A randomised, multi-center, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane with and without addition of 0.3% lidocaine hydrochloride

Study products:	Restylane Lidocaine Restylane
Clinical Trial Number (CTN):	43CH1504
Co-ordinating 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

Confidentiality Statement

Summary of Changes in Clinical Study Protocol 43CH1504 from Version 3.0 to Version 4.0

Added text is written in **bold** and deleted text is written as strikethrough.

Section in the clinical study protocol	Rational for changes	Description of changes
Cover Page	Co-ordinating Investigator changed	PPD
Investigators and Study Administrative Structure	Co-ordinating Investigator changed and site changed.	Co-ordinating Investigator PPD Principal Investigator PPD

Synopsis- co-ordinating Investigator/ Principal Investigators	Co-ordinating Investigator changed and site changed.	PPD
Section 8.4.5 Reporting of Serious Adverse Events	SAE reporting process changed according to new issued regulation by CFDA and the email address updated	**After aware of any SAE, t**~~T~~he Investigator shall report ~~any~~ **SAE** ~~to the Sponsor~~ ~~**immediately but no later than 24 hours of awareness**~~ ~~of the event.~~ **it to his/her administrative department of medical device clinical trials under the clinical trial institution, which in turn shall notify the Sponsor in writing.** This initial report can be made via fax or e-mail or submitted via the eCRF. **E-mail** for SAE reporting: ~~complaints.q-med@galderma.com~~ **safety.q-med@galderma.com** In addition, according to national regulations, ~~the Investigator should report the event~~ **within 24 hours of awareness** ~~to the Regulatory authority (RA, including China Food and Drug Administration (CFDA) and relevant Provincial Food and Drug Administration). The Investigator shall also report SAEs to the responsible IEC without undue delay, if applicable according to national regulations or local IEC requirements. The PI is responsible for checking what reporting procedures are applicable for his/her IEC regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.~~ **the administrative department of medical device clinical trials should, within 24 hours, deliver a written report to the corresponding Ethics Committee and the local food and drug administrative department of province, autonomous region and municipality at the place where the clinical trial institution locates. In case of a death incident, the clinical trial institutions and investigators should furnish the Ethics Committee and the sponsor with all required materials.** The local office in Beijing of the Sponsor is responsible for ~~reporting SAE to the RA~~, **within**

		five (5) business days upon being informed, reporting any SAE or device defect with the likelihood of SAE to the food and drug administrative department where it has been registered and the competent authorities of health and family planning at the same level; meanwhile, the Sponsor should notify other clinical trial institutions and investigators participating in the clinical trial, and promptly report it to the Ethics Committee of the involved clinical trial institutions via the administrative department of medical device clinical trials according to national regulations.
Appendix 3	Batch Number of Restylane Lidocaine 1ml updated	Label of Restylane Lidocaine 1ml updated.
Subject information and informed consent form		Updates required: Yes ☐ No ☒
Electronic case report form (eCRF)		Updates required: Yes ☒ No ☐

Investigators and Study Administrative Structure

Co-ordinating Investigator	PPD
Principal Investigator	
Principal Investigator	
Sponsor	Q-Med AB Seminariegatan 21 SE-752 28 Uppsala, Sweden Telephone: +46 18 474 90 00 Facsimile: +46 18 474 90 01
PPD Medical Expert Study Director Clinical Project Manager Study Statistician Senior CRA	PPD

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

Signed Agreement of the Clinical Study Protocol

CTN: 43CH1504

Title of the CSP: A randomised, multi-center, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane with and without addition of 0.3% lidocaine hydrochloride.

I, the undersigned, have read and understand the protocol specified above, and agree on the contents. The study protocol, the Clinical Trial Agreement and the additional information given in the Instruction For Use for Restylane Lidocaine and 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 randomised, multi-center, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane with and without addition of 0.3% lidocaine hydrochloride
Clinical Trial Number:	43CH1504
Countries involved, number of sites/country, number of subjects:	The study will be conducted at approximately 3 sites located in China. The aim is to include approximately 70 subjects treated with Restylane Lidocaine in one nasolabial fold (NLF) and Restylane in the opposite NLF, as randomly assigned.
Co-ordinating Investigator / Principal Investigators:	PPD
Primary objective:	The primary objective is to evaluate the pain associated with injections of Restylane Lidocaine compared to Restylane using a visual analogue scale (VAS). The proportion of subjects that have a within-subject difference in VAS score (Restylane-Restylane Lidocaine) of at least 10 mm at injection will be calculated together with a two-sided 95% confidence interval. The objective is to show that the confidence interval lies above 50%.
Secondary objectives:	The secondary objectives are: • To evaluate the pain associated with injections of Restylane Lidocaine compared to Restylane by assessment of o Proportion of subjects that have a within-subject difference in VAS score (Restylane-Restylane Lidocaine) of at least 10 mm (at 15, 30, 45 and 60 minutes after injection). CCI CCI
Safety objectives:	The safety objectives are: • To evaluate the safety of Restylane Lidocaine and Restylane during the whole study by collecting Adverse Events (AEs). CCI
Study Design:	This is a randomised, multi-center, subject-blinded and evaluator-blinded study in China to evaluate the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane Lidocaine compared to Restylane for correction of moderate to severe nasolabial folds. Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to study randomisation on Day 1. Subsequent to screening eligible subjects will be enrolled in the study. Each subject will receive treatment on Day 1 with Restylane Lidocaine in one NLF and

