A randomized, multi-center, evaluator-blinded study to evaluate the efficacy and safety of Restylane Defyne compared to Restylane for correction of moderate to severe nasolabial folds.

Study products: Restylane® Defyne™

Restylane®

Clinical trial number (CTN): 43CH1508

Coordinating Investigator(s): PPD

Sponsor:
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Summary of Changes in Clinical Study Protocol 43CH1508 from version 4.0 to version 5.0.

The changes, including rationale, are described in the table below. Added text is written in bold and deleted text is written as strikethrough.

Section in the clinical study protocol	Rationale for changes	Description of changes
Investigators and Study Administrative Structure AND Sponsor Signatures	Change of Medical expert	PPD
	Change of Clinical project manager	PPD
Signed Agreement of the Clinical Study Protocol	A reference to the Restylane Defyne IB was added.	The CSP, the clinical trial agreement (CTA), and the additional information given in the **Investigator's Brochure (IB) and** Instructions for Use (IFU) for Restylane Defyne **as well as the IFU for** ~~and~~ Restylane will serve as a basis for co-operation in this study.
Abbreviations and Definitions of Terms	IB added	Investigator's Brochure (IB) added
Sections 2.7	A reference to the Restylane Defyne IB was added.	Detailed information on reported AEs relevant for Restylane Defyne and Restylane is provided in the Instruction for Use (IFU) **as well as in the IB for Restylane Defyne**.
Sections 6.1		is available in **the IB and** the instructions for use (IFU)) (Appendix 2).
Sections 8.4.8		Refer to the Restylane Defyne **IB and** EU IFU (Appendix 2) ~~and~~ **as well as** the Restylane China IFU (Appendix 3).
Appendix 3 Instruction for Use Restylane China	New version approved by CFDA	Version 8.0 of the Instructions for Use Restylane China (Extracts from QMS-5602) has been included in Appendix 3. Version 6.0 of the Instruction for Use has been removed.
Investigators Brochure (IB)		Updates required: Yes ☐ No ☒
Subject Information and Informed Consent Form (ICF)		Updates required: Yes ☐ No ☒
Electronic Case Report Form (eCRF)		Updates required: Yes ☐ No ☒

Summary of Changes in Clinical Study Protocol 43CH1508 from version 3.0 to version 4.0.

The changes, including rationale, are described in the table below. Added text is written in bold and deleted text is written as strikethrough.

Section in the clinical study protocol	Rationale for changes	Description of changes
Investigators and Study Administrative Structure	Change of role description	~~Study director~~ **Clinical Project Manager**
	Change of Clinical project manager	PPD
Sponsor Signatures	Change of role description	~~Study director~~ **Clinical Project Manager**
	Change of Clinical project manager	PPD
8.4.5 Reporting of serious adverse events	CFDA GCP Order No 25 regulation	In addition, **according to national regulation,** the Investigator should report any SAE event **using the CFDA SAE form to the administrative department of medical device clinical trials, who will report** within 24 hours of awareness to the**:** ▪ **Food and Drug Administration (FDA) of province, autonomous region, or municipality where the site is located** ~~CFDA and relevant Provincial regulatory authority (RA) according to local regulations.~~ ▪ **Commission of Health and Family Planning of province or autonomous region or municipality where the site is located** ▪ **Responsible IEC** A copy of the initial CFDA SAE report should be sent to Sponsor by e-mail or fax and one copy should be kept at the study site. Contact details to ~~CFDA and each provincial RA~~ **local FDA and Commission of**

		Health and Family Planning of province or autonomous region or municipality where the site is located should be available at the study sites. ~~The Investigator shall also report SAEs to the responsible IEC in accordance with local requirements.~~ The Investigator is responsible for confirming the reporting procedures applicable at his/her IEC regarding SAEs and to comply with such reporting procedures during the study period. The specific contact details to each IEC should be available at the study sites. Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported 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. Any follow-up information should be reported by the Investigator in the eCRF or faxed/e-mailed to the Sponsor if there are difficulties in accessing the eCRF system. The Investigator should also send a follow-up report **via the administrative department of medical device clinical trials** to **the local FDA, local Commission of Health and Family Planning,** ~~CFDA, provincial RA,~~ and IEC in accordance with local regulations. The Investigator will assure completeness of the SAE information and the supporting documentation. A copy of the fully completed SAE and CFDA **SAE** forms should be kept at the site. The Sponsor is in addition to the Investigator responsible for reporting ~~related~~ **all** SAE **and device**

		deficiencies with the likelihood of SAE, within 5 business days upon being informed to the Shanghai Municipal Food and Drug Administration and Shanghai Municipal Commission of Health and Family Planning. Sponsor should also notify other clinical trial institutions and investigators participating in the study, who promptly should report to their local IRB/IEC.~~to the CFDA according to national regulations~~.
8.4.7 Pregnancy	Clarification to reporting procedure	A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form in the eCRF **within 24 hours after the Investigator's awareness** ~~immediately upon acknowledge and contact the Sponsor according to contact details specified in Section 8.4.5~~. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports. **If outcome information becomes available after study completion, the Investigator shall complete a hard copy of the pregnancy report form and forward to the Sponsor**. Cases that led to foetal distress, foetal 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 Investigators awareness **in accordance with Section 8.4.5.** These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as

		AEs. **A copy of the fully completed pregnancy form and exposure in utero form should be kept at the site.**
Investigators Brochure (IB)		Updates required: Yes ☐ No ☒
Subject Information and Informed Consent Form (ICF)		Updates required: Yes ☐ No ☒
Electronic Case Report Form (eCRF)		Updates required: Yes ☐ No ☒

Investigators and Study Administrative Structure

Coordinating Investigator:

PPD

Sponsor:

Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala, Sweden
Telephone: +46 18 474 90 00
Facsimile: +46 18 474 90 01

Medical expert:

PPD

Clinical Project Manager:

Study statistician:

Further details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a clinical study protocol (CSP) amendment.

Sponsor Signatures

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

PPD	**Q-Med AB**	Electronically signed in the document management system within Q-Med quality management system
Sponsor's Medical Expert, PPD	**Q-Med AB**	Electronically signed in the document management system within Q-Med quality management system
Clinical Project Manager, PPD	**Q-Med AB**	Electronically signed in the document management system within Q-Med quality management system
Statistician, PPD	**Q-Med AB**	Electronically signed in the document management system within Q-Med quality management system

Signed Agreement of the Clinical Study Protocol

CTN: 43CH1508

Title of the CSP: A randomized, multi-center, evaluator-blinded study to evaluate the efficacy and safety of Restylane Defyne compared to Restylane for correction of moderate to severe nasolabial folds.

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

Principal Investigator

Printed name	Signature	Date

Study site

Synopsis

Title of study:	A randomized, multi-center, evaluator-blinded study to evaluate the efficacy and safety of Restylane Defyne compared to Restylane for correction of moderate to severe nasolabial folds.
Clinical Trial Number:	43CH1508
Countries involved, number of sites/country, number of subjects:	The study will be conducted at approximately 5 sites located in China. The aim is to include approximately 175 subjects treated with Restylane Defyne in one nasolabial fold (NLF) and Restylane in the opposite NLF, as randomly assigned.
Coordinating Investigator:	PPD
Primary efficacy objective and endpoint:	The primary objective is to evaluate the efficacy of Restylane Defyne compared to Restylane in correction of NLFs by comparing response rates based on the Wrinkle Severity Rating Scale (WSRS), as assessed by the Blinded evaluator, at 6 months after last treatment. A response rate is defined as percentage of subjects with at least one grade (≥1) improvement on the WSRS. The non-inferiority of Restylane Defyne *versus* Restylane will be shown if the two-sided 95% confidence interval of their difference at 6 months after last treatment excludes an inferiority of 15% or more.
CCI	
Safety objectives and endpoints:	The safety objectives are: ▪ To evaluate the safety of Restylane Defyne and Restylane during the whole study by collecting Adverse Events (AEs). CCI

Study Design:	This is a randomized, multi-center, evaluator-blinded study in China to evaluate the efficacy and safety of Restylane Defyne (Emervel Deep) compared to Restylane in correction of moderate to severe NLFs. Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 21 days prior to study randomization on Day 1. Subsequent to screening eligible subjects will be enrolled in the study. **Initial Treatment** Each subject will receive an initial treatment on Day 1 with Restylane Defyne in one NLF and Restylane in the opposite NLF, as randomly assigned. The first injection will always be given in the right NLF. CCI [redacted] In order to evaluate the pain of injection separated from the pain of the needle insertion alone, a pause of 3 to 5 second is required after insertion of the needle before starting injection. Aspiration should be performed prior to injection in order to avoid accidental intravascular injection. For initial treatment, it is recommended not to use more than 1.5 mL for each NLF. The injection procedure for the two NLFs will be standardized as far as possible in terms of volume, time for injection, and injection technique, and will be recorded in the eCRF. The aim of the treatment is to achieve optimal aesthetic improvement, defined as at least one (≥1) grade improvement from baseline on the WSRS, as assessed by the blinded evaluator. **Touch-Up Treatment** A touch-up treatment may be performed 4 weeks after the initial treatment if optimal aesthetic improvement has not been obtained, i.e., subjects who did not improve at least one (≥1) grade in WSRS (in one or both NLFs, as assessed by the blinded evaluator). Topical or local anesthetic or other pain-relieving medication, including ice, may be used before and after touch-up treatment. Touch-up treatment will not be performed if there are ongoing treatment related AEs or if optimal aesthetic improvement of both NLFs is already achieved. The touch-up treatment is optional and requires the subject's verbal consent. If a touch-up is performed it is preferably performed in both NLFs and it is recommended not to use more than 0.5 mL for each NLF. It is of outmost importance to ensure that the subject receives the same product as initial treatment in respective NLF. **Evaluation of efficacy** The blinded evaluator will evaluate the wrinkle severity (baseline value) using the WSRS. The WSRS will be completed CCI [redacted] by the blinded evaluator for efficacy assessment. CCI [redacted] The subjects will be photographed at baseline (before treatment) and at each follow-up visit (before treatment, when applicable) to document condition at baseline, CCI [redacted] and to document AEs in the treated area.

	CCI **Evaluation of safety** Information regarding AEs will be collected continuously during the study. CCI CCI
Scheduled visits:	Screening: Day -21 to Day 1 Baseline (initial treatment): Day 1 Follow-up and Touch-up treatment: Week 4 (Day 29) Follow-up: Week 4, Months 3, 6, and 9 (after last treatment) Follow-up/ Final visit: Month 12 (after last treatment)
Inclusion criteria:	The subject must meet the following criteria to be eligible for the study: 1. Signed and dated informed consent to participate in the study. 2. Men or women aged 18 years of age or older of Chinese origin. 3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim for the duration of the study (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency etc.). 4. Intent to undergo correction of both NLFs with a wrinkle severity in WSRS of either 3 on both sides or 4 on both sides, as assessed by the blinded evaluator.
Exclusion criteria:	The presence of any of the following exclusion criteria will exclude a subject from enrolment in the study: 1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel. 2. Known/previous allergy or hypersensitivity to local anesthetics, e.g., lidocaine or other amide-type anesthetics. 3. History of severe or multiple allergies manifested by anaphylaxis. 4. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, chemical peeling, or dermabrasion below the level of the lower orbital rim within 6 months before treatment. 5. Previous surgery (including aesthetic facial surgical therapy or liposuction) or tattoo in the area to be treated. 6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent facial tissue augmentation therapy or autologous fat or permanent implant below the level of the lower orbital rim.

	7. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months before treatment. 8. Previous use of neurotoxins below the level of the lower orbital rim (crow's feet line is acceptable) within 12 months before treatment. 9. History of radiation or cancerous or pre-cancerous lesions (e.g., actinic keratosis) in the area to be treated. 10. Scars or deformities, active skin disease, inflammation or related conditions such as infection, perioral dermatitis, seborrheic dermatitis, eczema, rosacea, acne, psoriasis, and herpes zoster near or in the area to be treated. 11. Subjects with dental or oral status on visual inspection that in the opinion of the Investigator would make the subject unsuitable for inclusion, or Subjects with dental, oral or sinus surgery within past 12 months prior to the treatment visit or planned surgery, including dental implants, during the study period. 12. Ongoing infection in mouth or dentals. 13. Chronic infection in head and neck region. 14. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis, or localized or systemic scleroderma. 15. Tendency to form keloids, hypertrophic scars, or any other healing disorder. 16. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation e.g., aspirin or other non-steroid anti-inflammatory drugs (NSAIDs), Omega-3, or vitamin E within 2 weeks before treatment. 17. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies), systemic or topical (facial) corticosteroids within 3 months before treatment (inhaled corticoids are allowed). 18. Concomitant treatment with topical (facial) retinoids within 3 months or systemic retinoids within 6 months before treatment. 19. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion (e.g., porphyria, a chronic, relapsing, or hereditary disease that may affect the general condition or may require frequent medical treatment, any abnormal screening laboratory value or ECG, or psychiatric disorders). 20. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g., subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments, or having unrealistic expectations of the treatment result. 21. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period. 22. Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company. 23. Participation in any other clinical study within 30 days before treatment.

