

 GALDERMA	Title 43CH1626 Clinical Study Protocol	Doc id MA-33281
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Effective date: 2016-12-09 17:18

Effective

A randomized, multi-center, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Restylane Volyme for correction of Midface Volume Deficit and/or Midface Contour Deficiency

Study product: Restylane Volyme

Clinical Trial Number (CTN): 43CH1626

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

This study protocol contains confidential information belonging to Q-Med AB. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and neither disclose it to any third parties (except where required by applicable law) nor use it for any other purpose than in relation to the clinical study described herein.

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Study Administrative Structure

Sponsor

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

Medical Expert

Clinical Project Manager

Study Statistician

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.

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Sponsor Signatures

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

PPD

Q-Med AB

PPD

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

Clinical Project Manager, 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

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Signed Agreement of the Clinical Study Protocol

CTN:

43CH1626

Title of the CSP:

A randomized, multi-center, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Restylane Volyme for correction of Midface Volume Deficit and/or Midface Contour Deficiency

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 Investigator Brochure for Restylane Volyme will serve as a basis for co-operation in this study.

Principal Investigator

Printed name

Signature

Date

Study site

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Synopsis

Title of study:	A randomized, multi-center, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Restylane Volyme for correction of Midface Volume Deficit and/or Midface Contour Deficiency
Clinical Trial Number:	43CH1626
Countries involved, number of sites/country, number of subjects:	The study will be conducted at approximately 5 sites in China. Group A: Up to 20 subjects (2 first treated subjects per Treating Investigator, each site will have 2 treating investigators as maximum) will be enrolled as group A. These subjects will all receive treatment with Restylane Volyme. Group B: Evaluator treatment-blind group with approximately 148 subjects will be randomized in a CC1 ratio to treatment group or no-treatment control group, i.e., 111 subjects assigned to the Treatment Group and 37 subjects assigned to the Control Group.
Objectives:	<ul style="list-style-type: none"> • To evaluate the effectiveness of Restylane Volyme in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency • To evaluate the safety of Restylane Volyme in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency
Endpoints:	<u>Primary effectiveness endpoint:</u> <ul style="list-style-type: none"> • Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the blinded evaluator at 6 months after last treatment in Treatment Group, and at 6 months after randomization in Control Group. <p>CC1</p>

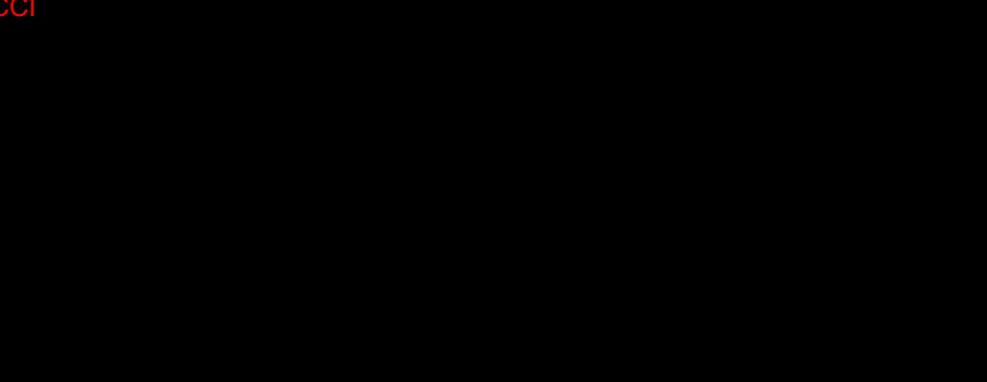
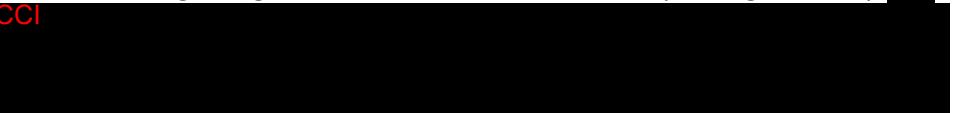
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	CCI <u>Safety endpoints:</u> <ul style="list-style-type: none"> Incidence, intensity, duration, and onset of adverse events (AEs) collected throughout the study. CCI	
Study Design:	<p>This is a randomized, evaluator-blinded, no-treatment controlled study in subjects with Midface Volume Deficit and/or Midface Contour Deficiency.</p> <p>Subjects will be screened for eligibility within 21 days prior to Baseline. The first 2 eligible subjects for each Treating Investigator will receive treatment as Group A. Before start of enrolment into Group B, the injection technique will be evaluated by the Sponsor and performed after the subjects in Group A for each site have received their first treatment. If treatments are found to be correctly performed, no further training is needed, there are no outstanding questions regarding the injection technique and no other corrective actions are identified, the enrolment in Group B can start for that site. Subjects in group B will be randomized either to the Treatment Group or the Control Group in a CCI ratio.</p> <p>Summaries of the results for Group A and B will be done separately in the study report.</p> <p><u>Treatment</u></p> <p>Each subject assigned to Group A or the Treatment Group in Group B will receive an initial treatment on Day 1. A touch-up treatment may be performed 4 weeks after the initial treatment if optimal midface augmentation has not been obtained. Optimal midface augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the treating investigator and subject.</p> <p>Subjects assigned to the Control Group in Group B will not receive treatment at baseline but will return for routine follow-up for 12 months. At month 6 visit, subjects in Control Group will be offered a treatment and an optional touch-up treatment.</p> <p><u>Evaluation of effectiveness</u></p> <p>Midface fullness will be assessed using a separate Four-Point MMVS with photo guides for the right and left side by CCI; and by the blinded evaluator at screening, baseline, ^{cc1} 6, CCI months after last treatment in Group A and Treatment Group, and at screening, baseline, ^{cc1} and 6 months after randomization, as well as ^{cc1} and 6 months after last treatment in Control Group.</p> <p>CCI</p>	

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	CCI  <u>Evaluation of safety</u> Information regarding AEs will be collected continuously during the study. CCI CCI 
Inclusion criteria:	The subject must meet the following criteria to be eligible for the study: <ol style="list-style-type: none"> 1. Signed and dated informed consent to participate in the study. 2. Men or women aged 18 years of age or older of Chinese origin. 3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim for the duration of the study (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency etc.). 4. Subjects seeking augmentation therapy for the midface. 5. MMVS score of 2, 3 or 4 on each side of the face as assessed by the blinded evaluator.
Exclusion criteria:	The presence of any of the following exclusion criteria will exclude a subject from enrolment in the study: <ol style="list-style-type: none"> 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. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, ultrasound, cryotherapy, chemical peeling or dermabrasion in the midface within 6 months before treatment. 5. Previous surgery (including aesthetic facial surgical therapy or liposuction) or tattoo in the area to be treated. 6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent filler, autologous fat, lifting threads or permanent implant below the level of the lower orbital rim. 7. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months before treatment.

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	<p>8. Previous use of any neurotoxin below the level of the lower orbital rim within 9 months before treatment.</p> <p>9. History of radiation or cancerous or pre-cancerous lesions (e.g. actinic keratoses) in the area to be treated.</p> <p>10. 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.</p> <p>11. Subjects with a 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.</p> <p>12. Ongoing or chronic infection in mouth or dentals.</p> <p>13. Ongoing or chronic infection in head and neck region.</p> <p>14. Tendency for edema, puffiness or swelling in the area to be treated.</p> <p>15. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis or localized or systemic scleroderma.</p> <p>16. Subjects presenting with porphyria.</p> <p>17. Tendency to form keloids, hypertrophic scars, or any other healing disorder.</p> <p>18. 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.</p> <p>19. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (facial) corticosteroids within 3 months before treatment (inhaled corticoids are allowed).</p> <p>20. Treatment with topical (facial) retinoids within 3 months or systemic retinoids within 6 months before treatment.</p> <p>21. The presence of moderate or severe abnormal rating for midface symmetry, i.e. more than 1 point difference in MMVS score between each side of the face.</p> <p>22. 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).</p> <p>23. 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</p>	