	Restylane in the opposite NLF, as randomly assigned. The first injection will always start in the right NLF. No topical or local anesthetic or other pain-relieving medication, including ice, should be used before all VAS assessments are finished. The second injection, that is the injection in the left NLF, will be performed 20±5 minutes after the first injection in order to reduce possible influence of immediate acute pain from the first injection on the pain perception of the second injection. 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 injection. Aspiration should be performed prior to injection in order to avoid accidental intravascular injection. The injection procedure for the two NLFs will be standardised as far as possible in terms of volume used, time needed for injection, and injection technique and will be recorded in the CRFs. Due to the similar method of administration, the treatment can be masked from the subject by simply preventing them from viewing the syringes during the injection procedure. This will be accomplished by placing an opaque drape or patch over the subject's eyes during the time that the injections are administered. The subject will assess pain experienced during treatment on a 100 mm VAS scale at the end of each injection (before massaging the treatment area).The time should be recorded in the CRF and the pain will thereafter be assessed by the subject at 15±3, 30±3, 45±3, and 60±3 minutes on the VAS after the injection on the right and left NLF, respectively. CCI [redacted]
Scheduled visits:	Visit 1 — Screening — Day -14 to Day 1 Visit 2 — Baseline (treatment) — Day 1 Visit 3 — Follow-up/Final visit — Day 15 (after 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). CCI [redacted]
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 anaesthetics, e.g. lidocaine or other amide-type anaesthetics. 3. History of severe or multiple allergies manifested by anaphylaxis. 4. 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. 5. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (facial) corticosteroids within 3 months before study treatment (inhaled corticoids are allowed). 6. Previous use of any permanent (non-biodegradable) or semi-permanent facial tissue augmentation therapy or autologous fat 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. Previous tissue revitalisation treatment with laser or light, mesotherapy, radiofrequency, chemical peeling or dermabrasion in the midface within 6 months before treatment. 10. Previous surgery (including aesthetic facial surgical therapy or liposuction) or tattoo in the area to be treated. 11. Scars or deformities, active skin disease, inflammation or related conditions, such as infection, perioral dermatitis, seborrheic eczema, rosacea, acne, psoriasis and herpes zoster near or in the area to be treated. 12. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis or localized or systemic scleroderma. 13. Tendency to form keloids, hypertrophic scars, or any other healing disorder. 14. History of radiation or cancerous or pre-cancerous lesions (e.g. actinic keratosis) in the area to be treated. 15. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion (e.g. 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). 16. Subjects with abnormal 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. 17. Concomitant treatment with topical (facial) retinoids within 3 months or systemic retinoids within 6 months before treatment. 18. Women who are pregnant or breast feeding, or Woman of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period. 19. 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. 20. 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. 21. Participation in any other clinical study or study within 30 days before treatment.
Investigational product, dose and mode of	Restylane 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 29G thin walled (TW) ×

administration:	½" needle will be used for injection. The Treating Investigator will check the randomisation 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 Lidocaine and the opposite NLF to treatment with Restylane. Restylane Lidocaine should be injected into the middle layer of the dermis of the facial skin in the NLF. The injection procedure should strictly follow the rules of aseptic surgical technique (refer to the Restylane Lidocaine Instructions For Use for details). For treatment, it is recommended not to use more than 1.5 mL for each NLF. The linear threading technique can be used to carefully lift up the wrinkle. The injection technique and the depth of injection 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. No topical or local anaesthetic or other pain-relieving medication, including ice, should be used before all VAS assessment finished.
Reference therapy, dose and mode of administration	Restylane 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 29G thin walled (TW) × 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 treatment, it is recommended not to use more than 1.5 mL for each NLF. The linear threading technique can be used to carefully lift up the wrinkle. The injection technique and the depth of injection 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. No topical or local anaesthetic or other pain-relieving medication, including ice, should be used before all VAS assessment finished.
Duration of treatment and follow-up:	Following screening and treatment, there is a follow-up/final visit at Day 15 (+3 days).
Efficacy Assessment:	<u>Pain Assessment:</u> The VAS is a subjective scale to measure pain intensity. The subject shall be instructed to put a vertical mark, approximating the pain experienced during the procedure, on a 100 mm horizontal line labelled "no pain" at the left end and "the worst pain you can imagine" at the right end. The distance in mm from the left end (no pain) to the subject's VAS mark shall be measured with a standard ruler. Each NLF will be evaluated independently. Subjects will evaluate injection site pain for each side of the face at the time of injection (before massaging) and at 15, 30, 45, and 60 minutes post-treatment by completing a VAS. Visual Analogue Scale (VAS) Put a vertical mark (|) on the line below to show your pain experience. No pain _____The worst pain you can imagine CCI [redacted]

	CCI [redacted]
	[redacted]
Safety Assessment:	AE will begin to be collected after ICF signed. Each subject will be questioned about AEs at follow-up 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 [redacted] or spontaneous reports from the subjects.
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Statistical Methods:	In general, all efficacy, safety and baseline characteristics variables will be presented using descriptive statistics and graphs as appropriate. Efficacy and safety variables will be presented by treatment. Continuous data will be summarized by descriptive statistics n (number of observations), mean, standard deviation, median, minimum and maximum value, while categorical data will be presented by frequency and percentage. **Primary analysis** The proportion of subjects that have a within-subject difference in VAS (Restylane-Restylane Lidocaine) of at least 10 mm at the time of injection will be calculated together with a two-sided 95% confidence interval. The objective is to show that the confidence interval lies above 50% based on the ITT analysis set. CCI **Secondary analysis** The proportion of subjects that have a within-subject difference in VAS of at least 10 mm at post injection timepoints (15, 30, 45 and 60 minutes after injection) will be calculated together with a two-sided 95% confidence interval. CCI **Sample size** CCI

Abbreviations and definitions of terms

AE	Adverse Event
Blinded Evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject.
CFDA	China Food and Drug Administration
Co-ordinating Investigator	An Investigator assigned the responsibility for the coordination of Investigators at different centers participating in a multicenter study
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
ECG	Electrocardiograph
eCRF	Electronic Case Report Form
G	Gauge
CCI	[redacted]
GCP	Good Clinical Practice
HA	Hyaluronic acid
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
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 clinical studies are conducted.
Investigator	The Principal Investigator or other qualified person, i.e. sub-Investigator, designated and supervised by the Principal Investigator at a study site to perform critical study-related procedures and/or make important study-related decisions as specified on the delegation log.
Investigator File	Essential documents relating to a clinical study as defined in GCP guidance document and maintained by the Investigator.
IRB	Institutional Review Board
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
NLF	Nasolabial fold
NSAIDs	non-steroid anti-inflammatory drugs

PI	Principal Investigator
PP	Per protocol
QA	Quality assurance
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
SDV	Source data verification
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
U-HCG	Urinary human chorionic gonadotropin
VAS	Visual analogue scale
WHO	World Health Organization

CCI [redacted]

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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), applicable Good Clinical Practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155: 2011shall be followed. The International Conference on Harmonisation (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 favourable 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 Lidocaine has been approved in the United States, Europe and several countries worldwide as a medical device for facial tissue augmentation. It is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

2.2 Investigational product description

Among the different materials used as raw materials in injectable fillers for aesthetic use, sodium hyaluronate, also denoted hyaluronic acid (HA) 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 of HA 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 eliminate the risk for contamination, the HA used in the manufacture of Galderma's HA gels is of non-animal source, biosynthesised from *Streptococcus* species of bacteria.