Investigational product, dose and mode of administration:	Restylane Defyne (with lidocaine) consists of stabilized hyaluronic acid of non-animal origin at a concentration of 20 mg/mL in phosphate buffered saline with lidocaine hydrochloride 3 mg/mL. The study product is supplied in sterile 1 mL syringes. A 27G × ½" ultra-thin wall needle will be used for injection. The treating Investigator will check the randomization *via* the eCRF system for study product, i.e,. the NLF on one side of the face will be randomly assigned to treatment with Restylane Defyne and the opposite NLF to treatment with Restylane. Restylane Defyne should be injected into the mid to deep dermis of the facial skin in the NLF. The injection procedure should strictly follow the rules of aseptic surgical technique (refer to the Restylane Defyne Instructions For Use for details). For initial treatment, it is recommended not to use more than 1.5 mL for each NLF. For touch up treatment, it is recommended not to use more than 0.5 mL for each NLF. The linear threading technique can be used to carefully lift up the wrinkle. The injection technique should be the same for both sides of the face in any one subject to limit variability due to technique. Sufficient amounts of product should be injected to fully correct the defect. Defects should be fully corrected, but not overcorrected CCI Restylane Defyne is approved under the brand name Emervel Deep Lidocaine in several countries.
Reference therapy, dose and mode of administration	Restylane (without lidocaine) consists of stabilized hyaluronic acid of non-animal origin at a concentration of 20 mg/mL, in phosphate buffered saline. The study product is supplied in sterile 1 mL syringes. A 30G × ½" needle will be used for injection. Restylane should be injected into the middle part of the dermis layer of the facial skin in the NLF. The injection procedure should strictly follow rules of aseptic surgical technique (refer to the Restylane Instructions For Use for details). For initial treatment, it is recommended not to use more than 1.5 mL for each NLF. For touch up treatment, it is recommended not to use more than 0.5 mL for each NLF. The linear threading technique can be used to carefully lift up the wrinkle. The injection technique should be the same for both sides of the face in any one subject to limit variability due to technique. Sufficient amounts of product should be injected to fully correct the defect. Defects should be fully corrected, but not overcorrected CCI
Duration of treatment and follow-up:	Following screening and treatment (initial and optional 4-week touch-up) there is a follow-up period of 12 months including follow-up visits at 4 weeks (±3 days), 3 months (±7 days), 6 months (±7 days), 9 months (±2 weeks) and 12 months (±2 weeks).

Efficacy Assessment:	**NLF severity Assessment:** The Wrinkle Severity Rating Scale (WSRS) is a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds. Scoring of fold severity is based on visual assessment of the length and apparent depth of the NLF at a certain time-point and the result is not based on a comparison to the baseline or pre-treatment appearance. Each score in the WSRS is exemplified by a photograph of NLFs. At screening, baseline and each follow up visit, the WSRS will be used by the blinded evaluator for NLF severity assessment. Wrinkle Severity Rating Scale (WSRS):

Grade	Description
1	Absent: No visible fold; continuous skin line
2	Mild: Shallow but visible fold with a slight indentation; minor facial feature Implant is expected to produce a slight improvement in appearance
3	Moderate: Moderately deep folds; clear facial feature visible at normal appearance but not when stretched. Excellent correction is expected from injectable implant
4	Severe: Very long and deep fold; prominent facial feature; less than 2-mm visible fold when stretched Significant improvement is expected from injectable implant
5	Extreme: Extremely deep and long fold; detrimental to facial appearance; 2- to 4-mm V-shaped fold when stretched. Unlikely to have satisfactory correction with injectable implant alone

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[redacted]

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Safety Assessment:	Each subject will be questioned about AEs at each clinical visit following the screening visit. The question asked will be "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, observations by the study personnel, CCI laboratory tests, or spontaneous reports from the subjects. CCI
Statistical Methods:	**Primary analysis** Non-inferiority testing for Restylane Defyne relative to Restylane will be based on the 95% confidence interval approach with a non-inferiority margin of 15%. The confidence interval will be constructed for the difference (Restylane minus Restylane Defyne) in response rates at the 6 month follow-up visit. Non-inferiority will be declared if the 2-sided 95% interval is fully below 15% (i.e., the upper bound of the interval is less than 15%) in both the FAS and PP populations.

	CCI [redacted]
	Safety CCI [redacted] Adverse event incidences will be summarized by MedDRA system organ class (SOC) and preferred term (PT). **Sample size** CCI [redacted]

Abbreviations and Definitions of Terms

AE	Adverse event
Blinded evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must be blinded to the treatment and not involved in the treatment of the subject.
CFDA	China Food and Drug Administration
Coordinating Investigator	Investigator who is appointed by the Sponsor to coordinate work in a multicenter study
CRO	Contract research organization
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
FAS	Full Analysis Set
G	Gauge
CCI	[redacted]
GCP	Good clinical practice
HA	Hyaluronic acid
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for use
Investigational product	Medical device being assessed for safety or performance in a study. "Investigational product" is the same as "study device", "investigational device", or "investigational medical device".
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

Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
ISO	International Organization for Standardization
MedDRA	Medical dictionary for regulatory activities
NLF	Nasolabial fold
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
RA	Regulatory authority
Reference product	Medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a study
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
S-HCG	Serum human chorionic gonadotropin
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.
Study files	The Investigator file and the Sponsor file
Study products	The investigational product and the reference product under study
Study site	Institution or site where the study is carried out
Touch-up	Repeated treatment to be performed 4 weeks ± 3 days after initial treatment if optimal aesthetic improvement was not obtained, i.e., subjects who did not improve ≥1 grade on WSRS in one or both NLFs, (as assessed by the blinded evaluator).
U-HCG	Urinary human chorionic gonadotropin
CCI [redacted]	
WHO	World Health Organization
WSRS	Wrinkle severity rating scale

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1 ETHICAL CONSIDERATIONS

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2011 shall be followed. The International Conference on Harmonization (ICH) guideline for GCP (E6) shall be followed as applicable for medical device. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix 1).

1.2 Application to independent ethics committee and/or regulatory authorities

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

2 BACKGROUND INFORMATION

2.1 Indication and population description

Restylane Defyne is an injectable filler used for facial tissue augmentation and, in this study, intended for the correction of moderate to severe nasolabial folds (NLFs) in subjects over the age of 18.

2.2 Investigational product description

Among the different materials used as raw materials in dermal fillers, sodium hyaluronate, also denoted hyaluronic acid when found in vivo and hereinafter referred to as HA, is the most frequently used[1]. Hyaluronic acid is a naturally occurring polysaccharide found in all vertebrates and in some bacteria[1,2]. The chemical structure is very simple with repeating disaccharide units of glucuronic acid and N-acetylglucosamine. As the chemical structure of HA is identical in all species and tissues, it is non-allergenic.

To minimize the risk for contamination, the HA used in the manufacture of Galderma's HA gels is of non-animal source, biosynthesized from *Streptococcus* species of bacteria. During manufacturing, cross-links are introduced between the HA chains to obtain a gel network and as a result the duration of the gel in the body is several months, as compared to only a few

days for a solution of native HA. The HA gel is insoluble in water and organic solvents; however, the gel is highly hydrophilic and swells in water. Hyaluronic acid based fillers typically exhibit better biocompatibility and fewer adverse reactions than fillers based on other materials. The gel, when injected, acts by increasing the tissue volume, thereby improving tissue structure and support. The gel is gradually degraded over time and eventually the correction made will subside.
Restylane Defyne is a sterile, biodegradable, transparent gel of non-animal cross-linked HA containing a concentration of 20 mg HA per mL in a physiological buffer system. Lidocaine hydrochloride (3 mg/mL) is added to the formulation to diminish the pain resulting from the injection during the treatment. When the gel is injected and the tissue expands some pain can be experienced and it is therefore desirable to have a local anesthetic effect at the site of injection.

Restylane Defyne has been regulatory cleared under the brand name Emervel Deep Lidocaine in more than 50 countries from most continents of the world including the Europe, North America (only Canada), Latin America, Australia, and Asia. The intended use, in the region of origin (Europe), is facial tissue augmentation for the correction of severe wrinkles or to redefine the shape of the face (cheekbones, tear troughs, or lips). The regulatory cleared intended use differs between different countries. Depending on the area to be treated and the tissue support, the product should be injected in the mid to deep dermis, submucosal layer of the lips, subcutis, or supraperiostic zone.

The gel in Restylane Defyne is, as all the Emervel filler products, produced using the Optimal Balance Technology (OBT) process.

2.3 Reference product description

The reference product in the study is Restylane, another HA-based dermal filler. The HA content in Restylane is 20 mg/mL in a physiological buffer system, however, Restylane does not contain any lidocaine as compared to Restylane Defyne, the investigational product of the study. Restylane is produced using the NASHA™ technology producing a gel containing stabilized non-animal HA gel.

Restylane was CE-marked in Europe in 1996 and is now regulatory cleared in more than 80 countries including the US and in several Asian countries. In 2008, Restylane received marketing registration in China as a medical device to be used for facial dermal tissue augmentation to correct moderate to severe NLFs.

2.4 Previous experience

2.4.1 Nonclinical documentation

Products manufactured using the OBT process have been tested and meet all biocompatibility requirements specified in the international standard ISO 10993:1 (Biological Evaluation of Medical Devices; i.e., having no toxic or injurious effects on the human body)[3,4]; it is neither cytotoxic nor genotoxic, and it does not give rise to acute toxicity, pyrogenicity, skin irritation, or delayed sensitization.

In in vivo animal studies, the OBT products demonstrated good filler longevity, similar or superior to comparator products, and all products were well tolerated with minimal microscopic inflammation scores secondary to limited tissue disturbance.

2.4.2 Clinical documentation

Restylane Defyne has been evaluated in a 1-year, randomized, evaluator-blinded, active-controlled, multi-center, split-face comparison US study of the two HA fillers Restylane Defyne and Juvéderm Ultra Plus with the objective to compare efficacy and safety[5].

One hundred sixty-two (162) subjects with moderate to severe NLFs were treated with Restylane Defyne in one NLF and Juvéderm Ultra Plus in the other.

The primary efficacy analysis in the intent-to-treat population at Week 24 showed a mean change from baseline of -1.1 in wrinkle severity rating scale (WSRS) score for both Restylane Defyne and Juvéderm Ultra Plus. Non-inferiority of Restylane Defyne compared with Juvéderm Ultra Plus was demonstrated. For mean change from baseline in WSRS score, Restylane Defyne and Juvéderm Ultra Plus were clinically comparable at all-time points up to Week 48.

The benefit of pre-incorporated lidocaine in Restylane Defyne was observed immediately at the time of injection and up to 1 hour post-injection.

Restylane Defyne showed a favorable safety profile in subjects with moderate to severe wrinkles and folds, and was comparable to Juvéderm Ultra Plus. The percentage of subjects with adverse events (AEs) after treatment with Restylane Defyne was similar to the percentage of subjects with AEs after treatment with Juvéderm Ultra Plus. The AEs that were assessed by the Investigators as product-related were mostly mild in intensity. Most of the AEs related to study products were associated with treatment side (right or left) and the distribution between the two treated sides was similar. The most common AEs related to study products were injection site swelling and injection site erythema. Two subjects had AEs with causal relationship to study products, allergic contact dermatitis and interstitial granulomatous dermatitis, respectively that led to study discontinuation. In the two subjects, the AE was reported for both sides of the face, i.e., for both products. Both events resolved without sequelae.

Another randomized, evaluator-blinded study in Europe comparing Emervel Deep (identical to Restylane Defyne but without lidocaine) with Restylane Perlane in 86 subjects, demonstrated similar safety between the dermal fillers and a superior, albeit of limited clinical relevance, efficacy of Emervel Deep after NLF correction[6].

Restylane was registered in China 2008 as a medical device for facial tissue augmentation to correct moderate to severe NLFs. Restylane has been extensively evaluated worldwide in clinical studies[7-21] and has also been proven safe and efficacious in a clinical trial in a Chinese study population[18]. The study was performed in China and the aim was to study the safety and efficacy of Restylane for facial tissue augmentation (i.e., NLFs; n=86). Efficacy was sustained with a significant improvement from baseline at all-time points up to the last observation at 6 months post-treatment. The study also showed that Restylane was well tolerated and no systemic reactions or other safety concerns were raised. Some transient anticipated post-injection reactions were reported, generally of mild intensity. These reactions resolved spontaneously without need of specific treatment. The results from the study demonstrated that Restylane is, at least, as efficacious in a Chinese study population as in a

US study population[12,13,15] and that the frequency of AEs related to treatment was similar in a Chinese study population as in US study population[12,13,15].

2.5 Study rationale

Restylane has been proven to be safe and efficacious in a clinical trial in a Chinese study population[18]. By comparison, Restylane in a Chinese study population was at least as efficacious as in a US study population and with similar safety as in a US study population[12,13,15]. The efficacy and safety of Restylane Defyne for correction of the NLFs in a Chinese population has not yet been evaluated. This study will provide documentation on the efficacy and safety of Restylane Defyne for facial augmentation, to correct NLFs in a Chinese population. The documentation will be used to support registration of the product in China.

This study aims to evaluate the efficacy and safety of Restylane Defyne compared to Restylane for correction of NLFs in a Chinese population. This study will follow the subjects for 12 months.

2.6 Justification for the design of the study

The purpose of the study is to evaluate the efficacy of Restylane Defyne compared to Restylane in correction of NLFs by evaluation of wrinkle severity response rates at 6 months after last treatment. CCI [redacted] Safety information will be collected CCI [redacted] by collecting AEs throughout the 12 month study period. The study will be used as clinical documentation for registration of Restylane Defyne in China.

A split-face design, where each patient receives one treatment in one NLF and another treatment in the opposite NLF, is the standard design to evaluate the efficacy and safety of dermal filler compared to another[10]. The evaluation will be carried out by a blinded evaluator to enable unbiased assessments of the WSRS CCI [redacted].

The rationale for choosing a primary efficacy endpoint of 6 months is that this is in line with the previously conducted randomized studies carried out with Emervel Deep / Restylane Defyne, which have proven to generate reliable results. Six months efficacy data is in line with China Food and Drug Administration (CFDA) requirements for injectable facial fillers of sodium hyaluronate.

The 5-grade validated WSRS tool[22] has been used in the other studies with acceptable inter- and intra-rater correlation. The scale is validated and it is accepted by US FDA for registration studies. CCI [redacted]

2.7 Risks and benefits

By January 2016, Restylane is regulatory cleared in more than 80 countries including the US and China, and Restylane Defyne, regulatory cleared under the brand name Emervel Deep Lidocain, in more than 50 countries. Both products are considered safe and effective for facial dermal tissue augmentation to correct NLFs.

Restylane and Restylane Defyne, as all other injectable medical devices, have the potential to cause complications. Most events are related to the injected volume and injection technique, though some could be associated with properties or constitutes of the gel itself. After the injection of Restylane Defyne and Restylane, some common injection-related reactions might occur. These reactions include bruising, erythema, swelling, pain, tenderness, or itching at the implant site. Typically, resolution is spontaneous within a few days after injection into the skin. The intensity and duration of these events are usually considered tolerable by a majority of subjects. The study products will be administered in accordance with the instructions in Section 6.6.1.