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	<p>or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.</p> <p>24. 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.</p> <p>25. Intention to change a significant amount of weight (≥ 2 BMI) during the study period.</p> <p>26. 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.</p> <p>27. Participation in any other clinical study within 30 days before treatment.</p>	
Investigational product, dose and mode of administration:	<p>Restylane Volyme is a sterile, biodegradable, transparent gel of non-animal cross-linked hyaluronic acid with the addition of lidocaine hydrochloride 3mg/mL. The gel is supplied in a 1 mL prefilled plastic syringe. The contents of the syringe are sterilized using moist heat. The syringe is packaged individually in a blister, with two 27G x $\frac{1}{2}$" Ultra thin wall needles.</p> <p>Restylane Volyme should be injected into supraperiosteal zone or subcutis in the midface.</p> <p>Restylane Volyme will be administered inferior to the maxillary prominence, superior to the plane of nasal alae, including the area from the lateral canthus to the medial canthus and lateral to the nose on the subject's right and left sides. Investigators will be instructed to use the amount of dermal filler necessary to achieve an optimal aesthetic result.</p> <p>The injection procedure should strictly follow rules of aseptic surgical technique. Defects should be fully corrected, but not overcorrected. The injection site should be massaged to conform to the contour of the surrounding tissues.</p> <p>A maximum dosage of 2 mL per treatment site (i.e., right and left midface respectively) is recommended at each treatment session, i.e., initial treatment or touch-up treatment respectively.</p>	
Reference therapy, dose and mode of administration:	Not applicable.	
Duration of treatment and follow-up:	The total duration for each subject will be approximately 14 months.	
Effectiveness Assessment:	<p><u>Medicis Midface Volume Scale (MMVS):</u></p> <p>MMVS is a Four-Point scale that assesses the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4) as described below. The blinded evaluator and CCI [REDACTED] will rate the subject's right and left midface for severity of volume deficiency using the MMVS at all applicable study visits.</p> <p>CCI</p>	

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Safety Assessment:	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 <i>“Since your last clinical visit have you had any health problems?”</i> Information on AEs can also be obtained from laboratory test report, signs and symptoms detected during each examination, observations by the study

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	<p>personnel, subject diaries or spontaneous reports from the subjects.</p> <p>CCl</p>
Statistical Methods:	<p>All summaries will be done separately for Group A and B. CCl</p> <p>Primary analysis</p> <p>The percentage of responders (a responder will be defined as a subject with at least 1 point improvement from baseline MMVS on both sides of the face concurrently) will be calculated for Treatment Group at 6 months after last treatment, and for Control Group at 6 months after randomization based on the blinded evaluator's assessment. CCl</p> <p>CCl</p>
	<p>CCl</p>
	<p>Safety</p> <p>CCl</p> <p>Adverse event incidences will be summarized by MedDRA system organ class (SOC) and preferred term (PT).</p> <p>Sample size</p>

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There are no available clinical data for Restylane Volyme studied under conditions similar to the current study. However, based on what is seen in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a response rate of at least 70% in the Restylane Volyme treatment group at Month 6. For the no treatment control group, response rates as high as 35% have been observed in Glogau et al¹¹. Based on this, it was assumed that the response rate will be maximum 35% in the no-treatment control group at Month 6.

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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
FAS	Full Analysis Set
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.
MedDRA	Medical Dictionary for Regulatory Activities
MMVS	Medicis Midface Volume Scale

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NSAIDs	non-steroid anti-inflammatory drugs
PI	Principal Investigator
PP	Per protocol
QA	Quality assurance
RA	Regulatory authority
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
SOC	System organ class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
U-HCG	Urinary human chorionic gonadotropin
WHO	World Health Organization

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Appendix 2	Photo guide for Medicis Midface Volume Scale

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1 Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the Clinical Trial Agreement (CTA), the Clinical Study Protocol (CSP), applicable Good Clinical Practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2011 shall be followed. The International Conference on 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

By June 2016, Restylane Volyme has been regulatory cleared in 24 countries/regions, including EU, Canada, Australia, Hong Kong, Korea, India, etc. as a medical device for facial tissue volume augmentation. It is not intended for pediatric use. In Europe, the label recommends the product to be used for the correction of facial volume, for instance cheeks and chin.

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 used¹. 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.

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During manufacturing, cross-links are introduced between the HA chains to obtain a gel network and as a result the duration of the gel in the body is several months, as compared to only a few days for a solution of native HA.

Restylane Volyme is a sterile, biodegradable, transparent gel of non-animal cross-linked hyaluronic acid with the addition of lidocaine hydrochloride 3mg/mL, produced using the Optimal Balance Technology (OBT) process. The gel is supplied in a 1 mL prefilled plastic syringe. The contents of the syringe are sterilized using moist heat. The syringe is packaged individually in a blister, with two 27G x ½" Ultra thin wall needles.

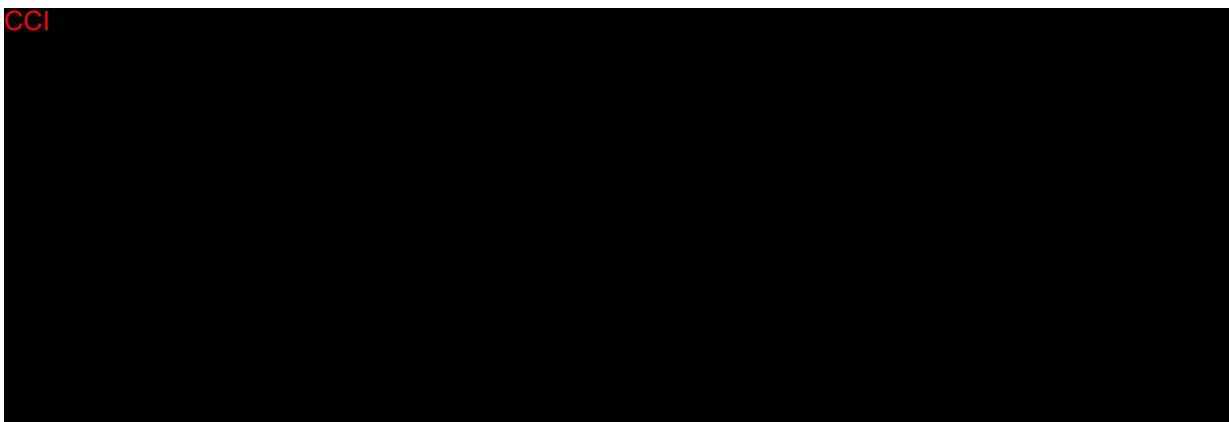
Restylane Volyme was previously under the brand name Emervel Volume Lidocaine, however, it has been re-branded as Restylane Volyme from 2016.

2.3 Reference product description

Not applicable as no dermal filler intended for midface volume deficit and/or midface contour deficiency is available in China at the time of this protocol

2.4 Previous experience

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2.4.2 Clinical Documentation

The safety and performance of Restylane Volyme have been demonstrated in two open multi-center clinical trials ^{5, 6, 7}, an observational study⁸ as well as in post-market surveillance.

In the study of Talarico et al⁵, 60 subjects were treated for full face augmentation including cheek (N=27). Most subjects (71.6%) had 3 or 4 indications injected. For cheek treatment, proportion of subjects with improvement based ratings on a 4-point Volume Loss Scale after Restylane Volyme treatment were 100% at week 3 and 66.6% at month 18. For all indications, more than 60% of the volume gained at 3 weeks was sustained at 18 months based on 3D digital imaging. At 18 months, 95.0% of subjects had improved full-face GAIS and all subjects were satisfied with their aesthetic outcome. A majority of the subjects reported anticipated local tolerability reactions after treatment. The most common are mild erythema and edema. The tolerability reactions typically resolved spontaneously within 3 weeks. One subject (1.6%) had treatment-related adverse events and resolved without

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treatment before the next visit 3 weeks later. There were no severe AE or AEs leading to study discontinuation.

In the 6 month study of Rzany et al⁶, up to 5 Restylane Emervel Collection of products were allowed for full face augmentation (at least 2 indications per patient) in 77 subjects. A total of 57 subjects received Emervel Volume (without lidocaine). A separate analysis was done and published by Kestemont et al⁷ to assess the effectiveness, patient satisfaction, and safety of Emervel Volume in patients with bilateral volume loss of the cheeks. Investigators evaluated the great majority of subjects as much or very much improved in terms of aesthetic improvement of their cheeks at week 3 and at months 3 and 6 (89.3%, 90.9%, and 76.4%, respectively). After six months, 65.8 percent of the correction achieved at week 3 (optimal correction) was maintained in terms of cheek thickness (caliper assessments), confirmed by 67.7 percent of the volume maintained based on 3-D volume analyses. The majority of subjects (92.1%) were satisfied or very satisfied with their aesthetic outcome. A good tolerability profile was observed.