During manufacturing, cross-links are introduced between the HA chains using the NASHA(TM) technology in order to obtain a gel network. 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.

Restylane Lidocaine also consists of lidocaine hydrochloride 3 mg/ml.

2.3 Reference product description

Except not containing lidocaine, Restylane has the same composition and property as Restylane Lidocaine.

2.4 Previous experience

2.4.1 Non-Clinical Documentation

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2.4.2 Clinical Documentation

Restylane Lidocaine has been proven safe and efficacious in a clinical trial[3]. The study was performed in US and the purpose was to study the safety and effectiveness of wrinkle treatment with Restylane-L for the correction of moderate to severe nasolabial folds.

Sixty patients were treated with Restylane-Lidocaine and Restylane treatment in a "within-patient" model of bilateral NLF correction, with one treatment assigned to one side of the face and the other treatment to the remaining side. The primary efficacy analysis showed that 71.7% of subjects had a within-subject difference in VAS (Restylane minus Restylane Lidocaine) of at least 10 mm at the time of injection. Mean within-subject difference on VAS (Restylane –Restylane Lidocaine) was statistically significantly larger than zero at all timepoints (at injection and at 15, 30, 45 and 60 minutes post injection). The results showed the addition of lidocaine to Restylane has a substantial effect on reducing pain experienced by the subjects.

The study also indicates that the safety profile of Restylane is maintained. There were no AEs of severe intensity recorded during the study. The majority of related events were mild in severity. Most related AEs were typical of local reactions associated with implantation, such as swelling, pain, and haematoma (bruising) and the AE profile was similar for the two products. There were also no SAEs and no AE resulted in subject discontinuation of the study.

The use of Restylane in the NLFs have been extensively evaluated in clinical studies[3-17,] Restylane has also been proven safe and efficacious in a clinical trial in a Chinese study population[14]. This 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). The study showed that efficacy was very well sustained with a significant improvement from baseline at all-time points up to the last observation at 6 months post-treatment. Restylane was also well tolerated and no systemic reactions or other safety concerns were raised. Some transient anticipated

post-injection reactions were reported which were in general classified as being of mild severity. 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 [8,9,11] and that the frequency of AEs related to treatment was similar in a Chinese study population as in US study population [8,9,11].

Post market surveillance data for Restylane-L also support that the AE profile is acceptable [18].

2.5 Study rationale

Injectable lidocaine HCL as an analgesic is commonly used by physicians to help control or prevent pain and inflammation by numbing the area prior to performing minor surgical procedures. Many physicians are known to inject subjects with lidocaine HCL or similar analgesics in association with Restylane injections.

Since lidocaine HCL is a widely used, well characterized analgesic that is a component of a number of currently marketed dermal fillers, the sponsor proposed to add 0.3% lidocaine HCL to the Restylane formulation as a convenience for physicians and their patients and undertook a two week study to assure that this modification of Restylane would not impact the safety of the product in US population. The results showed addition of lidocaine to Restylane has a substantial effect on reducing pain experienced by the subjects and the safety profile of Restylane is maintained. By June 2015, Restylane Lidocaine has been approved in 52 countries/regions, including US, EU, Hong Kong, Korea, India, etc.

According to the previous experience, a two-week study was anticipated to be adequate to confirm the safety of adding lidocaine hydrochloride to Restylane in Chinese population.

2.6 Justification for the design of the study

The purpose of this study is to investigate the pain associated with injections of Restylane Lidocaine compared to Restylane using a visual analogue scale (VAS) by measuring the proportion of subjects that have a within-subject difference in VAS score (Restylane-Restylane Lidocaine) of at least 10 mm at injection. Evaluation with standardised evaluation tools will be used in the study.

2.7 Risk and benefits

Restylane and Restylane Lidocaine are by June 2015 registered in more than 50 countries/regions including the US and in several Asian countries and considered safe and effective for facial dermal tissue augmentation to correct moderate to severe NLFs. The study products will be administered in accordance with the instructions in section 6.6.1.

Restylane and Restylane Lidocaine, 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 substance itself.

After the injection of Restylane with or without lidocaine, some common injection-related reactions might occur. These reactions include erythema, swelling, pain, itching, bruising or tenderness at the implant site. Typically resolution is spontaneous within a few days after injection into the skin.

The frequency of post market Adverse Event reporting is based on the number of units sold. The reporting frequency of adverse events assessed as related to Restylane Lidocaine is in

line with those for Restylane without lidocaine, 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).

Rare cases of hypersensitivity have been reported after treatment with Restylane Lidocaine. There may be an increased risk for these events in subjects with hypersensitivity to any ingredient of study products. To minimise this risk, subjects with hypersensitivity to any ingredient of study products shall be excluded from the study.

There is a risk that the subject will not gain the full aesthetic correction of NLF. There is also a risk for development of palpable Restylane/Restylane Lidocaine lumps or displacement of the injected Restylane/Restylane Lidocaine. Inflammation or infection has been reported in a few cases after Restylane/Restylane Lidocaine treatment. There may be risk of bruising and/or damaging body structures such as nerves or blood vessels connected to the injection site, however these risks are minor. Detailed information on reported Adverse Events relevant for Restylane/ Resylane Lidocaine is provided in the IFUs.

Given the anticipated low level of transient and acceptable adverse events (AE) in connection with the injection, the risk-benefit assessment of the use of Restylane/Restylane Lidocaine for correction of NLFs appears to offer a clinical benefit at reasonable risk.

3 Objectives and Endpoints

3.1 Primary objective and endpoint

The primary objective is to evaluate the pain associated with injections of Restylane Lidocaine compared to Restylane using a visual analogue scale (VAS).

The proportion of subjects that have a within-subject difference in VAS score (Restylane-Restylane Lidocaine) of at least 10 mm at injection will be calculated together with a two-sided 95% confidence interval. The objective is to show that the confidence interval lies above 50%.

3.2 Secondary objectives and endpoints

The secondary objectives and endpoints are:

- To evaluate the pain associated with injections of Restylane Lidocaine compared to Restylane by assessment of
    - Proportion of subjects that have a within-subject difference in VAS score (Restylane-Restylane Lidocaine) of at least 10 mm (at 15, 30, 45 and 60 minutes after injection).

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3.3 Safety objectives and endpoints

The safety objectives and endpoints are:

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

CCI [redacted]

4 Design of the Study

4.1 General Outline

This is a randomised, multi-center, subject-blinded and evaluator-blinded study in China to evaluate the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane Lidocaine compared to Restylane for correction of moderate to severe nasolabial folds.

Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to study randomisation on day 1. Subsequent to screening eligible subjects will be enrolled in the study.

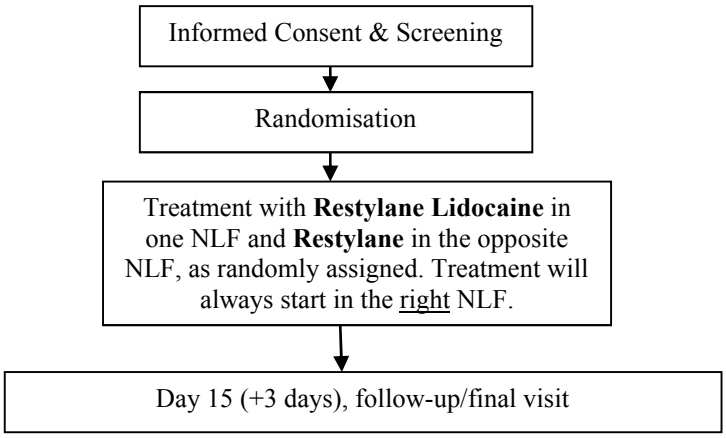
Each subject will receive treatment on Day 1 with Restylane Lidocaine in one NLF and Restylane in the opposite NLF, as randomly assigned. The first injection will always start in the right NLF. No topical or local anesthetic or other pain-relieving medication, including ice, should be used before all VAS assessments are finished. The second injection, that is the injection in the left NLF, will be performed 20±5 minutes after the first injection in order to reduce possible influence of immediate acute pain from the first injection on the pain perception of the second injection..

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 injection. Aspiration for blood should be done in order to avoid accidental intravascular injection. The injection procedure for the two NLFs will be standardised as far as possible in terms of volume used, time needed for injection, and injection technique and will be recorded in the CRFs.

The subject will assess pain experienced during treatment on a 100 mm VAS scale at the end of each injection (before massaging the treatment area). The time should be recorded in the CRF and the pain will thereafter be assessed by the subject at 15±3, 30±3, 45±3, and 60±3 minutes on the VAS after the injection on the right and left NLF, respectively.

CCI [redacted]

Figure 1. Flow chart



4.2 Number of Subjects

The study will be performed at approximately 3 hospitals in China and approximately 70 subjects will be randomised and treated.

4.3 Duration of Subject Participation

The study subjects will be treated at the baseline visit and thereafter followed for 2 weeks. A subject will be involved in the study for up to 28 days.

4.4 Randomisation and blinding

4.4.1 Randomisation

Each subject will be randomised to one of two treatment sequences; either Restylane Lidocaine 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 Lidocaine in the subject's left NLF. Treatment will always start in the subject's right NLF. The randomisation list will be prepared under the supervision of a designated statistician.

Each subject will be assigned a subject number as they arrive for the treatment visit. Randomisation will be assigned via the eCRF system. At the time for randomisation, the subject's initials, date of randomisation, subject number, randomised treatment sequence, and the signature of the Investigator must be documented in a randomisation log. The treatment information will be kept by the Treating Investigator during the study not to be disclosed to the Blinded Evaluator.

4.4.2 Blinding

Because the method of administration is similar, the treatment can be partially 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 treating investigator should also make sure that the subjects are kept blinded during the intervals between the two treatments.

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.

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 Medication, Treatment, and Procedure

Except as noted below, concomitant medications or other treatments or procedures may be utilised when the PI or his/her authorised 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 2 weeks before treatment to avoid increased bruising or bleeding at injection sites.
- Any other anaesthetics or agents structurally related to amide-type anaesthetics, e.g. certain antiarrhythmics, should not be used at day 1 visit.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (facial) retinoids and corticosteroids are prohibited (inhaled corticoids are allowed).
- Procedures involving an active dermal response in the treated area(s) (e.g. tissue augmenting therapy, contouring or revitalisation treatment with permanent or non-permanent fillers, mesotherapy, fat-injection, neurotoxin, laser or light treatment, chemical peeling or dermabrasion) are prohibited.
- Surgery (including aesthetic facial surgical therapy, liposuction, sinus surgery or dental root surgery), or tattoo in the area to be treated are prohibited.
- Participation in any other clinical study is prohibited.

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

4.7 Schedule of events

Table 1. Schedule of Events

Activity	Screening[1]	Baseline/ treatment	Follow-up/ final visit
	Day -14 to 1	Day 1	Day 15 (+3 days)
Visit Number	Visit 1	Visit 2	Visit 3
Informed consent	X		
Demography	X		
Medical history & concurrent diseases	X	X	
Vital signs		X[2]	
Laboratory tests	X		
ECG	X		
Pregnancy test[3]		X[2]	X
Inclusion and Exclusion criteria	X	X	
Randomisation		X	
Photography		X[4]	X
Treatment		X	
VAS evaluation[5]		X	
CCI			
Concomitant medication/procedures	X	X	X
Assessment of Adverse Events	X	X	X

1. Screening and baseline/treatment may be performed on the same day.
2. Should be done before randomization
3. Only for women with childbearing potential
4. Should be done before injection and after injection, also be done once AE occurs after injection
5. Subjects will evaluate injection site pain for each side of the face using the VAS at the end of treatment and 15, 30, 45 and 60 minutes post-treatment.

4.8 Visits

4.8.1 Visit 1: Screening (Day -14 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 such as date of birth, gender and ethnic origin, relevant medical history data as well as relevant ongoing medication and AEs will be collected by the Investigator. Screening laboratory tests and ECG will be performed in accordance to section 8.2 and 8.3 to verify

exclusion criteria 14. CCI [redacted]

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 14 days.

- Informed consent
- Demography (Initials, Date of birth, Gender and Ethnic origin)
- Screening laboratory assessments (haematology and serum chemistry)
- ECG
- Inclusion and exclusion criteria

CCI [redacted]

- Medical history/concurrent diseases
- Concomitant medications and treatments
- AE

4.8.2 Visit 2: Baseline (treatment) (Day 1)

The baseline visit can be performed in direct connection with the screening visit or at latest 14 days after the screening visit. If the screening and baseline visits are separated the inclusion/exclusion criteria will be re-checked and/or if any changes have occurred in the health status, concomitant medication or procedures performed before the subject can be included in the study. Standardized pre-treatment photographs will be taken as described in section 7.4 and a pregnancy test (U-HCG) will be performed in women of childbearing potential.