The primary potential benefit of the study is a perceived improvement in the visual appearance of the face, specifically the NLFs. However, there is a risk that the subject will not gain the full aesthetic correction of NLFs. There is also a risk for development of palpable lumps or displacement of the injected gel. Inflammation or infection have been reported in a few cases after HA filler treatment. There may be risk of damaging body structures such as nerves or blood vessels connected to the injection site, however these risks are minor. Detailed information on reported AEs relevant for Restylane Defyne and Restylane is provided in the Instruction for Use (IFU) as well as in the IB for Restylane Defyne.

Lidocaine can in rare cases give allergic reactions, and therefore subjects with known allergy or hypersensitivity to local anaesthetics should not be included in the study.

The frequency of post market AE reporting is based on the number of units sold. The reporting frequency of AEs assessed as related to Restylane and Restylane Defyne are ranging from seldom (approximately 1/1 000 – 1/10 000 events per sold unit) to rare/ isolated cases (i.e., <1/100 000 events per sold unit).

The risks related to HA filler injections for correction of wrinkles and folds have been judged to be low, based on nonclinical data (Section 2.4.1), experience from clinical studies (Section 2.4.2) and post-marketing data. Given the anticipated low level of transient and acceptable AEs in connection with the injection, the risk-benefit assessment of the use of Restylane Defyne and Restylane for corrections of NLFs appears to offer a clinical benefit at reasonable risk.

3 OBJECTIVE(S) AND ENDPOINT(S)

3.1 Objectives and endpoints

3.1.1 Primary objective and endpoint

The primary objective of the study is to evaluate the efficacy of Restylane Defyne compared to Restylane in correction of NLFs by comparing response rates based on the WSRS, as assessed by the blinded evaluator, at 6 months after last treatment.

A response rate is defined as percentage of subjects with at least 1 grade improvement on the WSRS. The non-inferiority of Restylane Defyne *versus* Restylane will be shown if the two-sided 95% confidence interval of their difference at 6 months after last treatment excludes an inferiority of 15% or more.

CCI

[redacted]

3.1.3 Safety Objectives

The safety objectives and endpoints are:

- To evaluate the safety of Restylane Defyne and Restylane during the whole study by collecting AEs.

CCI

[redacted]

4 DESIGN OF THE STUDY

4.1 General outline

This is a randomized, multi-center, evaluator-blinded study in China to evaluate the efficacy and safety profile associated with correction of moderate to severe nasolabial folds using Restylane Defyne (with lidocaine) compared to Restylane (without lidocaine). Blinding will be accomplished by a blinded evaluator, to whom randomization and treatment are concealed, to evaluate the wrinkle severity scale. The treating Investigator will not be blinded.

Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 21 days prior to study randomization on Day 1. Subsequent to screening, eligible subjects will be enrolled into the study.

Each subject will receive an initial treatment on Day 1 (baseline) with Restylane Defyne in one NLF and Restylane in the opposite NLF, as randomly assigned. The first injection will always start in the right NLF. CCI [redacted]

An optional second treatment (touch-up) will be offered 4 weeks after the initial treatment if optimal aesthetic improvement is not achieved, i.e., in subjects who did not improve ≥1 grade in WSRS in one or both NLFs as assessed by the blinded evaluator.

Restylane Defyne should be injected into the mid to deep dermis and Restylane should be injected into the middle part of the dermis layer of the facial skin in the NLF. For initial injections, it is recommended not to use more than 1.5 mL for each NLF and for touch-up injection it is recommended not to use more than 0.5 mL for each NLF. Administration of Restylane Defyne and Restylane will be performed by the treating Investigator according a standardized procedure described in Section 6.6.

After the treatment visits (initial and optional) there is a follow-up period of 12 months. Follow-up visits are scheduled at 4 weeks (±3 days), 3 months (±7 days), 6 months (±7 days), 9 months (±2 weeks), and 12 months (±2 weeks) after the last treatment for efficacy and safety assessments (Figure 1).

The aim of the treatment is to achieve optimal aesthetic improvement, defined as at least one (≥1) grade improvement from baseline on the WSRS, as assessed by the blinded evaluator. The blinded evaluator will evaluate the wrinkle severity using WSRS at baseline and at each follow-up visit for efficacy assessment.

CCI [redacted] The subjects will be photographed before treatment at the baseline visit and at the optional touch-up treatment visit as well as at each follow-up visit. The photographs will be used to document condition at baseline, CCI [redacted] and to document AEs in the treated area.

CCI [redacted]

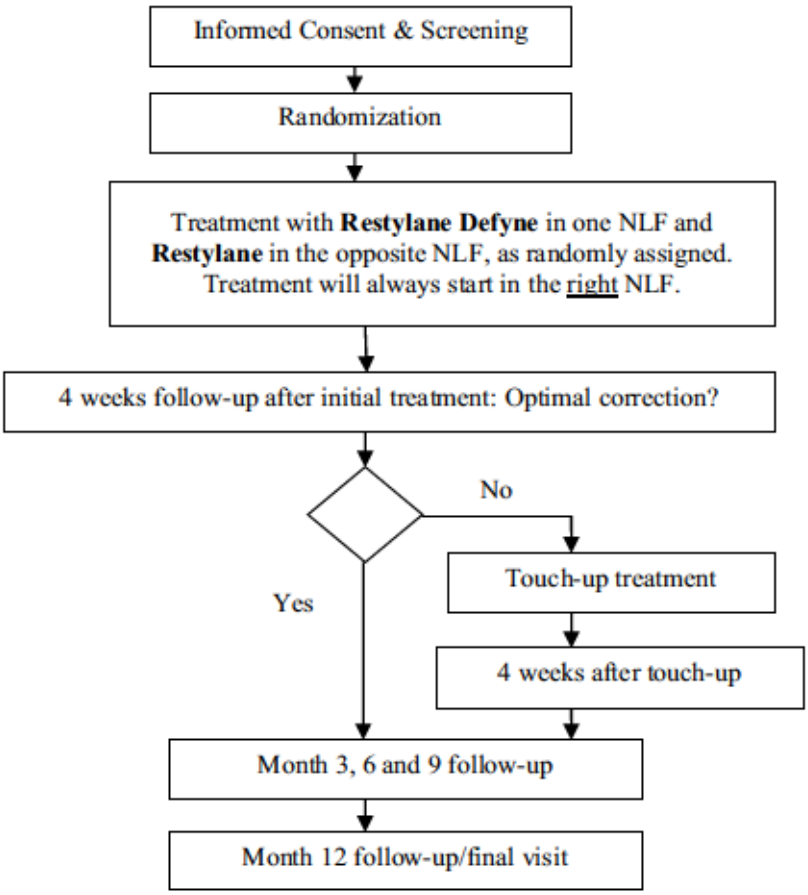


Figure 1. Flow chart: Study visits

CCI

Information regarding AEs will be collected continuously throughout the study from the signature of ICF at the screening visit. Device deficiency information will be collected after each treatment.

4.2 Number of subjects

The study will be performed at approximately 5 sites in China and approximately 175 subjects will be randomized and treated. Approximately 30 to 40 subjects are estimated to be enrolled per site.

4.3 Duration of subject participation

Subjects will be screened for eligibility within 21 days prior to study randomization on the baseline visit (Day 1). The study subjects will be treated at the baseline visit and thereafter followed for 12 months from the last treatment visit at either the initial (Day 1) or the

optional touch-up (Day 29) treatment visit. A subject will be involved in the study for up to 14.5 months.

End of study is when enrolment has reached the target number of subjects and all subjects have completed the last study visit.

4.4 Randomization and blinding

4.4.1 Randomization

Each subject will be randomized to one of two treatment sequences; either Restylane Defyne in the subject's right NLF followed by Restylane in the subject's left NLF, or Restylane in the subject's right NLF followed by Restylane Defyne in the subject's left NLF. Treatment will always start in the subject's right NLF. The randomization will be stratified by site and the randomization list will be computer generated under the supervision of a designated statistician.

Each subject will be assigned a subject number as they arrive for the treatment visit. Randomization will be assigned via the electronic case report form (eCRF) system when all inclusion criteria and exclusion criteria have been verified. At the time of randomization, the subject's initials, date, subject number, treatment sequence, and the signature of the Investigator must be documented in a randomization log. All treatment information will be kept by the treating Investigator during the study not to be disclosed to the blinded evaluator.

4.4.2 Blinding

Due to the differences in the physical characteristics (viscosity) of the study products and the difference in syringe design and material (size of syringe and plastic *vs* glass syringe), it is not possible to truly double-blind the study, and the treatment assignment cannot be obscured from the treating Investigator.

Because the method of administration is similar, the treatment can be masked from the subjects by simply preventing them from viewing the syringes during administration of the study products. This will be done by placing an opaque drape or patch over the subject's eyes during the injection procedure.

The blinded evaluator shall not be allowed to retrieve study supplies or to be present during opening of the study supplies or injections. The treating Investigator is not allowed to discuss treatments with the blinded evaluator or the subjects. All documents with information on study products shall be kept in a separate binder not available to the blinded evaluator. The blinded evaluator should not have access to eCRF pages with study product information.

The Sponsor and the Sponsor's representative at the site shall not be blinded during the study.

4.4.3 Emergency unblinding

Not applicable as the treating Investigator is unblinded.

4.5 Medical history

History of surgical events and medical conditions that are judged as relevant by the Investigator shall be documented in the eCRF using medical terminology.

4.6 Concomitant medications, treatments, and procedures

Except as noted below, concomitant medications or other treatments or procedures may be utilized when the PI or his/her authorized designee considers it medically necessary. Information regarding any use of concomitant medications, including over-the-counter medications administered during the study is to be recorded in the eCRF. The generic name or the trade name of all concomitant medication or a description of the procedure and the reason for its use shall be documented in the eCRF.

The following medications, treatments, and procedures are restricted or prohibited during the study:

- Anticoagulants or inhibitors of platelet aggregation (e.g., aspirin or other non-steroidal anti-inflammatory drugs [NSAIDs]), Omega-3, or Vitamin E should not be used within two (2) weeks before treatment to avoid increased bruising or bleeding at injection sites.

CCI [redacted]

- Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics e.g., certain anti-arrhythmics, since the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies) is prohibited.
- Long term concomitant treatment with systemic or topical (facial) corticosteroids is prohibited (inhaled corticoids are allowed). Corticosteroids should be used with caution and should be adjudged as necessary by the Investigator.
- Use of systemic or topical (facial) retinoic acid is prohibited.
- Procedures involving an active dermal response in the face below the lower orbital rim (e.g., tissue augmenting therapy, contouring or revitalization treatment with permanent or non-permanent fillers, permanent implant, mesotherapy, radiofrequency, fat-injection, neurotoxin, laser or light treatment, chemical peeling, or dermabrasion) are prohibited.
- Planned surgery including aesthetic facial surgical therapy or facial liposuction, sinus surgery or dental root surgery, or tattoo in the area to be treated is prohibited.
- Participation in any other clinical study is prohibited.

If a subject has used any of the above prohibited medications or performed any of the above prohibited procedures a protocol deviation should be documented and the subject should, for safety reasons, continue in the study for the scheduled follow-up visits.

4.7 Schedule of events

Table 1. Schedule of events

Activity	Screening[a]	Baseline[a] Initial treatment	Week 4 follow-up after Initial treatment/ Optional Touch-up treatment[b]	Week 4 follow-up after touch-up (for subjects who received touch-up)	Month 3, 6 and 9 follow-up	Month 12 follow-up / Final visit /Early termination
	Day -21 to 1	Day 1	Day 29 4 weeks (±3 days) after initial treatment	4 weeks (±3 days) after touch-up	3, 6 months (±7days) and 9 months (±2 weeks) after last treatment[c]	12 months (±2 weeks) after last treatment[c]
Informed consent	X					
Demography	X					
Medical history & concurrent diseases	X	X				
Concomitant medication/procedures	X	X	X	X	X	X
Vital signs		X				
Hematology	X					
Serum chemistry + Pregnancy Tests (S-HCG)	X					X
ECG	X					
Pregnancy test (U-HCG)		X[d,e]	X[d,e]			
Inclusion and Exclusion criteria	X	X				
Randomization		X				
Photography		X[f]	X[f]	X	X	X
Treatment		X	X[b]			
CCI						
WSRS (blinded evaluator)	X	X[g]	X[e]	X	X	X

Activity	Screening[a]	Baseline [a] Initial treatment	Week 4 follow-up after Initial treatment/ Optional Touch-up treatment[b]	Week 4 follow-up after touch-up (for subjects who received touch-up)	Month 3, 6 and 9 follow-up	Month 12 follow-Up / Final visit /Early termination
	Day -21 to 1	Day 1	Day 29 4 weeks (±3 days) after initial treatment	4 weeks (±3 days) after touch-up	3, 6 months (±7days) and 9 months (±2 weeks) after last treatment [c]	12 months (±2 weeks) after last treatment [c]
CCI						
Device deficiencies		X	X[h]			
CCI						
Assessment of Adverse Events		X	X	X	X	X
Study termination						X

a) Screening visit and baseline visit can be combined to one visit, if feasible.

b) Touch-up treatment may be performed for subjects who did not improve ≥1 grade in WSRS (in one or both NLFs, as assessed by the blinded evaluator). Touch-up treatment will not be performed without the subject's verbal consent, if there are ongoing treatment-related AEs or if optimal aesthetic improvement of both NLFs is already achieved.

c) Last treatment is either the initial treatment or the touch-up treatment.

d) A urine pregnancy test should be performed at the baseline visit, before treatment, if the screening visit and the first pregnancy test was performed ≥2 weeks before the baseline visit. A urine pregnancy test should be performed before treatment at the week 4 follow-up visit if touch-up is performed.

e) Prior to treatment, if treatment is performed.

f) Only pre-treatment

g) To obtain a baseline value, prior to treatment

h) Only to subject that receive the optional touch-up treatment

4.8 Visits

4.8.1 Screening (Day -21 to Day 1)

Study subject will be informed about the study and the risks and benefits of participating. Information will be given, both verbally and in writing, and the Informed Consent Form (ICF) will be signed and dated by the subject and the Investigator before performing any study related procedures. Inclusion and exclusion criteria will be checked and demographic data, relevant medical history as well as relevant ongoing medication will be collected by the Investigator. Screening laboratory tests and ECG will be performed in accordance to Sections 8.2 and 8.3 to verify exclusion criteria 19. The blinded evaluator will make a live assessment to evaluate the wrinkle severity using the WSRS to verify inclusion criteria 4. Collection of AE will start when the ICF has been signed by the subject.