In a non-interventional study of Farhi et al⁸, 1822 patients were treated with one or more of the Restylane Emervel Collection of products. As it was a non-interventional study product choice and injection volumes were at the discretion of the 58 participating physicians. Emervel Volume (without lidocaine) was primarily used for cheek augmentation (n=121) but also for other indications including tear trough (n=66), nasolabial folds (n=64), and marionette lines (n=33). More than 90% of patients had no or just mild erythema, bruising, edema and pain. No serious adverse events were reported up to 15 months after injection.

Post market surveillance data for Restylane Volyme also support that the AE profile is acceptable.

2.5 Study rationale and Justification for design

Based on pre-clinical testing/previous clinical experience as described in Section 2.4, it is considered justified to conduct a study to investigate superiority of Restylane Volyme relative to no-treatment in the treatment of Midface volume Deficit and/or Midface Contour Deficiency by measuring the percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face, at 6 months. The study will be used as clinical documentation for registration of the product in China. No treatment control is chosen as no dermal filler intended for midface volume deficit and/or midface contour deficiency is available in China at the time of this protocol

Evaluation with standardised evaluation tools will be used in the study. The MMVS is a validated scale⁹ and was used in the Restylane Lyft registration clinical trial¹⁰ for midface augmentation in US and accepted by FDA.

2.6 Risk and benefits

By June 2016, Restylane Volyme has been regulatory cleared in 24 countries/regions and considered safe and effective for facial dermal tissue augmentation. As all other injectable medical devices, Restylane Volyme has the potential to cause complications. After the injection of Restylane Volyme, some common injection-related reactions might occur. These reactions include bruising, erythema, swelling, pain, tenderness, or itching at the implant site. Typically, resolution is spontaneous within one week after injection into the skin. The

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intensity and duration of these events are usually considered tolerable by a majority of subjects. The study products will be administered in accordance with the instructions in Section **Error! Reference source not found..**

The primary potential benefit of the study is a perceived improvement in the treated areas. However, there is a risk that the subject will not gain the full aesthetic correction of Midface volume Deficit and/or Midface Contour Deficiency. There is also a risk for development of palpable lumps or displacement of the injected gel. Inflammation or infection have been reported in a few cases after HA filler treatment. There may be risk of damaging body structures such as nerves or blood vessels connected to the injection site, however these risks are minor. Following facial aesthetic treatments isolated rare cases have been reported regarding ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction. Detailed information on reported AEs relevant for Restylane Volyme is provided in the IB.

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

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 Perlane Lidocaine for treatment of Midface volume Deficit and/or Midface Contour Deficiency appears to offer a clinical benefit at reasonable risk.

Only study investigators qualified by education and experience, and who are skilled in the use of dermal fillers from their clinical practice and participation in clinical research, will be chosen in order to assure proper device implantation and management of study risk.

3 Objectives and Endpoints

3.1 Objectives of the study

- To evaluate the effectiveness of Restylane Volyme in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.
- To evaluate the safety of Restylane Volyme in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.

3.2 Endpoints of the study

3.2.1 Primary effectiveness endpoint:

- Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by blinded evaluator at 6 months after last treatment in Treatment Group, and at 6 months after randomization in Control Group.

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3.2.3 Safety endpoints:

- Incidence, intensity, duration, and onset of adverse events (AEs) collected throughout the study.

CCI

4 Design of the Study

4.1 General Outline

This is a randomized, evaluator-blinded, no-treatment controlled study in subjects with Midface Volume Deficit and/or Midface Contour Deficiency.

Subjects will be screened for eligibility within 21 days prior to Baseline. The first 2 eligible subjects for each Treating Investigator (each site will have 2 treating investigators as maximum) will receive treatment as Group A. Before start of enrolment into Group B, the injection technique will be evaluated by the Sponsor and performed when the subjects in Group A for each site have received their first treatment. If treatments are found to be correctly performed, no further training is needed, there are no outstanding questions regarding the injection technique and no other corrective actions are identified, the enrolment in Group B can start for that site. Subjects in group B will be randomized either to the Treatment Group or the Control Group in a CCI ratio.

Summaries of the results for Group A and B will be done separately in the study report.

Treatment

Each subject assigned to Group A or the Treatment Group in Group B will receive an initial treatment on Day 1. A touch-up treatment may be performed 4 weeks after the initial treatment if optimal midface augmentation has not been obtained. Optimal midface augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the treating investigator and subject.

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Subjects assigned to the Control Group in Group B will not receive treatment at baseline but will return for routine follow-up for 12 months. At month 6 visit, subjects in control group will be offered a treatment and an optional touch-up treatment.

Evaluation of effectiveness

Midface fullness will be assessed using a separate Four-Point MMVS with photoguides for the right and left side [REDACTED]; and by the blinded evaluator, at screening, [REDACTED] 6, [REDACTED] months after last treatment in Group A and Treatment Group, and at screening, [REDACTED] 6 months after randomization, as well as [REDACTED] 6 months after last treatment in Control Group.

[REDACTED]
[REDACTED]

Evaluation of safety

Information regarding AEs will be collected continuously during the study. [REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

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4.2 Number of Subjects

The study will be performed at approximately 5 sites in China and approximately 168 subjects will be enrolled.

4.3 Duration of Subject Participation

The total duration for each subject will be approximately 14 months.

4.4 Randomization and blinding

4.4.1 Randomization

Approximately 148 subjects will be randomized in a **CC1** ratio to treatment with Restylane Volyme or to no treatment. Before starting the study, a computer generated randomization list will be prepared under the supervision of a designated statistician. The randomization list will be stratified by center.

Each subject will be assigned a subject number as they arrive for the treatment visit. For group B, randomization will be assigned via the eCRF system. At the time for randomization, the subject's initials, date of randomization, subject number, randomized treatment, and the signature of the Investigator must be documented in a randomization 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

Only the evaluator will be blinded, both treating investigator and subjects will be open-labelled.

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.

Any concomitant medications and any relevant medical history (including prior facial dermatological procedures performed, and fillers or implants used) or concurrent diseases will be asked for.

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4.6 Concomitant Medication, Treatment, and Procedure

Except as noted below, concomitant medications or other treatments or procedures may be utilized when the PI or his/her authorized designee considers it medically necessary.

Information regarding any use of concomitant medications, including over-the-counter medications administered during the study is to be recorded in the eCRF. The generic name or the trade name of all concomitant medication or a description of the procedure and the reason for its use shall be documented in the eCRF.

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

- Anticoagulants or inhibitors of platelet aggregation (*e.g.* aspirin or other non-steroidal anti-inflammatory drugs [NSAIDs]), Omega-3, or Vitamin E should not be used within two weeks before treatment to avoid increased bruising or bleeding at injection sites.
- Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics *e.g.*, certain antiarrhythmics, since the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (*e.g.*, monoclonal antibodies) is prohibited.
- Long term concomitant treatment with systemic or topical (facial) corticosteroids is prohibited (inhaled corticoids are allowed). Corticosteroids should be used with caution and should be adjudged as necessary by the Investigator.
- Use of systemic or topical (facial) retinoic acid is prohibited.
- Facial tissue augmenting therapy, contouring or revitalization treatment with fillers, lifting threads, permanent implant, mesotherapy, radiofrequency, ultrasound, cryotherapy, fat-injection, neurotoxin, laser or light treatment, chemical peeling or dermabrasion below the level of the lower orbital rim are prohibited.
- Planned surgery including aesthetic facial surgical therapy or facial liposuction, sinus surgery or dental root surgery, or tattoo in the area to be treated is prohibited.
- Participation in any other clinical study is prohibited

If a subject has used any of the above prohibited medications or performed any of the above prohibited procedures, a protocol deviation 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 for Group A and Treatment Group