For each subject, one NLF will be randomly assigned to treatment with Restylane Lidocaine and the opposite NLF to treatment with Restylane. Treatment will be administered according to the instructions in section 6.6. Any device deficiencies or AEs experienced during/after the treatment will be reported and post-treatment photographs will be taken.

CCI [redacted]

- Vital signs (pulse rate, blood pressure, respiratory rate, axillary temperature)
- Inclusion and exclusion criteria
- Pregnancy test for childbearing potential women
- Medical history/concurrent diseases
- Concomitant medications and treatments
- Photography (before and after injection)
- Randomization
- Treatment

- VAS evaluation

CCI [redacted]

- AE

4.8.3 Visit 3: Follow-up/Final visit (day 15 (+3 days)) or early termination

Standardized photographs will be taken. CCI [redacted] any AEs experienced since the treatment or medications used will be reported. A final pregnancy test (U-HCG) will be performed in women of childbearing potential.

- Pregnancy test for childbearing potential women

CCI [redacted]

- Photography

CCI [redacted]

- Concomitant medications and treatments
- AE

4.8.4 Demographics and baseline assessments

Demographics and baseline assessments include:

- Informed consent date
- Date of birth
- Gender
- Initials
- Ethnic origin
- Screening laboratory assessments (haematology and serum chemistry) and ECG
- Inclusion and exclusion criteria

CCI [redacted]

- Relevant medical history/concurrent diseases
- Concomitant medications and treatments
- Pregnancy test (for women of childbearing potential)

5 Subjects

5.1 Subject information and informed consent

The PI or his/her authorised designee must always use the IEC-approved subject information and Informed Consent Form 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 authorised designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study, e.g. explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the 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 authorised designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and transferred to countries outside China. The data will not contain any information that can be used to identify any subject.

All signed Informed Consent Forms shall be filed in the Investigator file. The subject shall be provided with 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 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 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.).

CCI [redacted]

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 lidocaine or other amide type anaesthetics.
3. History of severe or multiple allergies manifested by anaphylaxis.
4. 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

5. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (facial) corticosteroids within 3 months before study treatment (inhaled corticoids are allowed)
6. Previous use of any permanent (non-biodegradable) or semi-permanent facial tissue augmentation therapy or autologous fat 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. Previous tissue revitalisation treatment with laser or light, mesotherapy radiofrequency, chemical peeling or dermabrasion in the midface within 6 months before treatment
10. Previous surgery (including aesthetic facial surgical therapy or liposuction) or tattoo in the area to be treated
11. Scars or deformities, active skin disease, inflammation or related conditions, such as infection, perioral dermatitis, seborrheic eczema, rosacea, acne, psoriasis and herpes zoster near or in the area to be treated.
12. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis or localized or systemic scleroderma.
13. Tendency to form keloids, hypertrophic scars, or any other healing disorder.
14. History of radiation or cancerous or pre-cancerous lesions (e.g. actinic keratosis) in the area to be treated.
15. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion (e.g. 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).
16. Subjects with abnormal 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.
17. Concomitant treatment with topical (facial) retinoids within 3 months or systemic retinoids within 6 months before treatment.
18. Women who are pregnant or breast feeding, or Woman of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period.
19. 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.

20. 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.
21. Participation in any other clinical study or study within 30 days before treatment.

5.4 Screening and Subject Numbers

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.

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 the subject 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 judgement 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.
- **Withdrawal of informed consent:** 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 authorised 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 before declaring the subject lost to follow-up.
- **Other:** Examples of other reasons for withdrawal may be 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.

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 to document subject outcome for the primary and secondary endpoints. In these cases the eCRF for the early termination visit should be completed. The subject will need to follow the same requirements for the visit at day 15.

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, the Investigator shall follow-up the subject until the AE resolves or is assessed by the Investigator to be "chronic" or "stable". Follow-up information for at least three months shall be provided to the Sponsor.

6 Study Products

The term "study products" refers to Restylane Lidocaine and Restylane.

6.1 Investigational Product

Restylane Lidocaine is a sterilized injectable gel consisting of stabilized HA of non-animal origin with concentration 20 mg/mL in phosphate buffered saline with lidocaine hydrochloride 3 mg/ml. The gel is transparent and colorless. The product is supplied in single use syringes with a luer-lock fitting. Each syringe contains 1 mL gel. The syringe is labeled and packaged in a blister.

6.2 Reference Product

Restylane is a sterilized injectable gel consisting of stabilized HA of non-animal origin with concentration 20 mg/mL in phosphate buffered saline. The gel is transparent and colorless. The product is supplied in single use syringes with a luer-lock fitting. Each syringe contains 1 mL gel. The syringe is labeled and packaged in a blister. The reference product is commercial product intended for the Chinese market. An Instruction for Use (IFU) is included in the carton.

6.3 Additional Products and Material

Restylane Lidocaine and Restylane will be supplied by the Sponsor. Two 29G thin walled (TW) × ½" needles are packed together with the Restylane Lidocaine and two same 29G thin walled (TW) × ½" needles are provided separately for Restylane injection. Any other materials will be supplied by the site.

6.4 Packaging, Labelling and Storage

Restylane Lidocaine and Restylane are manufactured by Q-Med AB, Uppsala, Sweden who will supply the study products. Restylane Lidocaine and commercial Restylane will be used for the study.

The syringes are labelled with name of the product, 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 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 25°C and protected from sunlight and freezing. Opened syringes should not be re-used. Accountability will be performed as specified in section 6.5.

6.5 Product accountability

The study product will be released to the PI or his/her authorised designee after study approvals have been received from the IEC and the CTA has been signed by all parties.

The PI must ensure that the study product is kept in a secure location, with access limited to those authorised by the PI.

The study product must be traceable from the manufacturer to its 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 product, deliveries, and return of study product between the Sponsor or a third-party vendor 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, batch number, expiration date, and amount received. In addition, dispensing logs shall be maintained including the product name, dispense date, the number of syringes used, the number of syringes left in stock, and the subject receiving study product. 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. Any malfunctioning study products shall be reported as described in Section 8.5.3.

Product 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 product must not be used outside the study.

6.6 Treatment

6.6.1 Treatment Procedure

The Treating Investigator will check the randomisation 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 Lidocaine and the opposite NLF to treatment with Restylane. Treatment will always start in the subject's right NLF.