- Obtain Informed consent
- Obtain demographic data (initials, date of birth, gender, and ethnic origin)
- Interview for medical history and concurrent diseases
- Interview for concomitant medications and procedures
- Perform serum pregnancy test for all women of childbearing potential
- Screening laboratory assessments (hematology and serum chemistry)
- ECG
- Assess WSRS (by blinded evaluator) to verify inclusion criteria 4
- Assess eligibility (inclusion and exclusion criteria)

If the subject meets all of the inclusion criteria and none of the exclusion criteria a baseline visit will be performed immediately or scheduled within the next 21 days.

4.8.2 Baseline Visit - Initial treatment (Day 1)

The baseline visit can be performed in direct connection with the screening visit or at the latest 21 days after the screening visit.

If the screening and baseline visits are separated, the inclusion and exclusion criteria will be re-checked and if any changes have occurred in the health status, concomitant medication and procedures will be assessed before the subject can be included in the study.

Further, vital signs will be assessed, standardized pre-treatment photograph will be taken as described in Section 7.5, and a pregnancy test (U-HCG) will be performed in women of childbearing potential. Before treatment, the blinded evaluator will make a live assessment to evaluate the wrinkle severity on WSRS to obtain a baseline value.

- Interview for medical history and concurrent diseases
- Interview for concomitant medications and treatments
- Vital signs (pulse rate, blood pressure, respiratory rate, and axillary temperature)

- Perform urine pregnancy test for all women of childbearing potential (if ≥2 weeks since the pregnancy test performed at the screening visit)
- Assess WSRS to obtain a baseline value (by blinded evaluator)
- Confirm eligibility criteria

For each eligible subject, one NLF will be randomly assigned to treatment with Restylane Defyne (with lidocaine) and the opposite NLF to treatment with Restylane (without lidocaine). Treatment will be administered according to the instructions in Section 6.6. Any device deficiencies or AEs since last visit, during or after the treatment will be reported. CCI [redacted]

- Randomize the subject and arrange for blinding of the subject
- Obtain a pre-treatment photograph (baseline)
- Perform treatment in the right NLF according to randomization (Section 6.6)

CCI [redacted]

- Perform treatment in the left NLF according to randomization (Section 6.6)

CCI [redacted]

- Interview for AE since last visit and evaluate the subject for post-treatment AEs
- Evaluate device deficiencies

4.8.3 Week 4 follow-up after initial treatment (Day 29 ± 3 days) / Optional touch-up

A follow-up visit will take place 4 weeks (D29 ± 3 days) after the initial treatment. An optional touch-up treatment may be performed if optimal aesthetic improvement was not obtained.

Standardized photographs will be taken, WSRS will be completed by the blinded evaluator, CCI [redacted] any AEs since the initial treatment or change in medications used will be reported.

- Assess WSRS (by blinded evaluator)
- Obtain photographs

CCI [redacted]

- Interview for concomitant medications and treatments
- Interview for AE

A touch-up treatment may be performed at this visit if optimal aesthetic improvement was not obtained, i.e., subjects who did not improve ≥1 grade on WSRS in one or both NLFs as assessed by the blinded evaluator. The touch-up treatment will not be performed without the subject's verbal consent, if there are ongoing treatment-related AEs, or if optimal aesthetic improvement is already achieved.

A pregnancy test (U-HCG) will be performed in women of childbearing potential before the touch-up treatment (described in Section 6.6). Device deficiencies and AEs in connection to the treatment will be reported. CCI [redacted] A second 4-week follow up visit should be scheduled.

- Perform urine pregnancy test for all women of childbearing potential
- Perform treatment (as initially randomized, start injection in the right NLF)

CCI [redacted]

- Evaluate the subject for post-treatment AEs
- Evaluate device deficiencies

4.8.4 Week 4 follow-up after touch-up treatment - only for subjects who received touch-up treatment (4 weeks ± 3 days)

A follow-up assessment will be performed 4 weeks after the touch-up treatment visit. Standardized photographs will be taken. WSRS will be completed by the blinded evaluator CCI [redacted] any AEs since last visit or change in medications used will be reported.

- Assess WSRS (by blinded evaluator)
- Obtain photographs

CCI [redacted]

- Interview for concomitant medications and treatments
- Interview for AE

4.8.5 Month 3 (±7 days), 6 (±7 days), and 9 (±2 weeks) follow-up

Follow-up visits will be performed 3 months ±7 days, 6 months ±7 days, and 9 months ±2 weeks after last treatment. Standardized photographs will be taken. WSRS will be completed by the blinded evaluator CCI [redacted]. Any AEs since last visit or change in medications used will be reported.

- Assess WSRS (by blinded evaluator)

- Obtain photographs

CCI [redacted]

- Interview for concomitant medications and treatments
- Interview for AE

4.8.6 Month 12 (±2 weeks) follow-up/ Final visit or Early termination

A final follow-up visit will be performed 12 months ±2 weeks after the last treatment visit. In the case of subject withdrawal between regular visits (Section 5.5) the subject should, when possible, be scheduled for an early termination visit.

Standardized photographs will be taken. WSRS will be completed by the blinded evaluator CCI [redacted]. Any AEs since last visit or change in medications used will be reported. A final pregnancy test (U-HCG) will be performed in women of childbearing potential.

- Perform serum pregnancy test for all women of childbearing potential
- Laboratory assessments (serum chemistry)
- Assess WSRS (by blinded evaluator)
- Obtain photographs

CCI [redacted]

- Interview for concomitant medications and treatments
- Interview for AE

5 SUBJECTS

5.1 Subject information and informed consent

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

It is the responsibility of the PI or his/her authorized designee to give each subject 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. The information should be given to the subject prior to inclusion in the study and should 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 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 effect on 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 informed consent form and to consider participation in the study. Before any study-related activities are performed, the informed consent form 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 countries outside China. The data will not contain any information that can be used to identify the 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 ICF shall be filed in the Investigator file. The subject shall be provided a copy of the signed and dated informed consent form and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study.

5.2 Inclusion criteria

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

1. Signed and dated informed consent to participate in the study.
2. Men or women aged 18 years of age or older of Chinese origin.
3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim for the duration of the study (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency etc.).
4. Intent to undergo correction of both NLFs with a wrinkle severity in WSRS of either 3 on both sides or 4 on both sides, as assessed by the blinded evaluator.

5.3 Exclusion criteria

The presence of any of the following exclusion criteria will exclude a subject from enrolment in the study:

1. Known/previous allergy or hypersensitivity to any injectable HA gel.
2. Known/previous allergy or hypersensitivity to local anesthetics, e.g., lidocaine or other amide-type anesthetics.
3. History of severe or multiple allergies manifested by anaphylaxis.
4. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, chemical peeling, or dermabrasion below the level of the lower orbital rim within 6 months before treatment.
5. Previous surgery (including aesthetic facial surgical therapy or liposuction) or tattoo in the area to be treated.
6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent facial tissue augmentation therapy or autologous fat or permanent implant 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 before treatment.
8. Previous use of neurotoxins below the level of the lower orbital rim (crow's feet line is acceptable) within 12 months before treatment.
9. History of radiation or cancerous or pre-cancerous lesions (e.g., actinic keratosis) in the area to be treated.
10. Scars or deformities, active skin disease, inflammation or related conditions such as infection, perioral dermatitis, seborrheic dermatitis, eczema, rosacea, acne, psoriasis, and herpes zoster near or in the area to be treated.
11. Subjects with dental or oral status on visual inspection that in the opinion of the Investigator would make the subject unsuitable for inclusion, or Subjects with dental, oral or sinus surgery within past 12 months prior to the treatment visit or planned surgery, including dental implants, during the study period.
12. Ongoing infection in mouth or dentals.
13. Chronic infection in head and neck region.
14. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis, or localized or systemic scleroderma.
15. Tendency to form keloids, hypertrophic scars, or any other healing disorder.
16. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation e.g., aspirin or other non-steroid anti-inflammatory drugs (NSAIDs), Omega-3, or vitamin E within 2 weeks before treatment.
17. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g,. monoclonal antibodies), systemic or topical (facial) corticosteroids within 3 months before treatment (inhaled corticoids are allowed).
18. Concomitant treatment with topical (facial) retinoids within 3 months or systemic retinoids within 6 months before treatment.
19. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion (e.g., porphyria, a chronic, relapsing or hereditary disease that may affect the general condition or may require frequent medical treatment, any abnormal screening laboratory value or ECG, or psychiatric disorders).
20. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g., subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments, or having unrealistic expectations of the treatment result.
21. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period.
22. Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.

23. Participation in any other clinical study within 30 days before treatment.

5.4 Screening and subject numbers

Each subject who has signed the ICF will be assigned a screening number and shall be listed on a subject screening and inclusion log. Each screened subject will be assigned a screening number consisting of "S" and the site number followed by a consecutive number starting with 01 at each site, e.g., S101, S102. The screening number shall be listed on a subject screening and inclusion log.

A "screening failure" is defined as a subject who does not fulfil the eligibility criteria. For screening failures, the eCRF screening visit shall be completed to an extent that makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria. The reason for excluding a subject from entering the study shall also be specified in the subject screening and inclusion log.

When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each enrolled subject will be assigned a subject number by the eCRF consisting of the site number followed by a consecutive number starting with 01 at each site, e.g., 101, 102 etc.

The subject number, subject name, and other information sufficient to link the eCRF to the medical records (e.g., national identification number, chart number, etc.) shall be recorded on a subject identification list. The subject identification list shall only be available at the site, both throughout and after the study.

5.5 Withdrawal of subjects

Each subject shall be advised in the informed consent form that he/she has the right to withdraw from the study at any time, for any reason, without prejudice. Subjects may also be discontinued from this study if the Investigator determines that it is in the subject's best interest to do so, and may be withdrawn at the Investigator's discretion at any time.

The withdrawal criteria are:

- **Medical reasons**: If the subject suffers from a medical condition 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 shall document the specific condition for withdrawing the subject.
- **Subject request**: 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, e.g., call three times at different hours and leave messages, if applicable, or confirm with two 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, e.g., failure to comply with protocol requirements or to complete the protocol-specified evaluations.

The reason and date for withdrawal shall be documented in the eCRF. When possible, an explanatory comment shall be added in the study termination module/pages to further explain the reason for withdrawal. If withdrawal of a subject occurs during a regular study visit, the eCRF for that specific visit shall be completed as far as possible together with the study termination eCRF module and a final pregnancy test (U-HCG) will be done in women of childbearing potential.

If withdrawal of a subject occurs between regular study visits the subject should, when possible (irrespective of the reason for withdrawal), be scheduled for a termination visit. In these cases the eCRF for early termination visit should be completed.

If a subject is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses.

A withdrawn or discontinued subject must not be replaced or re-entered into the study.

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 please refer to Section 8.4.6.

6 STUDY PRODUCTS

The term "study products" refers to Restylane Defyne and Restylane. Both Restylane Defyne and Restylane will be supplied by the Sponsor.

6.1 Investigational product

Restylane Defyne (with lidocaine) is a sterilized injectable gel consisting of stabilized HA of non-animal origin with the addition of 3 mg lidocaine hydrochloride per mL. The product contains 20 mg/mL HA in a physiological phosphate buffer system. The gel is transparent and colorless. The product is supplied in a prefilled plastic syringe with a luer-lock fitting. Two 27G × ½" ultra-thin wall needles are packed together with each Restylane Defyne syringe. The syringe, containing 1 mL gel, is labeled and packaged in a blister. The investigational product is for single use only.

Commercial Restylane Defyne produced for the EU market will be provided to the sites and detailed product information is available in the IB and the instructions for use (IFU) (Appendix 2).

6.2 Reference product

Restylane is a sterilized injectable gel consisting of stabilized HA of non-animal origin with a concentration of 20 mg/mL in phosphate buffered saline. The gel is transparent and colorless. The product is supplied in single use glass syringe with a luer-lock fitting. Two 30G × ½" needles are packed together with each Restylane. The syringe, containing 1 mL gel, is labeled and packaged in a blister. The product is for single use only.

The reference product is commercial product intended for the Chinese market. An IFU is included in the carton and also available in Appendix 3.

6.3 Additional products and material

Restylane Defyne and Restylane, pre-packed in blister with two needles, will be supplied by the Sponsor.

Any other additional products required for the study, e.g., topical or local anaesthetic, pain relief, and adequate medical equipment in case of clinical emergency will be supplied by the Investigator.

6.4 Packaging, labelling, and storage

Restylane Defyne (with lidocaine) and Restylane (without lidocaine) are manufactured by Q-Med AB, Uppsala, Sweden, who will supply the study products. Restylane Defyne, the investigational product, is CE-marked, i.e., commercial product intended for the EU-market. The reference product, Restylane, is commercial product intended for the Chinese market. Commercial Restylane Defyne intended for the EU market and commercial Restylane intended for the Chinese market will be used in the study.

The syringes are labelled with name of the product and the name of the manufacturer (Q-Med AB). The syringes in its blister are packed in a carton. The carton will be labelled in local language, specifying the Sponsor name, protocol number, lot number, expiry date and that the product is to be used for clinical studies exclusively.

The study products should be stored at a temperature up to 25ºC and protected from sunlight and freezing. Opened syringes should not be re-used. The expiry date is indicated on package.

6.5 Product accountability

The study products will be released to the PI or his/her authorized designee after study approvals have been received from the IEC and other relevant authorities/institutions, as applicable, and the 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(s) 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, dispense date, the number of syringes used/amount dispensed, the subject receiving study product, and number of syringes left in stock at the site. A log for accountability procedure is provided by the Sponsor.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor or a third-party vendor for destruction or be destroyed locally at the site, with proper documentation, after agreement with the Sponsor. Any malfunctioning study products shall be reported as described in Section 8.5.3.