	Group A and Treatment Group					
	Screening ^a	Baseline ^a / Initial treatment	Optional Touch-up ^b	Follow-up	Follow-up	Final visit / Early termination
	D-21 to D1	D1	4W($\pm 3d$) after randomization	4W($\pm 3d$) after Last treatment	3M($\pm 1w$), 6M($\pm 1w$) and 9M ($\pm 2w$) after last treatment	12M ($\pm 2w$) after last treatment
Informed consent	X					
Height, Demography	X					
Weight	X	X	X	X	X	X
Medical history & concurrent diseases	X	X				
Concomitant medication/procedures	X	X	X	X	X	X
Vital signs		X ^c				
Laboratory tests	X				X ^e	X ^f
ECG	X					
Pregnancy test		X ^c	X ^c			X
Inclusion and Exclusion criteria	X	X				
Randomization		X				
Treatment		X	X			
MMVS (Blinded Evaluator)	X	X ^c			X	X
CCI						
Photography		X ^c	X ^c	X ^d	X	X



CCI

Device deficiencies		X	X			
Assessment of AE	X	X	X	X	X	X
Study termination						X

- a) Screening visit and baseline visit can be combined to one visit if feasible.
- b) This visit is only for subjects who receive touch-up (If no touch-up performed, subjects will conduct the 4w after last treatment visit).
- c) Prior to treatment.
- d) Extra set of Photographs (taken 10 minutes after the first photos) will be taken and used for validation purpose as needed.
- e) Only performed at 6M.
- f) Only performed at early termination if termination occurs before 6 months visit after last treatment

Table 2. Schedule of Events for Control Group

Activity	Control Group									
	Screening ^a	Baseline ^a	Follow-up	Follow-up	Follow-up /Treatment	Optional Touch-up ^b	Follow-up	Follow-up	Final visit / Early termination	
	D-21 to 1	D1	4W(±3d) after randomization	3M (±1w) after randomization	6M(±1w) after randomization	4W(±3d) after 6M treatment	4W(±3d) after last treatment	3M (±1w) after last treatment	6M (±1w) after last treatment	
Informed consent	X									
Height, Demography	X									
Weight	X	X	X	X	X	X	X	X	X	
Medical history & concurrent diseases	X	X								
Concomitant medication/procedures	X	X	X	X	X	X	X	X	X	



Vital signs		X			X ^c					
Laboratory tests	X				X ^c					X
ECG	X									
Pregnancy test		X			X ^c	X ^c				X
Inclusion and Exclusion criteria	X	X								
Randomization		X								
Treatment					X	X				
MMVS (Blinded Evaluator)	X	X		X	X ^c			X		X
CCI										
Photography		X	X ^d	X	X ^c	X ^c	X	X		X
CCI										
Device deficiencies					X	X				
Assessment of AE	X	X	X	X	X	X	X	X		X
Study termination										X

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

b) This visit is only for subjects who receive touch-up (If no touch-up performed, subjects will conduct the 4w after last treatment visit).

c) Prior to treatment.,

d) Extra set of Photographs (taken 10 minutes after the first photos) will be taken and used for validation purpose as needed.

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4.8 Visits

4.8.1 Visits for Group A and Treatment Group

4.8.1.1 Screening (D-21 to D1)

- Informed consent
- Demography (Initials, Date of birth, Gender and Ethnic origin)
- Height and Weight
- Screening laboratory tests (haematology and serum chemistry)
- ECG
- Inclusion and exclusion criteria
- MMVS (by Blinded Evaluator and **CCI** [REDACTED])
- Medical history/concurrent diseases including prior facial dermatological procedures performed, and fillers or implants used
- Concomitant medications/procedures
- AE during the visit

4.8.1.2 Baseline (D1)

- Weight
- Medical history/concurrent diseases
- Vital signs (pulse rate, blood pressure, respiratory rate, axillary temperature)
- Inclusion and exclusion criteria
- Pregnancy test for childbearing potential women
- Photography (before injection)
- Randomization
- MMVS (by Blinded Evaluator and **CCI** [REDACTED])
- Treatment
- **CCI** [REDACTED]
- Concomitant medications /procedures
- Device deficiencies
- AE since last visit

4.8.1.3 Optional Touch-up 4W ($\pm 3d$) after randomization (only for subjects who receive touch-up)

- Weight
- Photography (before injection)
- **CCI** [REDACTED]
- [REDACTED]
- Pregnancy test for childbearing potential women (before injection)
- Treatment
- **CCI** [REDACTED]
- [REDACTED]
- Concomitant medications/procedures

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- Device deficiencies
- AE since last visit

4.8.1.4 4W ($\pm 3d$) after last treatment

- Weight
- Photography
- Note: extra set of photos (taken 10 minutes after the first photos) will be taken and used for validation as needed.
- CCI
- [REDACTED]
- Concomitant medications /procedures
- AE since last visit

4.8.1.5 3M ($\pm 1w$), 6M ($\pm 1w$) and 9M ($\pm 2w$) Follow-up after last treatment

- Weight
- Photography
- MMVS (by Blinded Evaluator and CCI [REDACTED])
- CCI [REDACTED]
- Concomitant medications /procedures
- AE since last visit
- Laboratory tests (Only performed at 6M)

4.8.1.6 12M ($\pm 2w$) after last treatment Final visit or Early termination

- Weight
- Photography
- MMVS (by Blinded Evaluator and CCI [REDACTED])
- CCI [REDACTED]
- Pregnancy test for childbearing potential women
- Concomitant medications/procedures
- AE since last visit
- Laboratory tests (Only performed at early termination if termination occurs before 6 months visit after last treatment)
- Study termination

4.8.2 Visits for Control Group

4.8.2.1 Screening (D-21 to D1)

- Informed consent
- Demography (Initials, Date of birth, Gender and Ethnic origin)
- Height and Weight
- Screening laboratory tests (haematology and serum chemistry)

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- ECG
- Inclusion and exclusion criteria
- MMVS (by Blinded Evaluator and **CCI** [REDACTED])
- Medical history/concurrent diseases including prior facial dermatological procedures performed, and fillers or implants used
- Concomitant medications/procedures
- AE during the visit

4.8.2.2 *Baseline (D1)*

- Weight
- Medical history/concurrent diseases
- Vital signs (pulse rate, blood pressure, respiratory rate, axillary temperature)
- Inclusion and exclusion criteria
- Pregnancy test for childbearing potential women
- Photography
- Randomization
- MMVS (by Blinded Evaluator and **CCI** [REDACTED])
- Concomitant medications /procedures
- AE since last visit

4.8.2.3 *4W ($\pm 3d$) Follow-up after randomization*

- Weight
- Photography

Note: extra set of photos (taken 10 minutes after the first photos) will be taken and used for validation as needed.
- **CCI** [REDACTED]
- [REDACTED]
- Concomitant medications /procedures
- AE since last visit

4.8.2.4 *3M ($\pm 1w$) Follow-up after randomization*

- Weight
- Photography
- MMVS (by Blinded Evaluator and **CCI** [REDACTED])
- **CCI** [REDACTED]
- [REDACTED]
- Concomitant medications /procedures
- AE since last visit

4.8.2.5 *6M ($\pm 1w$) Follow-up after randomization / treatment*

- Weight
- Vital signs (pulse rate, blood pressure, respiratory rate, axillary temperature)
- laboratory tests (haematology and serum chemistry)
- Pregnancy test for childbearing potential women (before injection)

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- MMVS (by Blinded Evaluator and CCI [REDACTED])
- Photography (before injection)
- CCI [REDACTED]
- [REDACTED]
- Treatment
- CCI [REDACTED]
- Concomitant medications /procedures
- Device deficiencies
- AE since last visit

4.8.2.6 Optional Touch-up 4W ($\pm 3d$) after 6M treatment (only for subjects who received touch-up)

- Weight
- Photography (before injection)
- CCI [REDACTED]
- [REDACTED]
- Pregnancy test for childbearing potential women (before injection)
- Treatment
- CCI [REDACTED]
- [REDACTED]
- Concomitant medications /procedures
- Device deficiencies
- AE since last visit

4.8.2.7 4W ($\pm 3d$) Follow-up after last treatment

- Weight
- Photography
- CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- Concomitant medications /procedures
- AE since last visit

4.8.2.8 3M ($\pm 1w$) Follow-up after last treatment

- Weight
- Photography
- MMVS (by Blinded Evaluator and CCI [REDACTED])
- CCI [REDACTED]
- [REDACTED]
- Concomitant medications /procedures
- AE since last visit

4.8.2.9 6M ($\pm 1w$) after last treatment Final visit / early termination

- Weight
- Photography

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- MMVS (by Blinded Evaluator and **CCI** [REDACTED])
- **CCI** [REDACTED]
- [REDACTED]
- Pregnancy test for childbearing potential women
- laboratory tests (haematology and serum chemistry)
- Concomitant medications /procedures
- AE since last visit
- Study termination

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 of age or older of Chinese origin.