The Treating Investigator should keep the subject blind to the treatment by placing an opaque drape or patch over the patient's eyes during the time that the injections are administered. See section 4.4 for details of randomisation and blinding of subjects and Blinded Investigator.

To avoid breakage of the needle, no attempt to bend or otherwise manipulate it 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. 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 injection. 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. For VAS assessment please refer to section 4.1,

Restylane Lidocaine and Restylane should be injected into the middle part of the dermis layer of the facial skin in the NLF. The injection sites may be gently massaged by the Treating Investigator to conform the contour of the surrounding tissue (but only after VAS assessment of the pain at injection).

The linear threading technique can be used to carefully lift up the wrinkle. Information regarding injection technique, time needed for injection, lot number and volume of study product used per NLF will be collected in connection to each treatment.

6.6.2 Treatment regimen (dose)

The maximum volume is 1.5 mL for each NLF.
Sufficient amount of study product should be injected to achieve optimal correction of NLF. The same volume should preferably be used in both NLFs to be able to standardize the evaluation of pain.

6.6.3 Post-treatment Care

Ice in appropriate packaging can be applied on the treatment site for a short period after all VAS assessments are finished to reduce swelling and discomfort.
After the injection, some common injection-related reactions might occur. These reactions include erythema, swelling, pain, itching, bruising or tenderness 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 patient 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 finalised Q-Med AB 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 treatment is an injectable gel administered by the Treating Investigator and the following details of the injection are to be recorded in the eCRF:

- Date for administration
- Time point for administration per NLF
- Administration completion time per NLF
- Administered volume per NLF

- Injection technique or procedure
- Post-treatment care (massage, cooling，etc)
- Time of VAS assessment per NLF

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 Visual analogue scale (VAS)

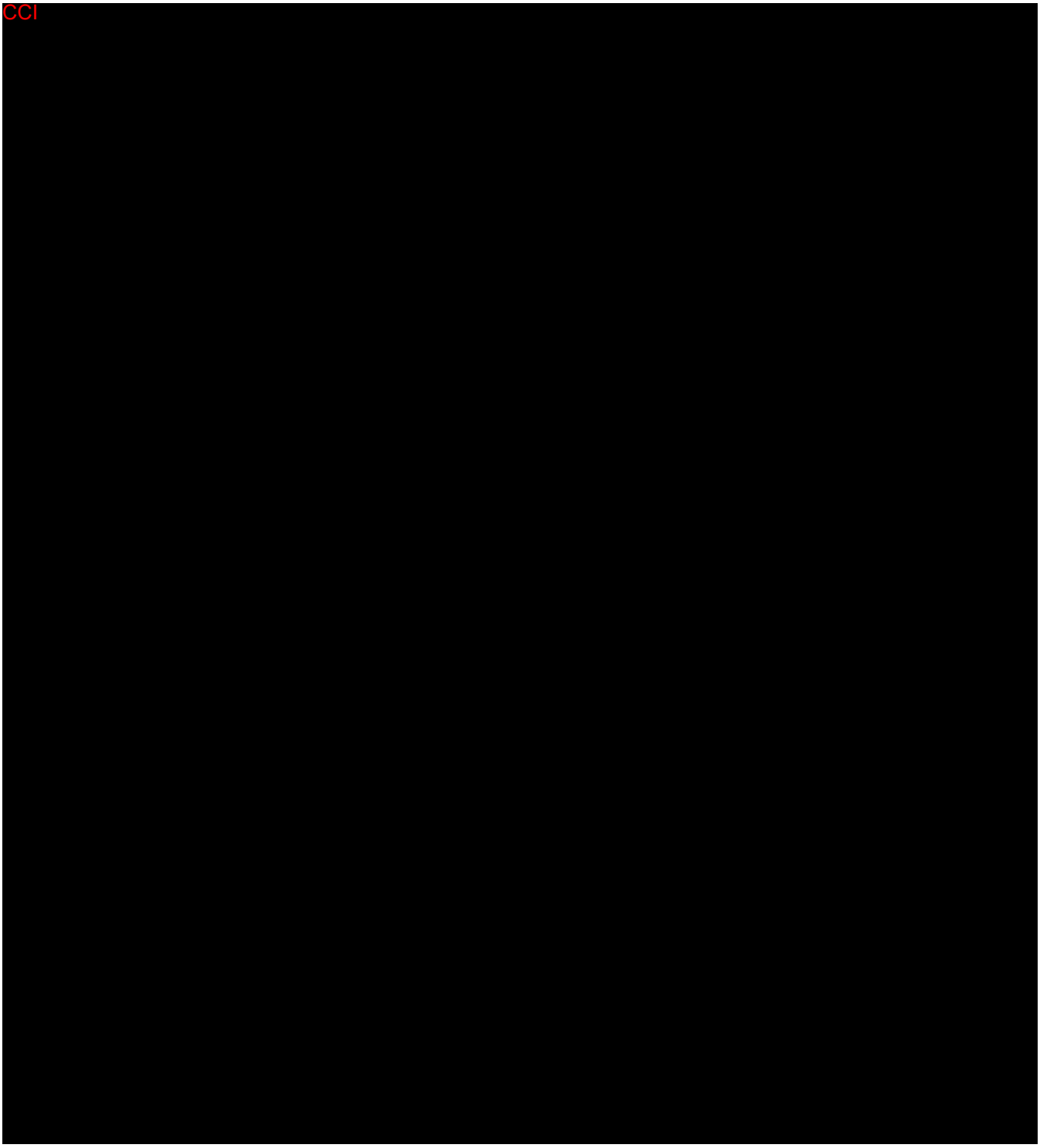
The VAS is a subjective scale to measure pain intensity. The subject shall be instructed to put a vertical mark, approximating the pain experienced during the procedure, on a 100 mm horizontal line labelled “no pain” at the left end and “the worst pain you can imagine” at the right end. The distance in mm from the left end (no pain) to the subject’s VAS mark shall be measured with a standard ruler. Each NLF will be evaluated independently.

Subjects will evaluate injection site pain for each side of the face at the time of injection (before massaging) and at 15, 30, 45, and 60 minutes post-treatment by completing a VAS.

Visual Analogue Scale (VAS)

Put a vertical mark (|) on the line below to show your pain experience.

No pain_____**The worst pain you can imagine**



7.4 Photography

Digital photographs will be taken of each subject at baseline and at follow-up visit. Photographs will be taken both pre- and post-treatment at baseline when treatment is performed. If necessary, the photo should be taken when AEs occurred.