Products deliberately or accidentally destroyed during shipment or at a study site shall be accounted for and documented. Used syringes, disposable needle 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. The study products must not be used outside the study.

6.6 Treatment

6.6.1 Treatment procedure

The subjects will be informed about the indications, expected result, precautions, and potential AEs.

Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections should be observed at all times including the use of disposable gloves during the injection procedure. The subject should not wear make-up on the day of treatment, if make-up was already applied this must be completely removed prior to any injection. The treatment site should be thoroughly cleaned at least twice with a suitable antiseptic solution.

The treating Investigator will confirm randomization *via* the eCRF system for study products i.e., the NLF on one side of the face will be randomly assigned to treatment with Restylane Defyne and the opposite NLF to treatment with Restylane. Treatment will always start in the subject's right NLF. Restylane Defyne should be injected into the mid to deep dermis of the facial skin in the NLF and Restylane should be injected into the middle part of the dermis layer of the facial skin in the NLF.

The treating Investigator should keep the subject blind to the treatment by placing an opaque drape or patch over the subject's eyes during the time that the injections are administered. The details regarding randomization and blinding of subjects and blinded evaluator are in Section 4.4.

To avoid breakage of the needle, no attempt to bend or otherwise manipulate the needle before or during treatment is recommended. Before injecting, the air should be removed by pressing the rod carefully until a small droplet is visible at the tip of the needle. Aspiration prior to injection in order to avoid accidental intravascular injection is recommended. The linear threading technique can be used to carefully lift up the wrinkle. The injection technique should be the same for both sides of the face in any one subject to limit variability due to technique. Both products should be injected slowly while pulling the needle backwards. Injection should stop just before the needle is pulled out from the skin to prevent material from leaking out from the injection site. 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. Separate sterile needles should be used for each NLF. The injection sites may be gently massaged CCI [redacted] by the treating Investigator to conform the contour of the surrounding tissue.

At the initial treatment visit (Day 1) subjects should assess the pain experienced during treatment. CCI [redacted] In order to be able to

evaluate the pain of injection, separated from the pain of the needle insertion alone, a pause of 3 to 5 second is required after insertion of the needle before starting the injection. Both products should be injected slowly as injection pace could affect the pain experienced; the time required for each injection will be recorded in the eCRF. CCI [redacted]

The injection procedure for the two NLFs will be standardized as far as possible in terms of volume, time required for injection, depth of injection, and injection technique and will be recorded in the eCRF.

6.6.2 Treatment regimen (dose and interval)

The recommended maximum volume for each NLF at the initial treatment and the touch-up treatment combined is 2.0 mL gel.

6.6.2.1 Initial treatment

For initial injection, it is recommended not to use more than 1.5 mL for each NLF. The aim of the treatment is to achieve optimal correction of each NLF, defects should be fully corrected but not overcorrected. CCI [redacted]

CCI [redacted]

6.6.2.2 Touch-up treatment

A touch-up treatment may be performed four weeks after the initial treatment if optimal correction has not been achieved, as assessed by the blinded valuator. If a touch-up is performed it should preferably be performed in both NLFs. For subsequent touch-up treatment, it is recommended not to use more than 0.5 mL for each NLF. It is of outmost importance that the subject receives the same product as received at the initial treatment in respective NLF.

Topical or local anesthetic or other pain-relieving medication, including ice, may be used before and after touch-up treatment.

Touch-up will not be performed without the subject's verbal consent, if there are ongoing treatment-related AEs, or if optimal aesthetic improvement is already achieved.

6.6.3 Post-treatment care

Ice in appropriate packaging "ice-pack" can be applied on the treatment site for a short period to reduce swelling and discomfort. CCI [redacted]

After the injection, some common injection-related reactions might occur. These reactions include bruising, erythema, swelling, pain, tenderness, and itching at the implant site. Typically resolution is spontaneous within a few days. The patient must avoid exposing the treated area to heat (sun bathing, sauna, steam baths, etc.) or extreme cold least until any initial swelling and erythema has resolved. In order to prevent infections, the subject should avoid touching the treated area and no creams or cosmetics should be applied before the skin has healed completely.

6.6.4 Post-trial provisions

After the study is finalized Sponsor will not supply any more treatments to the subjects, even if the result does not persist.

6.6.5 Electronic case report form recordings

The following details of the injection at initial treatment and touch-up, if applicable, are to be recorded in the eCRF:

- Date for administration
- Time required for each injection, only recorded at the initial treatment visit
- Administered volume per NLF (by scale on syringe)
- Injection technique (linear threading or other)
- Depth of injection per NLF (mid dermis, deep dermis, or other)
- Lot number
- Post-treatment care (massage, ice-pack, or other)
- Local anaesthetic used at touch-up treatment (product name, volume injected/amount applied, and concentration)

In addition, any technical problems (device deficiencies) or clinical complications (AEs) associated with the injection will be recorded in the eCRF.

6.6.6 Treatment compliance

The treatment is an implant administered by the treating Investigator and the details of the administration are recorded in the eCRF. No other measurements of treatment compliance will be made.

7 EFFICACY ASSESSMENTS

7.1 General information

The methods for collecting efficacy data include assessment of WSRS[22] (Section 7.2), CCI [redacted], and photography (Section 7.5). A description of the laboratory assessments is given in Section 8.2 and the ECG assessment in Section 8.3.

Assessments will be performed [redacted] the blinded evaluator, as described in the respective section.

To avoid 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.

7.2 Wrinkle severity rating scale

The WSRS is a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds (Table 2). Scoring of fold severity is based on visual assessment of the length and apparent depth of the NLF at a certain time-point and the result is not based on a comparison to the baseline or pre-treatment appearance. Each score in the WSRS is exemplified by a photograph of NLFs[22] (Appendix 4).

Live assessments will be performed through-out the study.

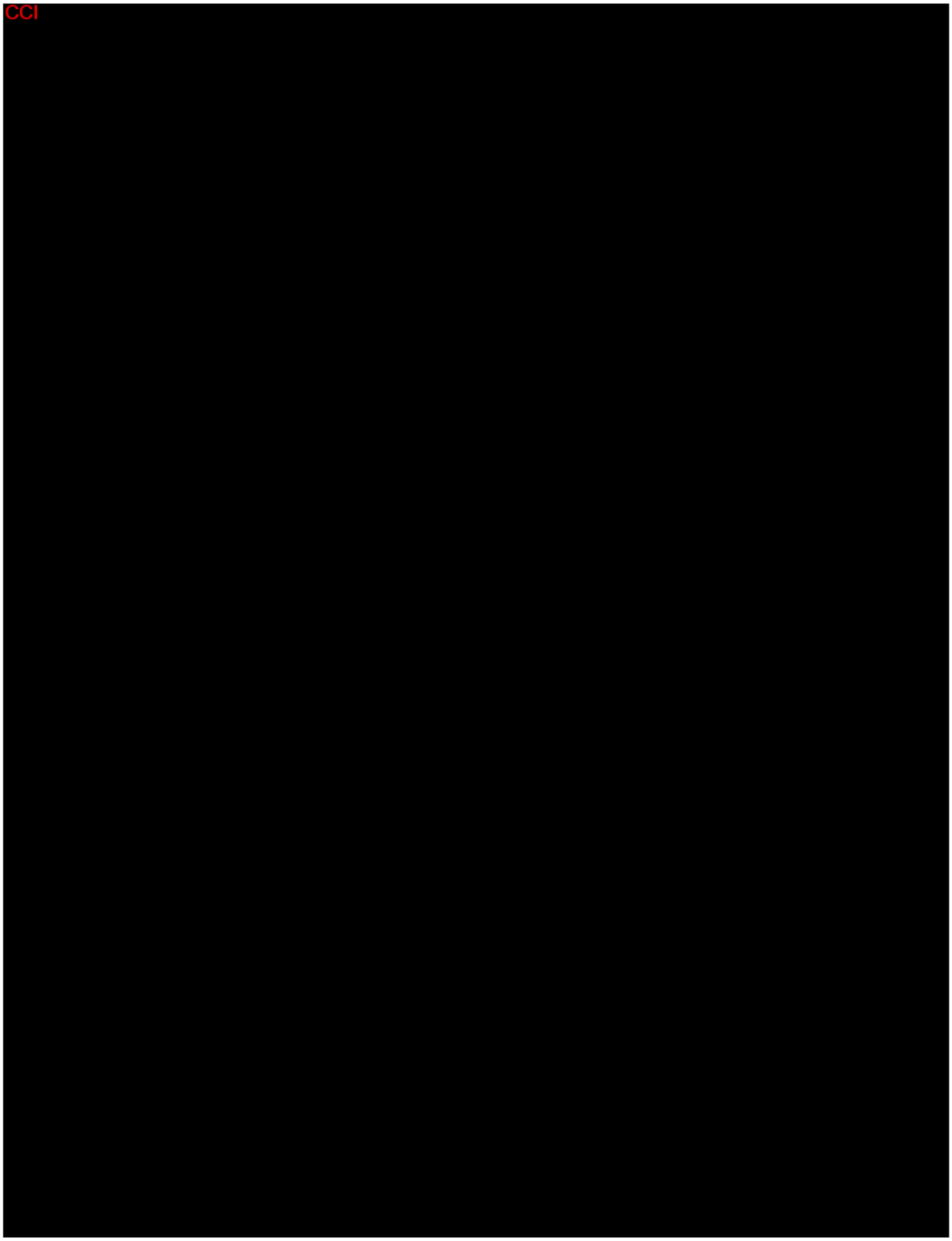
Table 2. Wrinkle severity rating scale

Grade	Description
1	**Absent:** No visible fold; continuous skin line.
2	**Mild:** Shallow but visible fold with a slight indentation; minor facial feature. Implant is expected to produce a slight improvement in appearance.
3	**Moderate:** Moderately deep folds; clear facial feature visible at normal appearance but not when stretched. Excellent correction is expected from injectable implant.
4	**Severe:** Very long and deep folds; prominent facial feature; less than 2-mm visible fold when stretched. Significant improvement is expected from injectable implant.
5	**Extreme:** Extremely deep and long folds; detrimental to facial appearance; 2- to 4-mm visible V-shaped fold when stretched. Unlikely to have satisfactory correction with injectable implant alone.

The blinded evaluator will evaluate WSRS at the screening and baseline visits to verify inclusion criteria 4 and further evaluate the WSRS before the initial treatment. The WSRS will also be assessed by the blinded evaluator at each follow-up visit (4 weeks after initial treatment and touch-up, if applicable, as well as 3, 6, 9, and 12 month after the last treatment) for efficacy assessment. At the Week 4 follow-up visit after the initial treatment, the WSRS assessment will be used for treatment guidance, e.g., to decide if touch-up treatment should be performed. A clinically significant improvement is defined as ≥1 grade improvement in the WSRS.

Each NLF (right/left) will be evaluated separately, thus generating two wrinkle severity score results per subject. A subject should preferably be assessed by the same blinded evaluator throughout the entire study.

When treatment is administered at the same visit as the WSRS assessment, it is important to asses wrinkle severity prior to injection.



7.5 Photography

Digital photographs will be taken of each subject pre-treatment at visits when treatment is performed and at each follow-up visit. The photographs will be used to document condition at baseline, CCI and to document AEs in the treated area. If necessary, the photo should be taken when AEs occur. Note that no covering make-up should be used on the photographs.

Each Investigator and other study site personnel designated to take photographs, if applicable, shall be thoroughly trained in the equipment and techniques, and how to upload photographs to the secured web portal, if applicable, before study start. The same photographic equipment and standardized setting must be used at each visit (e.g., distance, light, facial position and expression). For further details, please see the instruction of image procedures in the photo user guide

All photos should be taken from a straight frontal view with full face frame. The subject shall have a neutral facial expression.

Each photograph shall be labelled with the subject initials, subject number, as well as the visit ID and visit date at which the photograph was taken. In order to maintain confidentiality, the photographs must not include any information that may reveal the subject's identity.

8 SAFETY ASSESSMENTS

8.2 Laboratory assessments

Both the hematology and the serum chemistry laboratory assessments including S-HCG will be performed at the screening visit (Day -21 to Day 1). Serum chemistry laboratory assessments and S-HCG will also be performed at the Month 12 follow-up or Early termination visit:

Laboratory assessments:

- Hematology: hemoglobin, red blood cells, white blood cells, differential count and platelet count.
- Serum chemistry: renal function tests (creatinine and BUN); and liver function tests (aspartate amino transferase (ASAT), alanine amino transferase (ALAT) total bilirubin, direct bilirubin, and indirect bilirubin).

The results from the laboratory assessments at the screening visit will be used for screening purposes by the Investigator. No laboratory results will be reported in the eCRF, however, the dates will be recorded in the eCRF.

A serum pregnancy test (S-HCG) in women of childbearing potential will be performed at screening and at the 12 month follow-up or early termination visit. A urine pregnancy test (U-HCG) in women of childbearing potential will be performed prior to the baseline treatment, if the screening serum pregnancy test was done ≥2 weeks before the baseline visit, as well as prior to touch-up treatment. The pregnancy tests will be recorded in the eCRF.

Other laboratory test might be performed at the discretion of the investigator. All laboratory assays will be performed at a local laboratory. Reference ranges will be supplied by the laboratory and used by the Investigator to assess the laboratory data for clinical significance and out of range pathological changes.

Any clinical significant abnormal laboratory values at the 12 month follow-up or early termination visit will be reported as AEs in the eCRF.

8.3 ECG-screening

ECG will be taken at the screening visit (Day -21 to Day 1) and assessed by the Investigator for clinical significance. The results of ECG will only be used for screening purposes and will not be collected in the eCRF.

8.4 Adverse events

8.4.1 Definition of an adverse event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons[23], whether or not related to the study product.

This definition includes:

- events related to the investigational product or the reference product
- events related to the procedures involved

8.4.2 Definition of a serious adverse event

A serious adverse event (SAE) is an AE that:

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening[24] illness or injury, or
  - a permanent impairment of a body structure or body function, or
  - in-patient or prolonged hospitalization[25], or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- led to foetal distress, foetal death, or a congenital abnormality or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (Section 8.4.4).