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3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim for the duration of the study (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency etc.).
4. Subjects seeking augmentation therapy for the midface.
5. MMVS score of 2, 3 or 4 on each side of the face as assessed by the blinded evaluator.

5.3 Exclusion Criteria

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

1. Known/previous allergy or hypersensitivity to any injectable HA gel.
2. Known/previous allergy or hypersensitivity to local anaesthetics, e.g. lidocaine or other amide-type anaesthetics.
3. History of severe or multiple allergies manifested by anaphylaxis.
4. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, ultrasound, cryotherapy, chemical peeling or dermabrasion in the midface within 6 months before treatment.
5. Previous surgery (including aesthetic facial surgical therapy or liposuction) or tattoo in the area to be treated.
6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent filler, autologous fat, lifting threads or permanent implant below the level of the lower orbital rim.
7. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months before treatment.
8. Previous use of any neurotoxin below the level of the lower orbital rim within 9 months before treatment.
9. History of radiation or cancerous or pre-cancerous lesions (e.g. actinic keratosis) in the area to be treated.
10. Scars or deformities, active skin disease, inflammation or related conditions, such as infection, perioral dermatitis, seborrheic eczema, rosacea, acne, psoriasis and herpes zoster near or in the area to be treated.
11. Subjects with a dental or oral status on visual inspection that in the opinion of the Investigator would make the subject unsuitable for inclusion, or Subjects with dental, oral or sinus surgery within past 12 months prior to the treatment visit or planned surgery, including dental implants, during the study period.
12. Ongoing or chronic infection in mouth or dentals.
13. Ongoing or Chronic infection in head and neck region.
14. Tendency for edema, puffiness or swelling in the area to be treated.

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15. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis or localized or systemic scleroderma.
16. Subjects presenting with porphyria.
17. Tendency to form keloids, hypertrophic scars, or any other healing disorder.
18. 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).
19. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (facial) corticosteroids within 3 months before treatment (inhaled corticoids are allowed).
20. Treatment with topical (facial) retinoids within 3 months or systemic retinoids within 6 months before treatment.
21. The presence of moderate or severe abnormal rating for midface symmetry, i.e. more than 1 point difference in MMVS score between each side of the face.
22. 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).
23. 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.
24. 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.
25. Intention to change a significant amount of weight (≥ 2 BMI) during the study period
26. 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.
27. Participation in any other clinical 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.

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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. In these cases the eCRF for the early termination visit should be completed. The subject will need to follow the same requirements for the final visit.

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, such events shall be

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followed-up after the last study visit until resolved, assessed as chronic or stable, or for at least three months.

6 Study Products

6.1 Investigational Product

Restylane Volyme is a sterile, biodegradable, transparent gel of non-animal cross-linked hyaluronic acid with the addition of lidocaine hydrochloride 3mg/mL. The gel is supplied in a 1 mL prefilled plastic syringe. The contents of the syringe are sterilized using moist heat. The syringe is packaged individually in a blister, with two 27G x ½" Ultra thin wall needles.

6.2 Reference Product

Not applicable.

6.3 Additional Products and Material

The study product is supplied in sterile 1 mL syringes, with two 27G x ½" Ultra thin wall needles for injection. Any other materials will be supplied by the site.

6.4 Packaging, Labelling and Storage

Restylane Volyme is manufactured by Q-Med AB, Uppsala, Sweden who will supply the study products. Restylane Volyme 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

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

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

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. 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.

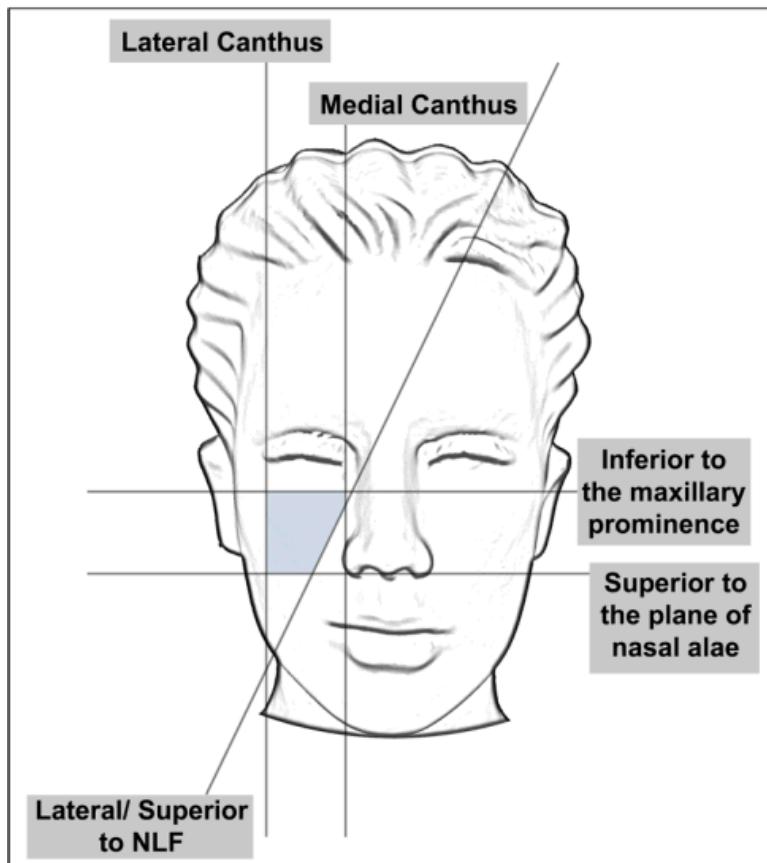
Restylane Volyme should be injected into supraperiosteal zone or subcutis in the midface.

Restylane Volyme will be administered inferior to the maxillary prominence, superior to the plane of nasal alae, including the area from the lateral canthus to the medial canthus and lateral to the nose on the subject's right and left sides (Figure 2). If Restylane Volyme is injected too superficially this may result in visible lumps and/or bluish discolouration. Investigators will be instructed to use the amount of dermal filler necessary to achieve an optimal aesthetic result. A touch-up treatment may be performed 4 weeks after the initial treatment if optimal midface augmentation has not been obtained. Defects should be fully corrected, but not overcorrected.

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Care should be taken to avoid intramuscular injection. This can often be recognized by an increased force of injection required compared to subcutaneous injection. Care should also be taken to avoid excess deposition of material into individual areas. After each injection, the area should be observed to assess the degree of enhancement and the uniformity of the implant. The area should be gently palpated to ensure an even deposition of the implant. Palpated “skip areas” should be treated with additional implant material or by gentle massage/kneading of the area until a uniform implant is palpable.

Figure 2. Injection Area



Information regarding the local anaesthetic used, injection technique, depth of injection and volume used per side will be recorded.

6.6.2 Treatment regimen (dose)

A maximum dosage of 2 mL per treatment site (i.e., right and left midface respectively) is recommended at each treatment session, i.e., initial treatment or touch-up treatment respectively.

6.6.3 Post-treatment Care

Ice in appropriate packaging can be applied on the treatment site for a short period to reduce swelling and discomfort.

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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 one week. 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 following details of each injection are to be recorded in the eCRF:

- Date for administration
- Lot number
- Local anaesthetic used (product name, volume injected/amount applied, and concentration)
- Administered volume per side
- Injection technique per side
- Depth of injection per side
- Post-treatment care (massage, ice pack, etc)

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 Effectiveness Assessments

7.1 General information

The methods for collecting effectiveness data include assessment of MMVS ⁹(Section 7.3), CCI

description of the laboratory assessments is given in Section 8.2 and the ECG assessment in Section 8.3.

Assessments will be performed by CCI the blinded evaluator, as described in the respective section. To avoid inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. If it is not

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possible to use the same evaluator [CC1] to follow the subject, evaluations should be overlapped (examine the subject together and discuss findings) for at least 1 visit.

7.2 Photography

Digital photographs will be taken of each subject pre-treatment at visits when treatment is performed and at each follow-up visit. Standardized 3D photographs will be achieved for effectiveness assessment. 2D photographs will be used to document condition at baseline, for [CC1] and to document AEs in the treated area. If necessary, the photo should be taken when AEs occur.