Photo 1: Straight frontal view

Photo 2 and 3: Oblique pictures, 45^{o}, right and left

The same photographic equipment and standardised setting must be used at each visit (e.g. distance, light, facial position and expression). No covering make-up should be used on the photographs.

Photographs will be identified by subject initials, subject number, visit number and date/time of visit. The photographs will be used to document condition at baseline, CCI and to document AEs in the treated area.

8 Safety Assessments

CCI

8.2 Laboratory assessment - Screening

Laboratory samples will be taken at the screening visit (day -14 to day 1).

The following laboratory assessments will be performed:

- Haematology: haemoglobin, 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).
- Urine: (U-HCG) Pregnancy test for women of childbearing potential (pregnancy test will be performed prior to treatment and at the study completion, in all women of childbearing potential).

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. The results will only be used for screening purposes by the investigator and will not be collected in the eCRF.

8.3 ECG-screening

ECG will be taken at the screening visit (day -14 to day 1) and assessed by investigator for clinical significance. The results of ECG will only be used for screening purposes by the investigator and will not be collected in the eCRF.

8.4 Adverse Events

8.4.1 Definition of Adverse Events

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*, 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

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

8.4.2 Definition of Serious Adverse Event

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

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1. a life-threatening** illness or injury, or
2. a permanent impairment of a body structure or body function, or
3. in-patient or prolonged hospitalisation***, or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

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

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

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

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

*** Planned hospitalisation 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).

8.4.3 Recording Instructions

AE will begin to be collected after ICF signed. 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 or from a laboratory test, observations by the study personnel, CCI [redacted] or spontaneous reports from the subjects.

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 module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form.

Investigators, or other study personnel, will 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 8.4.2)
- Causal relationship to study product and 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 sequele, death, chronic/ stable, not recovered at study end)

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

8.4.3.1 Intensity

For each reported AE, the intensity will be recorded. The following definitions of intensity are to be used:

Mild: A mild AE means awareness of symptoms or signs, but easily tolerated (acceptable).

Moderate: A moderate AE means enough discomfort to interfere with usual activity (disturbing).

Severe: A severe AE means incapacity to work or to do usual activity (unacceptable).

If the intensity changes over time the maximum intensity of the AE should be recorded.

8.4.3.2 Causal Relationship and Seriousness

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

A two-point scale (Yes or No) will be used for 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

AE reporting on each subject will start at the screening visit. The reporting will 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

After aware of any SAE, the Investigator shall report it to his/her administrative department of medical device clinical trials under the clinical trial institution, which in turn shall notify the Sponsor in writing. This initial report can be made via fax or e-mail or submitted via the eCRF.

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

- 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 Investigator)
- Name of study product
- Treatment specification

The Investigator will assure completeness of the SAE information and the supporting documentation.

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

Supporting documentation to be provided with the SAE report:

- Concomitant 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:	safety.q-med@galderma.com
Fax number for SAE reporting:	+46 18 474 91 01

E-mail address will be pre-programmed in the eCRF system.

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

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed or faxed to the Sponsor. A copy of the fully completed SAE form shall be kept at the site.

In addition, according to national regulations, the administrative department of medical device clinical trials should, within 24 hours, deliver a written report to the corresponding Ethics Committee and the local food and drug administrative department of province, autonomous region and municipality at the place where the clinical trial institution locates. In case of a death incident, the clinical trial institutions and investigators should furnish the Ethics Committee and the sponsor with all required materials.

The local office in Beijing of the Sponsor is responsible for, within five (5) business days upon being informed, reporting any SAE or device defect with the likelihood of SAE to the food and drug administrative department where it has been registered and the competent authorities of health and family planning at the same level; meanwhile, the Sponsor should notify other clinical trial institutions and investigators participating in the clinical trial, and promptly report it to the Ethics Committee of the involved clinical trial institutions via the administrative department of medical device clinical trials according to national regulations.

For a description of the procedure regarding emergency unblinding, see section 4.4.3.

8.4.6 Follow-up of Unresolved Events after study termination

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 three months. Final outcome after study end should be reported on an AE Follow-up module in the eCRF.

8.4.7 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period the subject must continue to be followed within the study and the outcome of pregnancy must be reported even if the expected date of delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge be submitted to 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.

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. 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 hospitalisation, shall be reported and handled as SAEs. Elective abortions without complications will not be reported as AEs.

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, as observed in the Chinese clinical study for Restylane and in consistent with international results for both products.

Refer to the Restylane Lidocaine EU IFU and Restylane China IFU.

8.5 Device Deficiencies

8.5.1 Definition of Device Deficiency

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

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

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

8.5.2 Recording Instructions

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

8.5.3 Reporting Device Deficiency

The Investigator will complete the Clinical Study Complaint Form to the Sponsor using the contact details specified in section 8.4.5. A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported within 24 hours after the Investigator's awareness in accordance to 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.

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 computerised 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) 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 will be transcribed directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorised study site personnel designated by the PI shall complete data collection. Appropriate training and security measures shall be completed with all authorised 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 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 within 5 working days after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

9.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency by 100%. 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 authorised 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 authorised 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

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

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 photographs, 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, should be clearly identified with the subject number. 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 and IEC review 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 should 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 should 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 shall 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 should be available in the medical record. The source data location log should 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 should be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorised 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 the SAS® system (version 9.0). Confidence intervals CCI [redacted] will be 2-sided and CCI [redacted].

Continuous or semi-continuous variables will be summarised using descriptive statistics, e.g. mean, median and standard deviation. Categorical variables will be presented in frequency tables with number and percent of observations for each level.

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.
- Intention to treat (ITT) efficacy — Includes all subjects who were injected in both NLFs. Subjects are analyzed according to the randomisation assignment.
- Per Protocol (PP) efficacy — Includes all ITT subjects who completed the VAS assessment at injection without any deviations considered to have substantial impact on the primary efficacy outcome.

The ITT population is the primary population for all efficacy analyses. All safety analyses will be based on the Safety population.

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

Primary analysis

The proportion of subjects that have a within-subject difference in VAS (Restylane-Restylane Lidocaine) of at least 10 mm at the time of injection will be calculated together with a two-sided 95% confidence interval. The objective is to show that the confidence interval lies above 50% based on the ITT analysis set. To assess the robustness of the results, the same analysis will be re-run using the PP analysis set.

