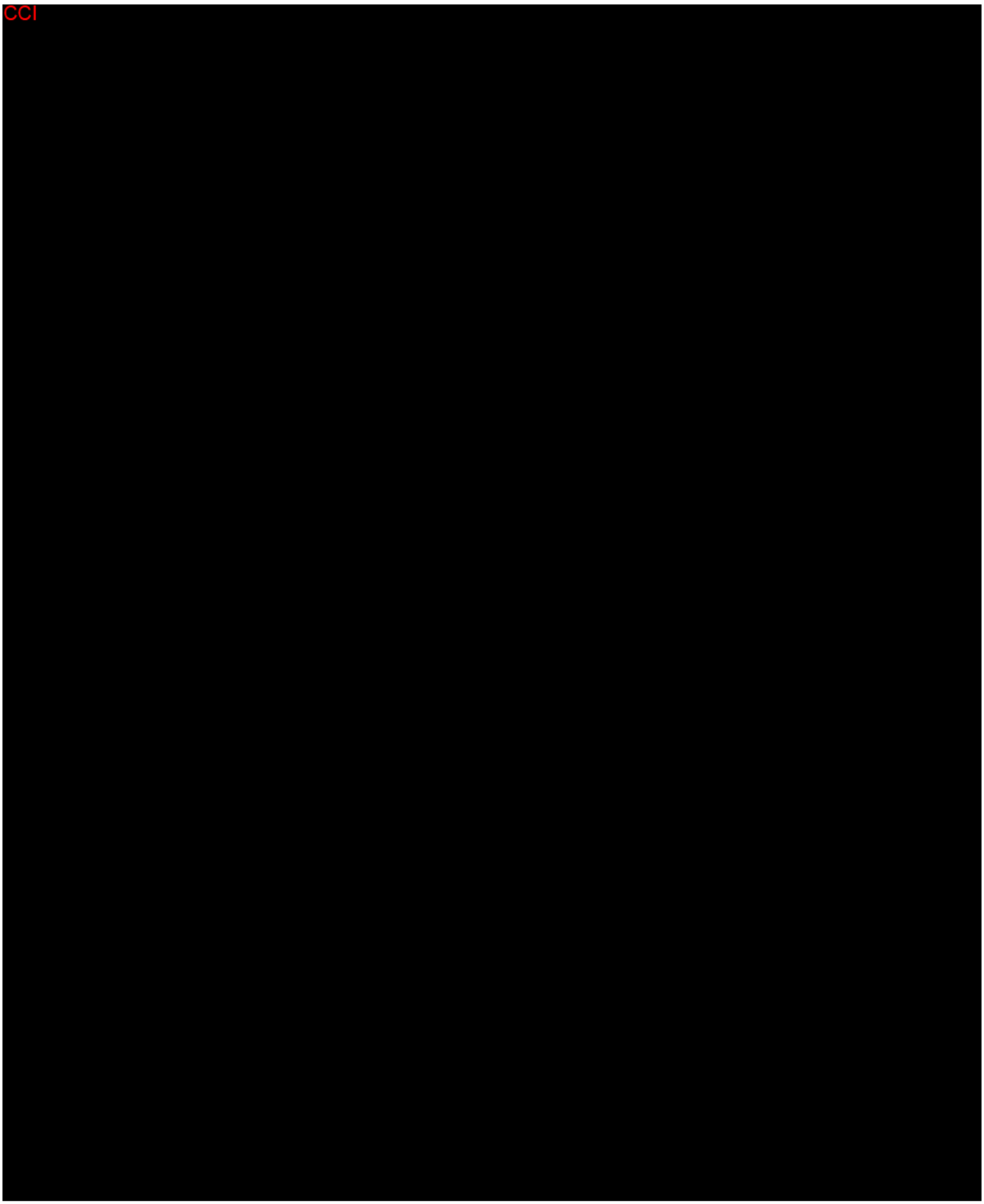

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SPONSOR SIGNATURES

The CSP is electronically signed in the document management system within the Q-Med AB quality management system.

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