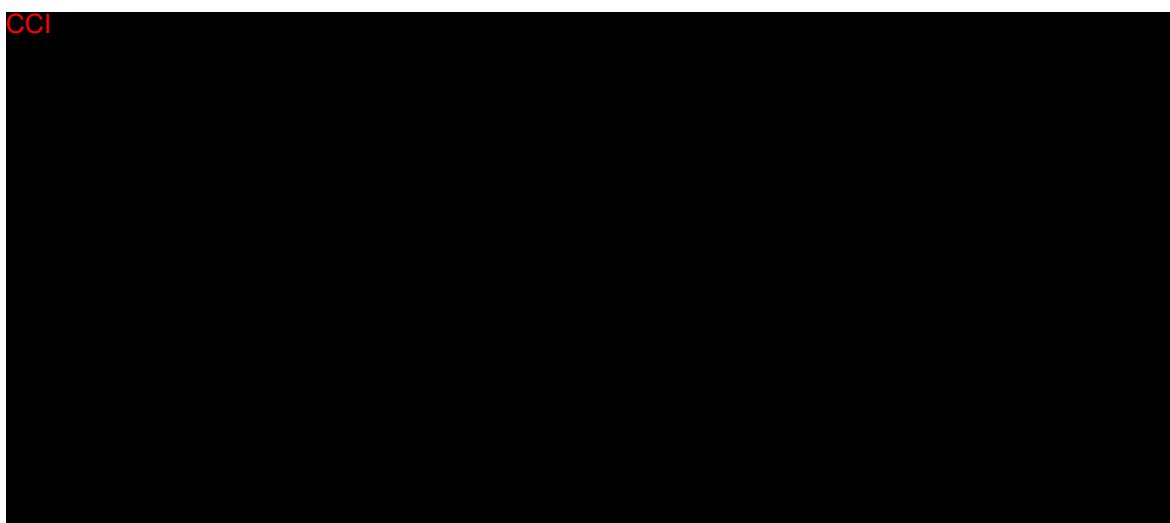
Photographs will be taken in a standardized way according to the instructions for image procedures. The subject shall have a neutral facial expression and no covering make-up should be used on the photographs.

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

7.3 Medicis Midface Volume Scale (MMVS)

MMVS is a Four-Point scale assesses the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4) as described below. A validation study concluded that the accuracy of this assessment tool was acceptable for use in assessing correction of midface volume loss and/or contour deficiency⁹. The blinded evaluator will rate the subject's right and left midface for severity of volume deficiency using the MMVS at screening, baseline, [CC1] 6, [CC1] months after last treatment in Group A and Treatment Group; and at screening, baseline, [CC1] 6 months after randomization, as well as [CC1] 6 months after last treatment in Control Group. [CC1]

[CC1] The blinded evaluator [CC1] will conduct their MMVS assessments using a photographic scale (Appendix 2).



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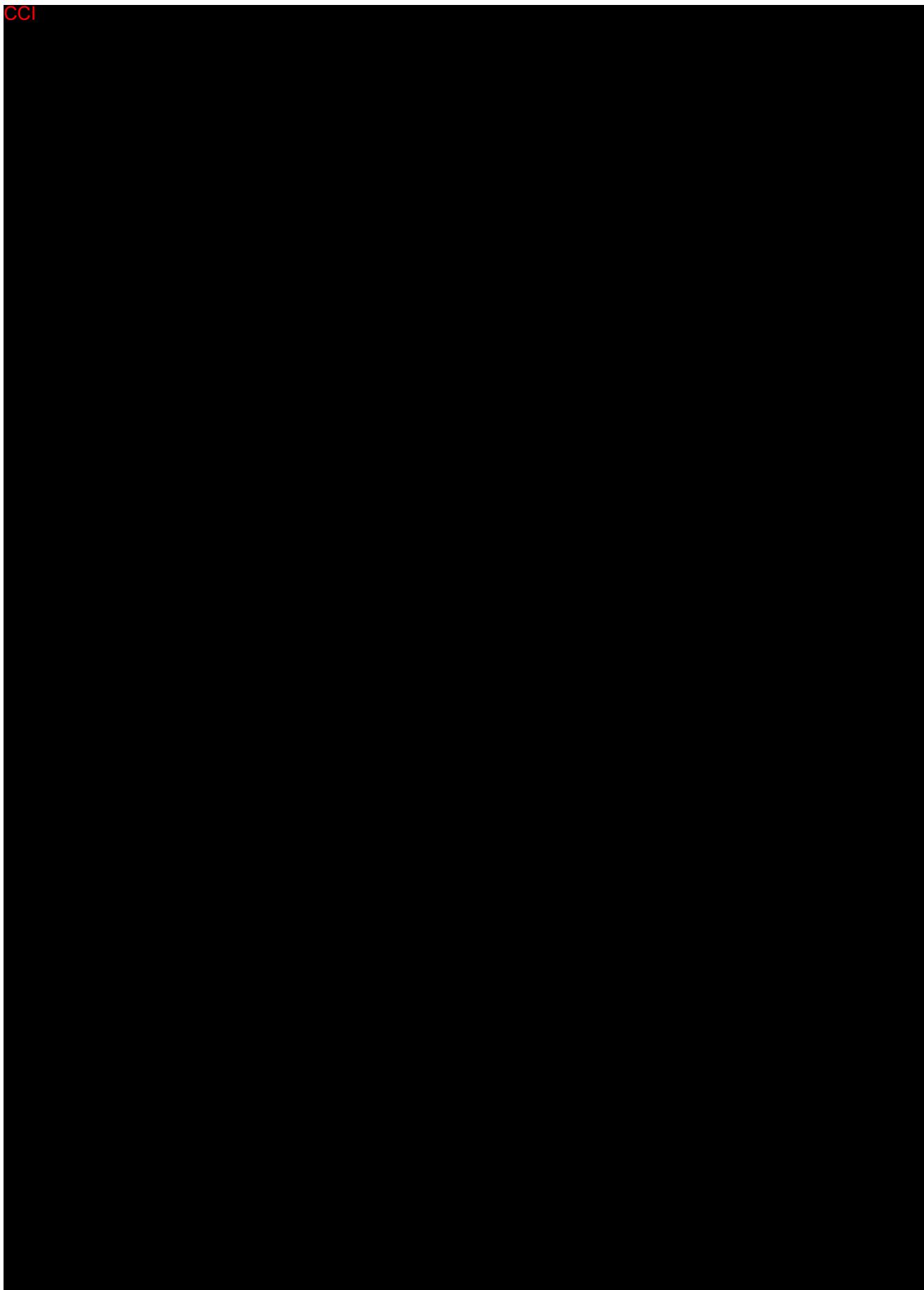
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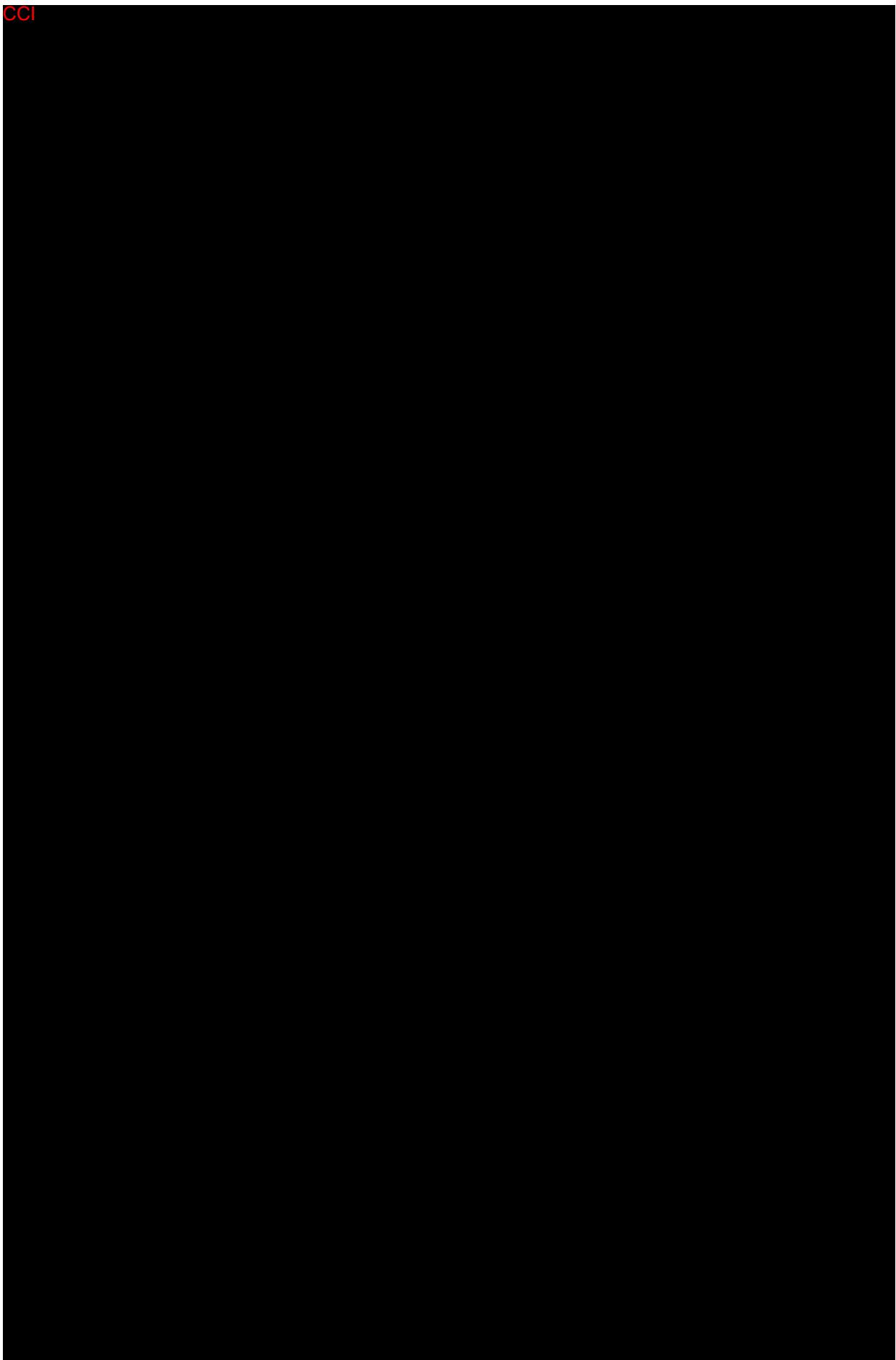
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CCI