8.4.3 Recording instructions

Each subject should be questioned about AEs at each study visit following the screening visit. The question asked should be: "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, CCI [redacted] spontaneous reports from the subjects.

CCI [redacted]

When an AE is related to a device deficiency (refer to Section 8.5), 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)

- Description of event and affected area (if applicable)
- Start date (first day with symptoms)
- Stop date (last day with symptoms)
- Intensity (mild, moderate, or severe according to definition in Section 8.4.3.1)
- Seriousness (serious or not serious, according to definition in Section 8.4.3.2)
- 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)

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

8.4.3.1 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.

8.4.3.2 Causal relationship and seriousness

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

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

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

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

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

8.4.4 Reporting of adverse events

Adverse event reporting on each subject shall start after the ICF has been signed at the screening visit. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

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

8.4.5 Reporting of serious adverse events

The Investigator should report any **SAE** to the Sponsor and relevant authorities **immediately but not later than 24 hours of awareness of the event**.

The initial report to the Sponsor will be made in the eCRF system. If there are difficulties accessing the eCRF, the SAE report could be sent to the Sponsor via email or fax.

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:

- Clinical trial number (CTN)
- Subject identification (age, gender, subject number)
- AE description
- Date when AE occurred
- Date when AE became serious
- Name of PI and original reporter (if other than the PI)
- Name of study product
- Treatment specification

Supporting documentation to be provided with the SAE report:

- Concomitant medication form/list
- Concomitant procedure/treatment form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

E-mail for SAE reporting: complaints.q-med@galderma.com

Fax number for SAE reporting: +46 18 474 91 01

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

Surface mail for providing complementary information:
Q-Med AB
Attn. Complaints QA
Seminariegatan 21
SE-752 28 UPPSALA, Sweden

In addition, according to national regulation, the Investigator should report any **SAE** event using the CFDA SAE form to the administrative department of medical device clinical trials, who will report **within 24 hours of awareness** to the:

- Food and Drug Administration (FDA) of province, autonomous region, or municipality where the site is located (local FDA)
- Commission of Health and Family Planning of province or autonomous region or municipality where the site is located
- Responsible IEC

A copy of the initial CFDA SAE report should be sent to Sponsor by e-mail or fax and one copy should be kept at the study site. Contact details to local FDA and Commission of Health and Family Planning of province or autonomous region or municipality where the site is located should be available at the study sites.

The Investigator is responsible for confirming the reporting procedures applicable at his/her IEC regarding SAEs and to comply with such reporting procedures during the study period. The specific contact details to each IEC should be available at the study sites.

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported 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. Any follow-up information should be reported by the Investigator in the eCRF or faxed/e-mailed to the Sponsor if there are difficulties in accessing the eCRF system. The Investigator should also send a follow-up report via the administrative department of medical device clinical trials to the local FDA, local Commission of Health and Family Planning, and IEC in accordance with local regulations. The Investigator will assure completeness of the SAE information and the supporting documentation. A copy of the fully completed SAE and CFDA SAE forms should be kept at the site.

The Sponsor is in addition to the Investigator responsible for reporting all SAE and device deficiencies with the likelihood of SAE, within 5 business days upon being informed to the Shanghai Municipal Food and Drug Administration and Shanghai Municipal Commission of Health and Family Planning. Sponsor should also notify other clinical trial institutions and investigators participating in the study, who promptly should report to their local IRB/IEC.

8.4.6 Follow-up of unresolved events after 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, shall be followed up after the subject's participation in the study is over. Such events shall be followed-up after the last study visit until resolved, assessed as chronic or stable, or for at least 3 months. Final outcome after the end of the study shall be reported on the AE follow up module in the eCRF.

8.4.7 Pregnancy

Pregnancy in 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 in the eCRF within 24 hours after the Investigator's awareness. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports. If outcome information becomes available after study completion, the Investigator shall complete a hard copy of the pregnancy report form and forward to the Sponsor.

Cases that led to foetal distress, foetal 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 Investigators awareness in accordance with Section 8.4.5. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

A copy of the fully completed pregnancy form and exposure in utero form should be kept at the site.

8.4.8 Anticipated adverse events

After the injection some common injection-related reactions might occur with both products. These reactions include bruising, erythema, swelling, pain, tenderness and itching at the injections site. Typically these reactions start on the day of treatment and resolve spontaneous within a few days after injection. This is in line with what has been observed in the Chinese clinical study for Restylane and is also consistent with international clinical study results for Restylane and Restylane Defyne.

Refer to the Restylane Defyne IB and EU IFU (Appendix 2) as well as the Restylane China IFU (Appendix 3).

8.5 Device deficiencies

8.5.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety[26], or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

8.5.2 Recording instructions

When a device deficiency is discovered the Clinical Study Complaint Form in the eCRF shall be completed by the Investigator. The type of complaint shall be described and injury to the subject, user or, unintended exposure to study product shall be reported, as applicable. If an injury has occurred, an AE module or an SAE form shall be completed following instructions in Section 8.4. 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

The Sponsor will make the same assessment the Clinical Study Complaint Form.

8.5.3 Reporting of device deficiencies

The Investigator shall complete the Clinical Study Complaint Form in the eCRF. A device deficiency that led to an SAE and any device deficiency that could have led to an SAE shall be reported within 24 hours after the Investigator's awareness in accordance with Section 8.4.5. In order to fulfil regulatory reporting requirements, all deficiencies with the study product must be assessed by both the Investigator and the Sponsor to determine if it could have led to an SAE.

If an SAE has resulted from a device deficiency or if either the Investigator or the Sponsor assesses that the device deficiency could have led to an SAE the event will be reported in accordance with Regulatory requirements, as applicable.

The deficient study product shall be kept, if applicable, by the study site until the Quality Assurance (QA) complaints group has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study site.

8.6 Data safety monitoring board (Not Applicable)

Not Applicable for this study.

9 DATA HANDLING AND MANAGEMENT

9.1 Data management

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 handling eCRFs, 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. 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 (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

9.2 Electronic case report forms

An eCRF is required and shall be completed electronically for each screened subject (screening visit) and included subjects (subsequent visits).

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 shall 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 PI shall complete data collection. Appropriate training and security measures shall be completed with all authorized study 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 shall not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study site as part of the Investigator file.

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

9.2.1 Data entry

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. Forms that will be completed by the subject CCI [redacted] should be translated into local language. The data will be translated and entered into the eCRF in English by the treating Investigator or delegated study site personnel. 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.

9.2.2 The query process

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 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.

9.2.3 User identification

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

9.2.4 Audit trail

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.

9.3 Source documents

The eCRF is essentially considered a data entry form and does not constitute the original (or source) medical records unless otherwise specified. 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 PI is responsible for maintaining source documents. These shall 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 photographs, shall be clearly identified with the CTN, subject number, and visit ID. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

9.4 Record keeping and access to source data

The PI/Institution shall permit study-related monitoring, audits, IEC review, and RA inspections and shall 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 shall be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records shall be documented and the Sponsor shall be informed in writing.

The Sponsor shall 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.

The source data location log specifies what data that shall be available in the medical record. The source data location log shall also specify the data for which the eCRF serves as the source. Such data only need to be recorded in the eCRF and are typically associated with study-specific procedures and not with normal clinical care practice. For this type of study data the Investigator would not be expected to duplicate the information into the medical record.

9.5 Document and data retention

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 after study completion according to national legislation and the CTA. Sponsor will inform the sites as to when these documents no longer needs to be retained. Measures shall 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). Refer to the CTA.

After study completion and database lock, a security sealed CD with electronic study data shall be provided by the eCRF vendor for archiving.

It is the PI's responsibility to inform Q-Med AB in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

10 STATISTICAL METHODS

10.1 General

All statistical analyses, including summary tables and data listings, will be performed using SAS®. Confidence intervals and p-values will be two-sided and performed at a significance level of 5%.

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.

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be written and finalized prior to database lock.

10.2 Analysis populations

The following populations will be defined:

- Safety — Includes all subjects who were injected in at least one NLF, based on the as treated principle.
- Full Analysis Set (FAS) — Includes all subjects who were injected in both NLFs. Subjects are analyzed according to the randomization assignment.
- Per protocol (PP) — Includes all FAS subjects who completed the Month 6 follow-up visit without any major deviations.

The FAS population is the primary population for all efficacy analyses. If there are any CSP deviations considered to have substantial impact on the efficacy outcome at the Month 6 follow-up visit, a PP population excluding those subjects will be defined. A detailed list containing such deviations will be included in the SAP. As this is a non-inferiority trial, non-inferiority will need to be shown in both FAS and PP analyses. Safety analysis is 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.

10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints and subject characteristics will be presented by study product using descriptive statistics.

10.4 Efficacy analysis

10.4.1 Primary analysis

Non-inferiority testing for Restylane Defyne relative to Restylane will be based on the 95% confidence interval approach with a non-inferiority margin of 15%. The confidence interval will be constructed for the difference (Restylane minus Restylane Defyne) in response rates at the 6 month follow-up visit. Non-inferiority will be declared if the two-sided 95% interval is fully below 15%, i.e., the upper bound of the interval is less than 15% in both the FAS and PP populations.

10.5 Safety analysis

All AEs will be coded according to MedDRA. All adverse events will be summarized by system organ class (SOC) and preferred term (PT). The same summaries will be generated for related AEs, severe AEs, AEs leading to discontinuation, and SAEs. 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 statistics.

10.6 Handling of missing data

As the study design is intra-individual, in which the outcome of both treatments to be compared is available on each subject, it is expected that when a data is missing, it will be missing for both NLFs in most of the cases. A majority of the deviations from the protocol can be expected to affect both NLFs and evaluations of the same subject the same way.

FAS analyses of WSRS will use multiple imputation method (MIM) as the primary method for imputing missing values. Rather than imputing each missing observation by a single value, this approach represents a random sample of the missing values, and therefore accounts for the prediction uncertainty of the unknown missing values.

Safety and PP analyses will be presented based on observed cases, i.e., no imputation of missing values will be performed.

10.7 Interim analysis (Not Applicable)

No interim analysis is planned.

10.8 Data monitoring committee (Not Applicable)

Not applicable in this study.

10.9 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 CSP deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to database lock.

10.10 Sample size

11 PROTECTION OF PERSONAL DATA

The study shall follow the requirements as specified in People's Republic of China (PRC) Provisions for Clinical Trials of Medical Devices with respect to the processing and protection of personal data. For the purposes of the study, Sponsor will be considered the data controller, and the Institution and PI will both be considered data processors.
All processing of personal data and photos must be carried out in accordance with national legislation concerning the protection of personal data and photos. The Institution and the PI are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and the PI are located. The Sponsor will ensure that all

requirements are complied with for data processing, which is carried out in Sweden by the Sponsor.

The informed consent form shall contain information about what personal data and photos to be collected in the study and that this will be kept confidential. The provided information shall be sufficient to enable all subjects to give their consent not only to the participation in the study, but also to the processing of personal data and photos. Such information includes information regarding the purposes of the collection, processing, data transfer to countries outside China, and the length of time during which personal data will be stored. The subject shall have the right of access to stored personal data, and the right to correction of incorrect information. If a subject decides to discontinue the study prematurely, data collected before withdraw of consent will be used in the evaluation of the study, however no new data may be collected. Authorized representatives from the Sponsor, clinical research organization (CRO) or a RA may visit the study site to perform audits/inspections, including source data verification, i.e., comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Quality control

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.

Any CSP deviation shall be reported in the eCRF which will be verified, discussed, and collected by the monitor and appropriate corrective and preventive actions will be taken. 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 as well as the IEC if required by national regulations. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations will be performed as described in the monitoring manual.

12.2 Quality assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the PI and other relevant study 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. The CV shall give name, date and place of birth, address and place of work, and shall show the training, appointments and, for the PI, any other information that will confirm the suitability of the PI to be responsible for the study.

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.

12.3 Changes to the clinical study protocol

The PI and other site personnel involved in the study must not implement any deviation from, or changes to, the CSP without agreement with the Sponsor and prior review and documented approval from the IEC, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a written protocol amendment. However, administrative changes are to be documented in the Sponsor file without requiring a protocol amendment.

13 FINANCING, INDEMNIFICATION, AND INSURANCE

The CTA 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. Q-Med AB'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.

14 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[28]. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

15 SUSPENSION OR PREMATURE TERMINATION

The Sponsor will suspend or terminate the study when so instructed by the IEC or RA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrolment or non-compliance with the CSP, 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.

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23. For users or other persons, this definition is restricted to events related to the investigational product.
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25. 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).
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APPENDICES

Appendix 1 Declaration of Helsinki
Appendix 2 Instruction for Use Restylane Defyne
Appendix 3 Instruction for Use Restylane China
Appendix 4 Photo guide for Wrinkle Severity Rating Scale (WSRS)

Appendix 1 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2 Instructions for Use Restylane Defyne

(Extract from QMS-8662 version 3.0)

INSTRUCTIONS FOR USE (EN)

I. COMPOSITION

Cross-linked hyaluronic acid	20 mg/mL
Lidocaine hydrochloride	3 mg/mL
Phosphate buffered saline pH 7	qs ad 1 mL

II. DESCRIPTION

Restylane® Defyne™ is a sterile, biodegradable, transparent gel of non-animal cross-linked hyaluronic acid with the addition of lidocaine hydrochloride 3 mg/mL. The gel is supplied in a prefilled plastic syringe. The contents of the syringe are sterilized using moist heat. The syringe is packaged individually in a blister, with two 27G x ½" Ultra thin wall needles. The needles have been sterilized using irradiation. The product is for single use only. To ensure traceability the package includes patient record labels that should be attached to patient records.

III. INTENDED USE

The product is intended to augment the volume of facial tissues. It is recommended to be used for correction of severe wrinkles, or to redefine the shape of the lips, cheeks or tear troughs. Depending on the area to be treated and the tissue support, the product should be injected in the mid to deep dermis, submucosal layer of the lips, subcutis or supraperiostic zone. Lidocaine is added to the formulation to diminish the pain resulting from the injection during the treatment.