CCI [redacted]

Secondary analysis

The proportion of subjects that have a within-subject difference in VAS of at least 10 mm at post injection timepoints (15, 30, 45 and 60 minutes after injection) will be calculated together with a two-sided 95% confidence interval.

CCI

[redacted]

10.5 Safety Analysis

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[redacted] A similar summary will also be presented by severity. A graph will be generated to illustrate the incidence over time.

All AEs will be coded according to MedDRA. All AEs will be summarised 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 serious AEs. For related AEs, the number of days to onset and the duration of event will be summarised by SOC and PT using mean, SD, min, max and median statistics.

10.6 Handling of Missing Data

As the 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 to the protocol can be expected to affect both NLFs and evaluations of the same subject the same way.

ITT analysis of VAS at the time of injection will impute a difference (Restylane-Restylane Lidocaine) of 0 mm as the primary method of imputation. This corresponds to assuming no pain relief using Restylane Lidocaine compared to Restylane and is considered as a worst case approach.

All other endpoints will be analyzed on available data, i.e. no imputations will be done.

10.7 Interim Analysis

No interim analysis is planned.

10.8 Data monitoring committee

Not applicable for 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.

Deviations from the statistical plan will be documented in protocol Deviation log.

10.10 Sample Size

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11 Protection of personal data

For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution 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 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. Such information includes information regarding the purposes of the collecting, 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 terminate 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. Authorised representatives from the Sponsoror 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 shall be verified, discussed, and collected, by the monitor and appropriate corrective and preventive actions shall 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 shall be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations shall 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 confirms 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, institutions, 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 multicentre 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*. 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 should 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.

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

15 Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IEC 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

16 References

1. Monheit GD, Coleman KM. Hyaluronic acid fillers. Dermatol 2006 May-Jun; 19(3):141-50.
2. Gold M. The science and art of hyaluronic acid dermal filler use in esthetic applications. J Cosmet Dermatol 2009 Dec; 8(4):301-7.
3. Brandt F1, Bank D, Cross SL, Weiss R. A lidocaine-containing formulation of large-gel particle hyaluronic acid alleviates pain. Dermatol Surg. 2010 Nov; 36 Suppl 3:1876-85..
4. Lindqvist C, Tveten S, Bondevik BE and Fagrell D. A randomized, evaluator-blind, multicenter comparison of the efficacy and tolerability of Lidocaine versus Zyplast in the correction of nasolabial folds. Plast Reconstr Surg. 2005 Jan; 115(1):282-9.
5. Carruthers A, Carey W, De Lorenzi C, Remington K, Schachter D and Sapra S. Randomized, double-blind comparison of the efficacy of 2 hyaluronic acid derivatives, restylane Lidocaine and hylaform, in the treatment of nasolabial folds. Dermatol Surg. 2005 Nov; 31(11 Pt 2):1591-8; discussion 1598.
6. Cohen J, Dayan S, Brandt F, Nelson D, Axford-Gatley R, Theisen M and Narins R. Systemic review of clinical trials of small- and large-gel-particle hyaluronic acid injectable fillers for aesthetic soft tissue augmentation. Dermatol Surg 2013; 39:205-231.
7. Narins RS, Brandt F, Leyden J, Lorenc PZ, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg 2003; 29: 588-95.
8. Taylor SC, Burgess CM, Callender VD. Efficacy of Variable-Particle Hyaluronic Acid Dermal Fillers in Patients with Skin of Color: A Randomized, Evaluator-Blinded Comparative Trial. Dermatol Surg. 2010 May; 36 Suppl 1:741-749.
9. Taylor SC, Burgess CM, Callender VD. Safety of nonanimal stabilized hyaluronic acid dermal fillers in patients with skin of color: a randomized, evaluator-blinded comparative trial. Dermatol Surg. 2009 Oct; 35 Suppl 2:1653-1660.
10. Glogau RG, Kane MA. Effect of injection techniques on the rate of local Adverse Events in patients implanted with nonanimal hyaluronic acid gel dermal fillers. Dermatol Surg. 2008 Jun;34 Suppl 1:S105-109.
11. Dover JS, Rubin MG, Bhatia AC. Review of the efficacy, durability, and safety data of two nonanimal stabilized hyaluronic acid fillers from a prospective, randomized, comparative, multicenter study. Dermatol Surg. 2009 Feb; 35 Suppl 1:322-330; discussion 330-331.
12. Narins RS, Dayan SH, Brandt FS, Baldwin EK. Persistence and improvement of nasolabial fold correction with nonanimal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. Dermatol Surg. 2008 Jun;34 Suppl 1:S2-8; discussion S8.
13. Narins RS, Brandt FS, Dayan SH, Hornfeldt CS. Persistence of Nasolabial Fold Correction with a Hyaluronic Acid Dermal Filler with Retreatment: Results of an 18-Month Extension Study. Dermatol Surg. 2011 May; 37(5):644-650.
14. Xiaoqing Y, Jun X, Changsheng L, Yongguang M, Wei L. A Multicenter Study of the Efficacy and Safety of Restylane in the Treatment of Nasolabial Folds in China. Plastic and Reconstructive Surgery. 2009 124(5); 256e-257e.
15. Heden P, Fagrell D, Jernbeck J, Rylander R, Samuelson U, Sellman G, Stark B. Injection of stabilized hyaluronic acid-based gel of non-animal origin for the correction of nasolabial folds: comparison with and without lidocaine. Dermatol Surg. 2010; 36:775-781.

16. Weiss R, Bank D, Brandt F. Randomized, double-blind, split-face study of small-gel-particle hyaluronic acid with and without lidocaine during correction of nasolabial folds. Dermatol Surg 2010; 36:750–7.

17. Hamilton RG, Strobos J, Adkinson NF Jr. Immunogenicity studies of cosmetically administered nonanimal-stabilized hyaluronic acid particles. Dermatol Surg. 2007 Dec; 33 Suppl 2:S176-85.

18. Q-Med AB internal report MA-27629. Periodic Safety Update Report 2014 - Restylane and Restylane Lidocaine.

17 Appendices

Appendix 1 Declaration of Helsinki

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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.

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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.

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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

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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.

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Appendix 3

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SIGNATURES PAGE

Date	Signed by
2016-06-15 07:23	PPD
Justification	Approved by Technical Expert

2016-06-15 07:25	PPD
Justification	Approved by Project Manager

2016-06-15 07:52	PPD
Justification	Approved by Owner

2016-06-15 08:07	PPD
Justification	Approved by Technical Expert