8 Safety Assessments

CCI

8.2 Laboratory assessment

Laboratory samples will be taken at the screening visit (day -21 to day 1) for all subjects. In Group A and Treatment Group, it will also be taken at 6 months visit after last treatment or at early termination if termination occurs before 6 months visit after last treatment. In control group, it will also be taken at 6 months visit before treatment and at final visit or early termination.

The following laboratory assessments will be performed:

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- 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 of the hematology and serum chemistry will only be used for safety assessment by investigator and will not be collected in the eCRF. The pregnancy test for women of childbearing potential will be recorded in the eCRF.

8.3 ECG-screening

ECG will be taken at the screening visit (day -21 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

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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

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, subject diaries 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 sequelae, death, chronic/ stable, not recovered at study end)

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

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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 after the ICF has been signed. 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 Representative 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

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- 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 via Sponsor's representative 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.)

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

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

Surface mail for providing complementary information:
Q-Med AB
Attn. Corporate Medical Affairs & Vigilance
Seminariegatan 21
SE-752 28 UPPSALA, Sweden

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.

The SAE form (CFDA template in Chinese) 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

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the SAE form, the fully completed and signed SAE form shall be e-mailed or faxed to the Sponsor (contact details refer to 24-hour contact person list in ISF). A copy of the fully completed SAE form shall be kept at the site.

In addition, according to national regulations, the investigator will report a SAE Form (CFDA SAE template) to the administrative department of medical device clinical trials in his/her hospital, and they 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 Representative with all required materials.

The Sponsor Representative is responsible for, within five (5) business days upon being informed, reporting any SAE or device defect with the likelihood of SAE to Shanghai Municipal FDA and Shanghai Municipal Commission of Health and Family Planning by fax or mail. The relevant correspondence will be documented in TMFI; meanwhile, the Sponsor Representative should notify other clinical trial institutions and investigators participating in the study, 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.

8.4.6 Follow-up of Unresolved Events after study termination and new 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 a paper AE form.

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure with onset after subject participation in the study has ended shall be collected and reported to Sponsor on a paper AE form or in the post marketing AE form or SAE paper form if applicable. The events shall thereafter be followed up until resolved or considered chronic or stable, or for at least three months. Final outcome shall be reported on the AE follow up form or in the post marketing AE form. The Investigator shall report any such AE or SAE including all previous Adverse events reported during the study and medical history of the patient to the Sponsor immediately but not later than 24 hours of awareness of the event. This report can be made via fax or e-mail according to contact details specified in section 8.4.5.

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 acknowledgement be submitted to the Sponsor

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

Refer to the Restylane Volyume Investigator Brochure.

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

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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 a SAE.

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

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

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.

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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.

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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

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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

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be written and finalized prior to database lock (DBL). All summaries for Group A and B will be done separately. CCI

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10.2 Analysis Populations

The following populations will be defined:

- Safety Includes all subjects in Group B who were treated with Restylane Volyme or randomized to no-treatment group. Subjects are analyzed based on the as treated principle.
- Full Analysis Set (FAS) Includes all subjects in Group B who were treated with Restylane Volyme or randomized to no-treatment group. Subjects are analyzed according to the randomisation assignment.
- Per Protocol (PP) Includes all subjects in FAS that comply to the protocol procedures with no deviations that can affect the evaluation of the primary variable.

The FAS population is the primary population for all effectiveness 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.

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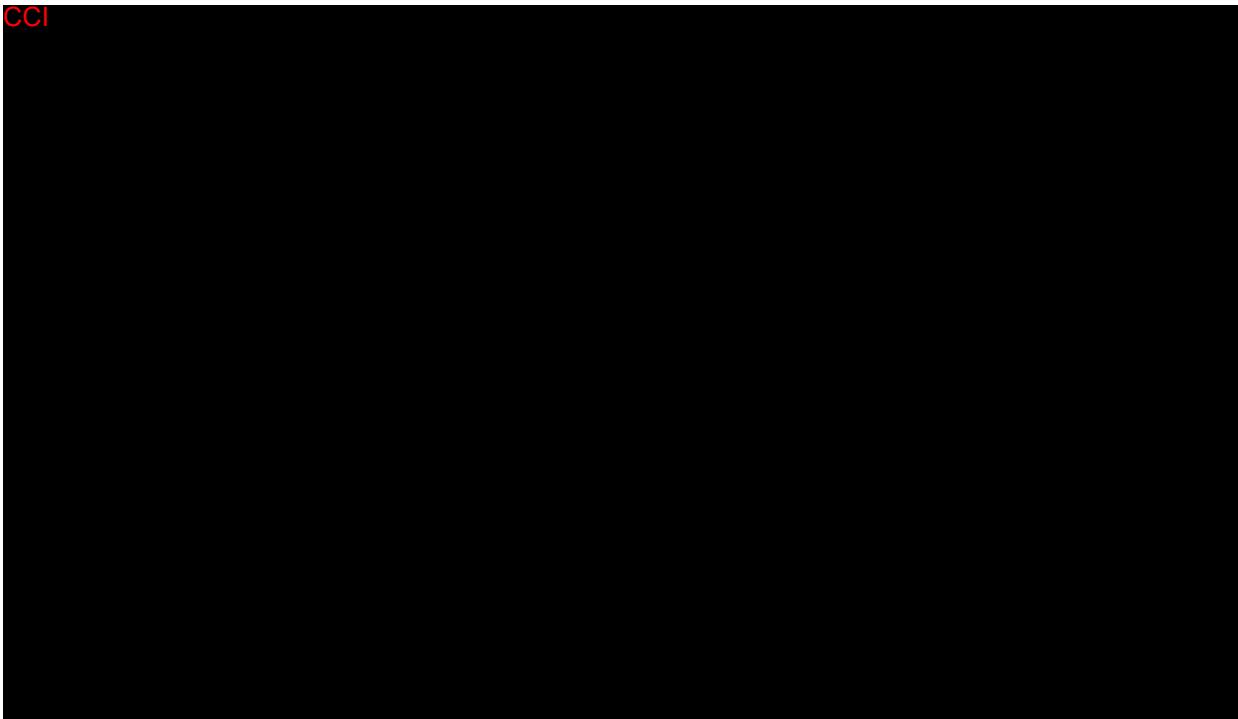
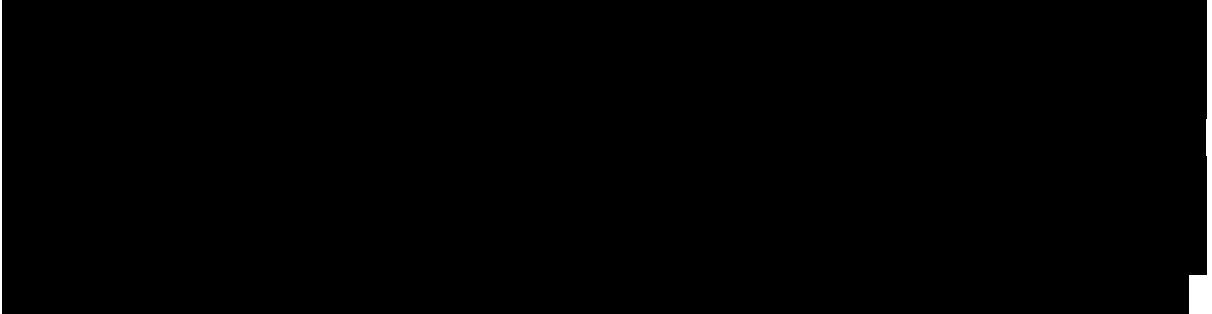
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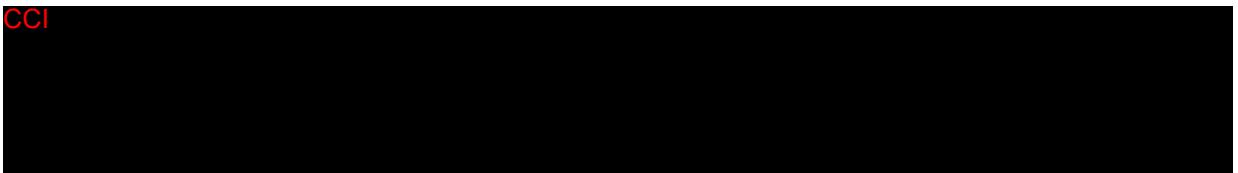
10.4 Effectiveness Analysis