The product is only intended to be used by authorized personnel in accordance with local legislation, trained in the appropriate injection techniques. Before the first treatment session, it is recommended to contact your local Galderma representative or Restylane distributor for information about training opportunities.

IV. MODE OF ACTION

The product adds volume to the tissue thereby restoring the skin contours of the face to the desired level. The volume and lifting capacity originate from the ability of cross-linked hyaluronic acid to bind water.

V. CONTRAINDICATIONS

- Patients presenting with known allergy to hyaluronic acid filler or amide local anaesthetics
- Patients presenting with porphyria

VI. WARNINGS

- Do not use where there is active disease, such as inflammation, infection or tumours, in or near the intended treatment site.
- Do not inject intravascularly. As for other injectable medical devices, inadvertent injection into or next to blood vessels could potentially lead to vascular occlusion or compression, ischemia and necrosis.
- Do not use in patients with bleeding disorders or in patients who are taking thrombolytics or anticoagulants.
- Do not inject this product into an area where an implant other than hyaluronic acid has been placed.
- Do not resterilize.
- Do not mix with other products.

VII. PRECAUTIONS FOR USE

General considerations relevant to injectable medical devices

- Knowledge of the anatomy of treatment site and special caution are required in order to avoid perforation or compression of vessels, nerves and other vulnerable structures.
- Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections are to be observed.
- Special caution should be exercised when treating areas with limited collateral circulation, due to increased risk of ischemia.
- Special caution should be exercised in treating facial areas with limited soft tissue support or soft tissue cover, such as the periorbital area, to avoid formation of palpable lumps.
- Patients with pre-existing pigmented dark lower eye lid circles, thin skin and pre-existing tendency toward oedema formation are not suitable candidates for treatment of the lower periorbital region.
- Patients using immunosuppressants are not suitable candidates for treatment.
- Special caution should be exercised in treating patients with a tendency to form hypertrophic scars or any other healing disorders.
- Injection procedures can lead to reactivation of latent or subclinical herpes viral infections.
- Patients who are using substances that affect platelet function, such as aspirin and nonsteroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.
- Patients with unattainable expectations are not suitable candidates for treatment.
- Do not use the product if the package is damaged.

- Do not use the product if the contents of the syringe are cloudy.

Specific considerations relevant to the use of this product

- Considerations should be given to the total dose of lidocaine administered if dental block or topical administration of lidocaine is used concurrently. High doses of lidocaine (more than 400 mg) can cause acute toxic reactions manifesting as symptoms affecting the central nervous system and cardiac conduction.
- Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g., certain anti-arrhythmics, since the systemic toxic effects can be additive.
- Lidocaine should be used cautiously in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function or severe renal dysfunction.
- If the product is injected too superficially this may result in visible lumps and/or bluish discoloration.
- The patient must avoid exposing the treated area to heat (sun bathing, sauna, steam baths, etc.) or extreme cold until any signs of local inflammation have disappeared.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is performed after treatment with this product there is a theoretical risk of eliciting an inflammatory reaction at the implant site. This also applies if the product is administered before the skin has healed completely after such a procedure.
- At each treatment session a maximum dosage of 2 mL per treatment site is recommended.
- This product has not been tested in pregnant or breastfeeding women.
- Do not use in children.

VIII. ADVERSE EVENTS

Patients must be informed of the potential risks and adverse events related to the injection procedure and to the use of this product.

The following post market adverse events have been reported (non-exhaustive list): angioedema, atrophy/scaring, blisters, bruising, capillary disorders such as telangiectasia, dermatitis, discoloration, erythema, hypersensitivity, induration, infection, inflammation, ischemia/necrosis, mass, neurological symptoms such as paraesthesia, pain/tenderness, papules/nodules, pruritus, reactivation of herpes infection, short duration of effect, swelling and urticaria.

Other potential adverse events that have been reported following injection of hyaluronic acid gels in general and may occur when using the product include the following: abscess, acne, device dislocation, fistula, granuloma, rash and visual disturbance.

Injection related adverse events such as bruising, erythema, itching, swelling, pain and tenderness generally resolve spontaneously within one week after injection.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as ischemia or necrosis at the implant site or in the area supplied by the blood

vessels affected; or rarely as ischemic events in other organs due to embolisation. Following facial aesthetic treatments isolated rare cases have been reported regarding ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction. After injections of the nose ischemia/necrosis may occur, especially in patients who had prior rhinoplasty.
Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions infections should be excluded and treated if necessary since inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended. In case of persistent or recurrent inflammatory symptoms, consider removal of the product by aspiration/drainage, extrusion or enzymatic degradation (use of hyaluronidase has been described in scientific publications). Before any removal procedure is performed, the swelling may be reduced by using e.g., NSAID for 2-7 days or a short course of corticosteroids for less than 7 days, in order to more easily palpate any remaining product.

For patients who have experienced medically important adverse events, a decision for retreatment should take into consideration the cause and severity of previous reactions.

For reporting adverse events contact your local Galderma representative or distributor for this product.

IX. PERFORMANCE

In a randomized controlled multicenter study with Restylane Defyne for correction of moderate to severe nasolabial folds, 69.8% of subjects maintained a clinically significant improvement at 48 weeks after treatment.

X. TREATMENT PROCEDURE

Inform the patient about the precautions to be taken, the expected result and the possible adverse events.
It is important to use a sterile, appropriate needle or blunt cannula. Suitable needles (27G x ½" Ultra thin wall) are supplied with the syringe in the blister pack. As an alternative, a blunt thin walled cannula with a recommended size of 27G can be used.
Assembling the needle/cannula and syringe:

- use surgical gloves
- unscrew the protective cap from the stopper
- carefully remove the stopper from the syringe
- firmly screw the needle/cannula with its shield onto the tip of the syringe
- remove the shield just before injection

Cleanse the area to be treated with an antiseptic and allow it to dry before injection.
To avoid breakage of the needle/cannula, do not attempt to bend or otherwise manipulate it before or during treatment.

Before injecting the product, depress the plunger rod carefully until a small droplet is visible at the tip of the needle/cannula.
Align the bevel of the needle by turning the syringe on its axis. If a blunt cannula is used, an entry point is made in the skin, for example with a sharp needle of appropriate size.
Aspiration is recommended prior to injection in order to reduce the risk of inadvertent injection into a blood vessel. Inject slowly. During injection, keep the side hole of the cannula facing downwards, away from the skin surface.
Inject the gel by gently pressing down on the plunger rod with the thumb or palm of the hand.
Choose from a variety of injection techniques, i.e., serial puncture, linear threading or cross-hatching.
It is recommended to change needle/cannula for each new treatment site.
Defects should be fully corrected, but not overcorrected, at each treatment session.
If "blanching" of the skin is observed as a result of over-superficial injection, the whitened area should be massaged gently until it returns to a normal colour.
Gently massage the treated area after injection.
The syringes and needles/cannulas must be discarded immediately after use in accordance with accepted medical practice and applicable national, local or institutional guidelines. The product shall not be reused due to risk for contamination of unused material and the associated risk including infection.
Standard precautions apply when handling the needles. Needles should be disposed in a container dedicated for sharp devices.

XI. SHELF LIFE AND STORAGE

Do not use after the expiry date indicated on package. Store up to 25°C. Protect from freezing and sunlight.

XII. MANUFACTURER

Q-Med AB, Seminariegatan 21, SE-75228 Uppsala, Sweden

Phone +46(0)18 474 90 00, Fax +46(0)18 474 90 01

www.q-med.com, e-mail: info.q-med@galderma.com

Appendix 3 Instruction for Use Restylane China

(Extract from QMS-5602 version 8.0)

Please read the Instruction for Use carefully, and use the product according to the instruction.

Modified Sodium Hyaluronate Gel for Injection

INSTRUCTIONS FOR USE

Name	
Trade Name:	瑞蓝
Chinese Pronunciation:	Rui Lan
Generic Name:	Modified sodium hyaluronate gel for injection
Chinese Pronunciation:	ZhuShe Yong XiuShi TouMingZhiSuan Na NingJiao
Model:	瑞蓝 2（Restylane）
Specification:	0.5 mL/syringe; Article number 10-70109 1 mL/syringe; Article number 10-70009

Registration Certificate Number for Imported Medical Device
CFDA(I) 20143640872

Registration Product Standard Code Number for Imported Medical Device
YZB/SWE 8120-2013 "Modified Sodium Hyaluronate Gel for Injection"

Note! Please identify genuine product via phone 400 650 1053 or on www.restylane.com.cn and keep the syringe label for traceability purposes (see "Product Package and Traceability Information" for further details).

Composition

Modified sodium hyaluronate

Include:	Sodium hyaluronate	20 mg/mL

Phosphate buffered saline

Include:	Sodium chloride (NaCl)	9 mg/mL
	Potassium dihydrogen phosphate (KH_2PO_4)	0.03 mg/mL
	Disodium hydrogen phosphate (Na_2HPO_4 x $2H_2O$)	0.14 mg/mL
	Water for injection	ad 1 mL

Description

瑞蓝 2（Restylane） contains a gel of modified hyaluronic acid of non-animal origin. Hyaluronic acid is naturally occurring and is an important structural element in the skin and in subcutaneous and connective tissues as well as in the synovial tissue and joint fluid. Hyaluronic acid is metabolized and degraded naturally by the body. All raw materials used in the manufacturing process are of non-animal origin.

瑞蓝2（Restylane） is sterile, transparent and viscous modified sodium hyaluronate gel for injection supplied in a disposable glass syringe with a luer-lock fitting. The contents of the syringe are sterile.

The range limits for gel particle size for 瑞蓝2 (Restylane) is between 0.08 – 1 mm for 80% of the total volume of gel particles. The median gel particle size is about 0.4 mm. The median gel particle size is the middle size that separates the half of the sample containing the larger particles from the half containing the smaller particles. The gel particles are measured as swelled gel particles.

Mode of Action

瑞蓝 2（Restylane） is a dermal tissue filler used to restore the skin contours to the desired level of correction through augmentation of facial skin.

瑞蓝 2（Restylane） will degrade gradually in the body, typically 6-12 months after injection. With degradation the filler effect will disappear. The patients, who want to keep the filler effect, can receive follow-up injections when the filler effect becomes less visible or disappears.

The filler effect remains for longer than 6 months in the majority of patients as shown in the Chinese study, where patients were injected with 瑞蓝 2（Restylane） in the nasolabial folds.

Indications

瑞蓝 2（Restylane）is intended to be used for facial tissue augmentation by injections into the mid dermis to correct moderate to severe nasolabial folds. 瑞蓝 2（Restylane）should be injected into the middle part of the dermis layer of the facial skin. The injection procedure should strictly follow the rules of aseptic surgical technique. The product should only be used by doctors who have appropriate training, and experience, and who are knowledgeable about the anatomy at and around the site of injection.

Note! Injections of 瑞蓝 2（Restylane）must only be done by plastic surgeons, dermatologists and cosmetic doctors at hospitals and medical plastic surgery institutions officially approved by the state administrative authorities. These institutions include clinics for medical cosmetic and plastic surgery, medical cosmetic outpatient departments and plastic surgery departments in general hospitals and specialized hospitals for medical cosmetic and plastic surgery, which must have obtained a "Medical Institution Business License". Doctors of those institutions should only use 瑞蓝2（Restylane）after being trained and certified by the after sales service agent of the Swedish company Q-Med AB, Q-Med International Trading (Shanghai) Co., Ltd., and its appointed agents. After obtaining the training certificate, the doctors must strictly follow the instructions in this document (Instructions for Use).

Product Package and Traceability Information

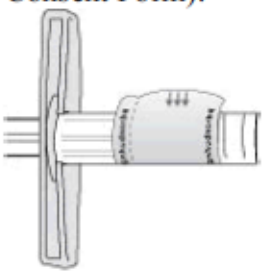
The fill volume and number of needles in the package are stated on the carton of 瑞蓝 2 (Restylane). The package for 瑞蓝 2 (Restylane) with fill volume 0.5 mL/syringe contains one glass syringe with 0.5 mL 瑞蓝 2 (Restylane) gel and one needle. The package for 瑞蓝 2 (Restylane) with fill volume 1 mL/syringe contains one glass syringe with 1 mL 瑞蓝 2 (Restylane) gel and two needles. All needles are 30 G x ½″ and sterilized by gamma irradiation.

There is a sticker (including traceability barcode and security code covered by wax like ink) on the carton for identification of genuine products. The security code will be visible after removing the wax like ink. Please instruct the patients to remove the wax like ink and confirm a genuine and authentic product via phone 400 650 1053 or on www.restylane.com.cn in accordance with the instruction on the carton. Please give the security code in accordance with the instructions given over the phone or on the website, and fill the number with successful identification into the Patient Record according to the requirement.

Do not use the product if the identification check showed that it is not 瑞蓝 2 (Restylane) manufactured by Q-Med AB, Sweden. If the product is a counterfeit product, please immediately contact the distributors or Q-Med International Trading (Shanghai) Co., Ltd., the after sales service agent of the Swedish company Q-Med AB.

The syringe filled with 瑞蓝 2 (Restylane) gel and the supplied needles are packed in a blister. On each syringe there is a peel-off label marked with "↓↓↓". Tear off the label and attach

the wide part (including the hologram, lot number and identification code) to the Patient Records and keep it at the clinic to ensure traceability of the syringe. The narrow part of the label (including the identification code) must be attached to the document kept by the patients themselves (for further details please see the requirement in 瑞蓝 2 (Restylane) Patient Consent Form).



Please instruct the patients to keep the carton of 瑞蓝 2 (Restylane), or to tear off the part containing hologram and product lot number and keep it in the document kept by the patients themselves.

The identification code and lot number must be submitted by doctors or patients when adverse events are reported, in order to trace the product used by patients.