Primary analysis

The percentage of responders (a responder will be defined as a subject with at least 1 point improvement from baseline MMVS on both sides of the face concurrently) will be calculated for each group at Month 6 (after last treatment for Treatment group, and after randomization for Control group) based on the blinded evaluator's assessment. **CCI**

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10.5 Safety Analysis

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All AEs will be coded according to MedDRA.

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Related AEs will be summarised by SOC, PT and intensity and by treatment. In addition, for related AEs the number of days to onset and the duration of event will be summarised by SOC and PT and treatment using mean, SD, min, max and median.

Serious AEs will be listed.

Non-related AEs will be summarised by SOC, PT, and intensity and by treatment.

10.6 Handling of Missing Data

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

Different assumptions regarding the missing data will be used. For the primary effectiveness analysis, missing values in the FAS will be assumed to be missing due to lack of effect. Therefore missing data up to the Month 6 visit will be imputed using the baseline observation carried forward (BOCF) method. As an alternative approach, missing data will be assumed to be unrelated to treatment effect. To impute data under this assumption, missing data up to the Month 6 visit will be imputed using the hot deck method. More details will be given in the SAP. Both of these alternatives will estimate the effectiveness of the treatment policy (irrespective of use of unallowed treatments, procedures, or medications) rather than the true, clinical treatment effect.

To obtain an estimate of the true, clinical treatment effect, the primary effectiveness analysis will be performed using the PP.

All other endpoints will be analysed 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 DBL.

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

10.10 Sample Size

There are no available clinical data for Restylane Volyme studied under conditions similar to the current study. However, based on what is seen in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a response rate of at least 70% in the Restylane Volyme treatment group at Month 6. For the no treatment control group, response rates as high as 35% have been observed in Glogau et al¹¹. Based on this, it was assumed that the response rate will be maximum 35% in the no-treatment control group at Month 6.

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

12 Quality Control and Quality Assurance

12.1 Quality control

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

Any CSP deviation shall be reported in the eCRF, which shall be verified, discussed, and collected, by the monitor and appropriate corrective and preventive actions shall be taken.

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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.

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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

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17 Appendices

- Appendix 1 Declaration of Helsinki
- Appendix 2 Photo guide for MMVS



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



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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



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addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

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

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

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

Research Ethics Committees

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

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

Privacy and Confidentiality

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

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.



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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

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

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

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



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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

Unproven Interventions in Clinical Practice

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

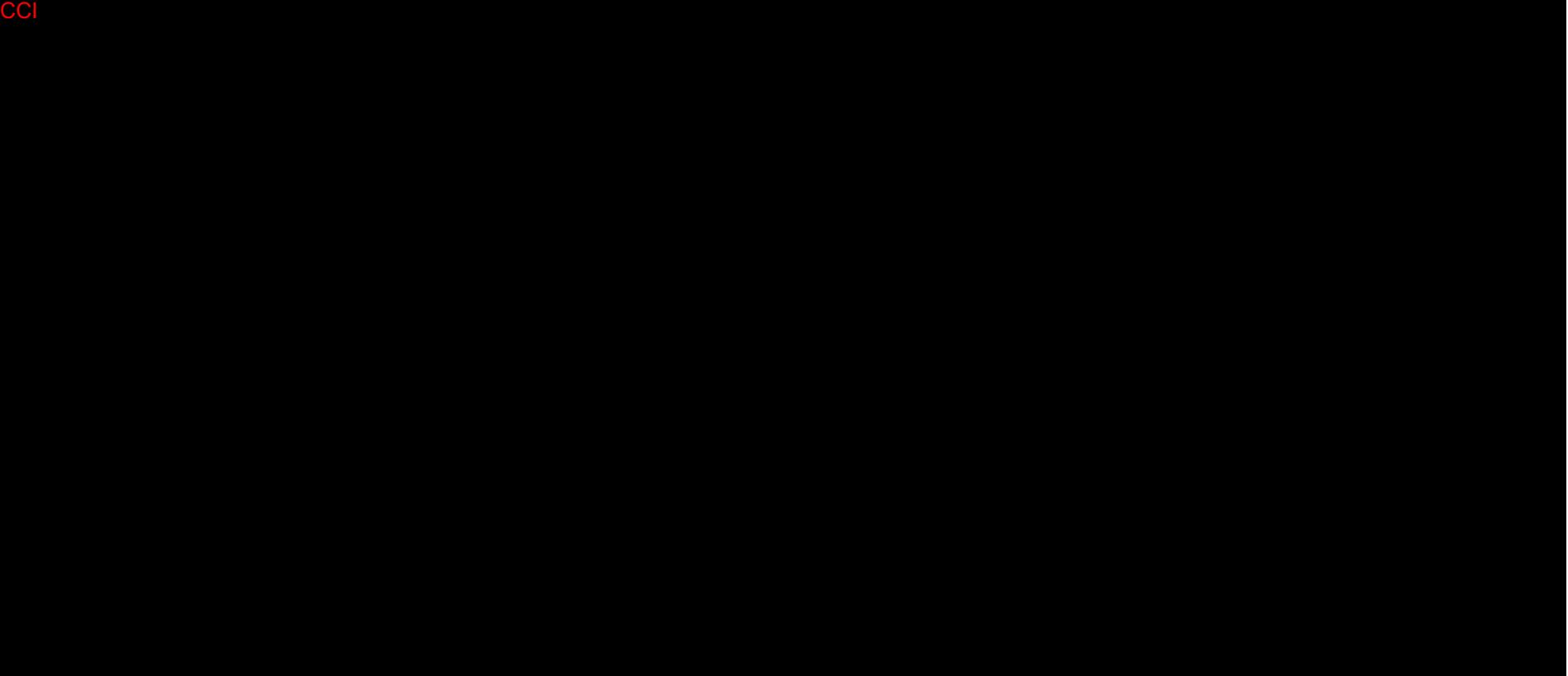


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Appendix 2

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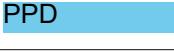
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SIGNATURES PAGE

Date	Signed by
2016-12-09 09:07	PPD 
Justification	Approved by Technical Expert
2016-12-09 09:14	PPD 
Justification	Approved by Project Manager
2016-12-09 10:45	PPD 
Justification	Approved by Owner
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Justification	Approved by Technical Expert