Treatment Procedure

The doctors have to inform the patients about the indications, expected result and duration of filler effect, contraindications, precautions, warnings and potential adverse events before treatment. Doctors shall also discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications. Before the treatment, the patient's suitability for the treatment and the need for pain relief should be assessed. For optimal patient comfort, topical or local anaesthesia is recommended. The injection technique and the administered quantity may vary. The linear threading technique can be used to carefully lift up the wrinkle, but some doctors prefer a series of punctual injections or a combination of the two. 瑞蓝2 (Restylane), is administered using a thin gauge needle (30 G x ½") by injecting the material into the dermis.

During injection it is recommended that the eye of the needle should face upwards. The contour of the needle should be visible but not the colour of it. An injection too superficial may give blanching effects and bumps on the treatment site. If the overlying skin turns a whitish colour (blanching), the injection should be stopped immediately and the area massaged until it returns to a normal colour. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection.

Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections are to be observed. Clean the treatment site thoroughly with suitable antiseptic solution.

To avoid breakage, do not attempt to bend or otherwise manipulate the needle before or during treatment.

Before injecting, remove the air by pressing the rod carefully until a small droplet is visible at the tip of the needle.
Aspiration prior to injection is recommended to verify that the needle is not intravascular.
Inject 瑞蓝 2（Restylane）slowly while pulling the needle backwards. Injection should stop just before the needle is pulled out from the skin to prevent material from leaking out from the injection site or ending up too superficially in the skin.
Do not apply excessive pressure to the syringe at any time. Presence of scar tissue may impede advancement of the needle. If resistance is encountered the needle should be partially withdrawn and repositioned or fully withdrawn and checked for function.
It is recommended to change needle for each new treatment site.
If there is pronounced skin laxity, it is recommended that 瑞蓝 2（Restylane） be injected on two or more separate occasions.
The correction site should be massaged to conform to the contour of the surrounding tissues.
Ice in appropriate packaging can be applied on the treatment site for about 15 minutes to reduce swelling and discomfort. This can be repeated for another 5-15 minutes if swelling and discomfort persist. Because prolonged exposure to cold temperature at or below 4℃ can lead to cold injury similar to frostbite, use of ice compress should be kept to as short a time as possible.
Additional implantations of 瑞蓝 2（Restylane） may be necessary to achieve the desired level of correction if patients are not satisfied with the filler effect.

Note! The time interval between the initial injection and subsequent touch up injection is at least
4 weeks.
For initial injections, it is recommended not to use more than 1.5 mL for each nasolabial fold.
For subsequent touch up injection, it is recommended not to use more than 0.5 mL for each nasolabial fold.

Note! Defects should be fully corrected, but not overcorrected at each treatment session.

Note! The correct injection technique is important for the final result of the treatment.
Please consult Q-Med International Trading (Shanghai) Co., Ltd., the after sales service agent of the Swedish company Q-Med AB, for more details about techniques and training opportunities.

The syringe, the needle and any gel that is unused and left in the syringe 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. Disposal should be in accordance with accepted medical practice and applicable national, local or institutional guidelines.

STERILE NEEDLE

- Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.

Contraindications

1. 瑞蓝 2（Restylane） is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
2. Do not use in patients with a history of hypersensitivity to streptococcal proteins, as the product may contain trace amounts of such material.
3. 瑞蓝 2（Restylane） should not be used in the following situations:
   - Permanent implant or implant other than hyaluronic acid in the same area
   - Non-permanent implant placed in the same area during the previous 6-12 months
   - If no information is available on the type of implant
4. Do not use in patients with bleeding disorders or patients who are taking thrombolytics or anticoagulants.
5. Do not use where there is active disease, such as inflammation, infection or tumours, in or near the intended treatment site.

Warnings

1. 瑞蓝 2（Restylane） is only intended for use as an intradermal implant. The product should not be used for breast site injections.
2. Do not resterilize 瑞蓝 2（Restylane）.
3. Do not inject intramuscularly or intravascularly. Aspiration prior to injection is recommended.
4. Unintentional introduction of soft tissue fillers into the vasculature in the face may lead to embolization, occlusion of the vessels, ischemia, necrosis or infarction at the implant site or in the area supplied by the blood vessels affected. Rare but serious adverse events include temporary or permanent vision impairment, blindness, cerebral ischemia or stroke. Stop the injection immediately if blanching occurs or if a patient complains of unusual pain or exhibits any symptoms suggestive of inadvertent intravascular injection. Such patients should receive prompt medical evaluation and attention.
5. 瑞蓝 2 (Restylane) should not be mixed with other products before implantation of the device.
6. The product is for single use only.
7. Do not use if package is damaged.

Precautions

1. Normal precautions associated with intradermal injections must be observed. Like any such procedure, the implantation of 瑞蓝 2（Restylane） is associated with an inherent risk of infection. The injection procedure should strictly follow the rules of aseptic surgical technique.
2. Use with caution in patients who are immunosuppressed.
3. Special caution should be exercised when treating areas in close proximity to permanent implant.
4. Special caution is required to avoid perforation or compression of vessels, nerves and other vulnerable structures. In order to minimize the risks of potential complications, inject the product slowly and apply the least amount of pressure necessary.
5. Patients who are using substances that may affect platelet function, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.
6. Injection procedures can lead to reactivation of latent or subclinical herpes viral infections.
7. If the product is injected too superficially this may result in visible lumps and/or bluish discoloration.
8. With cutaneous contour deformities the best results are obtained if the defect can be manually stretched to the point where it is eliminated. Markedly indurated defects may be difficult to correct. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique.
9. 瑞蓝 2（Restylane） should not be used for patients with unattainable expectations.
10. If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with 瑞蓝 2（Restylane），there is a theoretical risk of eliciting an inflammatory reaction at the implant site. This also applies if 瑞蓝 2（Restylane） is administered before the skin has healed completely after such a procedure. It is recommended that a period of 2 to 4 weeks elapses before applying different treatment modalities or until the skin has healed completely.
11. The patient should be informed that he or she should not expose the treated area to intense heat (e.g. solarium, sauna or excessive sun exposure), extreme cold, skin massage of the treatment area or face mask at least until the initial swelling and redness have resolved.
12. 瑞蓝 2（Restylane） has not been tested in pregnant or breastfeeding women or in children.
13. Please keep the traceability information and instruct the patients to identify genuine products.

Interactions

Treatment with 瑞蓝 2（Restylane） in combination with drugs or other medical devices, except for other Restylane products, has not been tested. Do not use 瑞蓝 2 (Restylane) together with any other injectable implant, except for other Restylane products.

Adverse events

Anticipated injection-related reactions

After the injection of 瑞蓝 2（Restylane）, short lived injection-related reactions are to be expected. These reactions include one or more of the following: erythema, swelling, pain, itching, bruising or tenderness at the implant site. Typically these reactions start on the day of treatment, last between 3 to 7 days and resolve spontaneously, as observed in the Chinese clinical study, which is consistent with international results. 瑞蓝 2（Restylane） can be palpable in some patients.

Post marketing adverse event reporting

The following post marketing adverse events have been reported (non-exhaustive list). The frequency of reporting is based on the number of estimated treatments performed with Restylane.

1/1 000 – 1/10 000	Mass/induration, Swelling with immediate onset and onset up to several weeks after treatment
1/10 000 – 1/100 000	Atrophy/scarring, Bruising/hematoma, Discoloration/ hyperpigmentation, Erythema, Extrusion of device, Hypersensitivity/ angioedema, Infection and abscess formation, Inflammation, Injection site reactions including burning sensation, exfoliation, irritation, and warmth, Ischemia/necrosis, Neurological symptoms including facial nerve paralysis, hypoaesthesia, and paraesthesia, Non-dermatological events including anxiety, dizziness, dyspnoea, headache, malaise, nausea, pyrexia, and sinusitis, Other dermatological events including alopecia, chapped lips, dry skin, and skin wrinkling, Pain/tenderness, Papules/nodules, Pruritus, Short duration of effect, Visual disturbances including blindness, transient blurred vision, eyelid ptosis, increased lacrimation, and reduced visual acuity
<1/100 000	Acne, Blisters/vesicles, Capillary disorders including telangiectasia, Dermatitis, Dermatophytosis, Device dislocation, Discharge/extravasation, Encapsulation, Granuloma, Muscle twitching, Rash, Reactivation of herpes infection, Urticaria

Vascular compromise may occur due to an unintentional intravascular injection or as a result of vascular compression associated with implantation of any soft tissue filler in the face. This may manifest as blanching, discoloration such as a dusky or reticular appearance of the tissue, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolisation. Rare but serious cases of ischemic events associated with temporary or permanent vision impairment, blindness, cerebral ischemia or stroke have been reported following facial aesthetic treatments.

Localized ischemia/necrosis and scarring may occur after injection in or near vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions infections should be excluded and treated if necessary since inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended.

The prolonged use of any medication, e.g., corticosteroids or antibiotics in treatment of adverse events has to be carefully assessed, since this may carry a risk for the patient. In case of persistent or recurrent inflammatory symptoms, consider removal of the product by aspiration/drainage, extrusion or enzymatic degradation (use of hyaluronidase has been described in scientific publications). Before any removal procedure is performed, the swelling may be reduced by using, e.g., NSAID for 2-7 days or a short course of corticosteroids for less than 7 days, in order to more easily palpate any remaining product.

Post inflammatory pigmentation changes have been observed in clinical studies in people with dark skin (Fitzpatrick Type IV-VI).

For patients who have experienced clinically significant reactions, a decision for retreatment should take into consideration the cause and significance of previous reactions.

No serious adverse events were reported in the Chinese clinical study with 瑞蓝2（Restylane）.

Adverse events must be reported to Q-Med International Trading (Shanghai) Co., Ltd., the after sales service agent of the Swedish company Q-Med AB.

Storage
Store up to 25° C. Protect from freezing and sunlight.

Date of manufacture
The date of manufacture is indicated on package.

Shelf life
The shelf life of the product is 36 months from the date of manufacture. The expiry date is indicated on package.

Manufacturer/Applicant

Name:	Q-Med AB
Registration address:	Seminariegatan 21, SE-752 28 Uppsala, Sweden
Manufacturing address:	Seminariegatan 21, SE-752 28 Uppsala, Sweden Seminariegatan 31, SE-752 28 Uppsala, Sweden
Phone:	+46 18 474 90 00
Fax:	+46 18 474 90 01

Legal Agent/After Sales Service Agent

Name:	Q-Med International Trading (Shanghai) Co., Ltd.
Address:	Room 2017, No.1 Ji Long Road, Free Trade Zone, 200131, (Shanghai), China
Phone:	021-58690300
Fax:	021-58690300

Others
For more information about the product, please consult Q-Med International Trading (Shanghai) Co., Ltd., the after sales service agent of the Swedish company Q-Med AB, or visit the website below:
www.restylane.com.cn

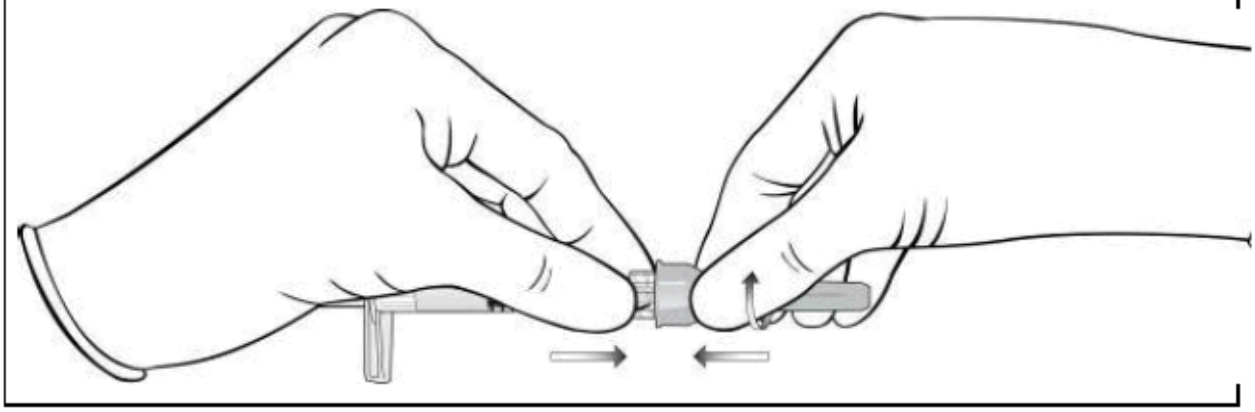
Restylane, 瑞蓝, NASHA and Galderma are trademarks owned by Nestlé Skin Health S.A.

Note! The product 瑞蓝 2（Restylane） to be sold in China must be specially packed by the Swedish company Q-Med AB according to the requirement of China Food and Drug Administration, P.R.China. 瑞蓝 2（Restylane） must only be purchased through the sales channels of the Swedish company Q-Med AB.

Assembly of Needle to Syringe

For safe use of 瑞蓝 2 (Restylane) it is important that the needle is properly assembled to the syringe. Improper assembly may result in separation of the needle and syringe during injection.

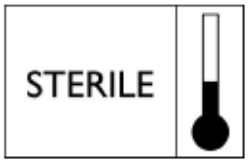
Hold firmly around the syringe barrel with the thumb and forefinger. Grasp the needle shield with the other hand. To facilitate proper fastening, both **push and rotate** them firmly together. See picture. Strict aseptic technique must be followed.



Symbols on Package

Lot Number

Use by



Sterile. The contents of the syringe have been sterilized by using moist heat.

Date of manufacture

Do not re-use

Sterile. The needles have been sterilized by using irradiation.

First issue date: *March 2009*
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Appendix 4 Photo guide for Wrinkle Severity Rating Scale (WSRS)

Grade 1:

Absent: No visible fold; continuous skin line

Grade 2:

Mild: Shallow but visible fold with a slight indentation; minor facial feature

Implant is expected to produce a slight improvement in appearance.

Grade 3:

Moderate: Moderately deep folds;
Clear facial feature visible at normal appearance but not when stretched.
Excellent correction is expected from injectable implant

Grade 4:

Severe: Very long and deep fold; prominent facial feature;
Less than 2-mm visible fold when stretched
Significant improvement is expected from injectable implant

Grade 5:

Extreme: Extremely deep and long fold;
Detrimental to facial appearance; 2- to 4-mm V-shaped fold when stretched.
Unlikely to have satisfactory correction with injectable implant alone

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