	Title Clinical Study Protocol 05DF1404 - RSB two and three sessions	Doc id MA-26423
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A randomised, multi-centre, parallel-group, efficacy and safety study evaluating two and three initial treatment sessions of Restylane[®] Skinboosters[™] Vital Lidocaine in the face

Study Product: Restylane Skinboosters Vital Lidocaine


Clinical Trial Number (CTN): 05DF1404

Sponsor: Q-Med AB

[REDACTED]
[REDACTED]
[REDACTED] [REDACTED]
[REDACTED] [REDACTED]

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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Sponsor Signatures

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

Head of Medical Affairs, Q-Med


[Redacted Signature]

Study Director, Q-Med

[Redacted Signature]

Study Statistician, Q-Med

[Redacted Signature]

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Signed Agreement of the Clinical Study Protocol

Clinical trial number: 05DF1404

Title of the CSP: A randomised, multi-centre, parallel-group efficacy and safety study evaluating two and three initial treatment sessions of Restylane[®] Skinboosters[™] Vital Lidocaine in the face

I, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the clinical trial agreement (CTA) and the additional information given in the Instructions for Use (IFU) shall 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 randomised, multi-centre, parallel-group efficacy and safety study evaluating two and three initial treatment sessions of Restylane [®] Skinboosters [™] Vital Lidocaine in the face
Protocol Number:	05DF1404
Countries involved, number of sites/ country, number of subjects:	The study shall be conducted at 2 sites in Germany. There shall be approximately 50 female subjects in total randomized in a 1:1 ratio to two or three initial treatment sessions of Restylane Skinboosters Vital Lidocaine.
Principal Investigators:	Dr Martina Kerscher and Dr Gerhard Sattler, Germany
Objectives:	<p>Efficacy objectives:</p> <ul style="list-style-type: none"> To evaluate the aesthetic change from baseline of the treated areas [REDACTED] assessed by subject and Investigator individually [REDACTED] using standardised photographs. <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Safety objectives:</p> <ul style="list-style-type: none"> To evaluate the safety of two different treatment regimens of Restylane Skinboosters Vital Lidocaine [REDACTED] by collecting Adverse Events (AEs) following treatment. To evaluate local tolerability, i.e. pre-defined, expected, post-treatment events [REDACTED] elicited by direct questioning to subjects in a diary [REDACTED] <p>[REDACTED]</p>


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Study Design:	<p>This is a prospective, randomised, multi-centre, parallel-group study to evaluate efficacy and safety of two initial treatment sessions and three initial treatment sessions of Restylane Skinboosters Vital Lidocaine in the face. Approximately 50 female subjects shall be randomised in a 1:1 ratio to either two (Group B) or three (Group A) initial treatment sessions.</p> <p>Approximately 25 subjects shall be treated with two initial treatment sessions [REDACTED] (Group B). Approximately 25 additional subjects shall be treated with three initial treatment sessions [REDACTED] Group A). The volume shall be distributed evenly to both sides of the face.</p> <p>[REDACTED] The subjects shall be followed 18 months after the initial treatment regimen has been completed.</p>
Assessments and follow-up visits	<p>Subsequent to screening and completed initial treatment regimen, there shall be an 18-month follow-up period [REDACTED]</p> <p>[REDACTED]</p>
Inclusion criteria:	<p>The subjects must meet the following inclusion criteria to be eligible for the study:</p> <ol style="list-style-type: none"> 1. Provision of signed and dated informed consent to participate in the study. 2. Non-pregnant, non-breast feeding female aged 35-45 years. 3. Visible signs of aging in the face [REDACTED] 4. Intent to improve skin hydration, skin structure and the elasticity of the skin using Restylane Skinboosters Vital Lidocaine.
Exclusion criteria:	<p>The presence of any of the following exclusion criteria shall exclude the subject from enrolment in the study:</p> <ol style="list-style-type: none"> 1. Extensively photo damaged and aged skin [REDACTED] 2. Woman who plan to become pregnant during the course of the study. 3. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel. 4. Known/previous allergy or hypersensitivity to local anaesthetics, e.g. lidocaine or other amide-type anaesthetics. 5. History of severe or multiple allergies manifested by anaphylaxis.


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	<ol style="list-style-type: none"> 6. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation [REDACTED] Omega-3 or Vitamin E within 10 days before study treatment [REDACTED] 7. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (facial) corticosteroids (inhaled corticoids are allowed) within three months before study treatment. 8. Previous tissue augmenting therapy or contouring with permanent filler or fat-injection in the face. 9. Previous tissue augmenting therapy, contouring or revitalisation treatment with non-permanent filler, neurotoxin or revitalisation preparations (e.g. Hyal System® or Restylane Skinboosters) in the face within 12 months before study treatment. 10. Previous tissue revitalisation treatment with laser or light, radiofrequency, focused ultrasound, chemical peeling, dermabrasion, mesotherapy or any other similar treatment with influence on skin quality in the face within 6 months before study treatment. 11. Previous aesthetic facial surgical therapy, liposuction or tattoo in the face. 12. Previous sinus surgery or dental root surgery within 3 months before study treatment. 13. Active skin disease, inflammation or related conditions, such as infection, perioral dermatitis, seborrheic eczema, rosacea, acne, psoriasis or herpes zoster in the face. 14. History of or active collagen diseases or autoimmune diseases such as systemic lupus erythematosus, rheumatic arthritis, skin or systemic sclerosis. 15. Tendency to form keloids, hypertrophic scars or any other healing disorder. 16. History of radiation of or cancerous or pre-cancerous lesions (e.g. actinic keratosis) in the face. 17. Use of systemic or facial topical retinoic acid within 12 months before study treatment. 18. Nicotine use within 6 months before study treatment. (Occasional smoking, such as 1-5 cigarettes per week, or similar amount of nicotine, is allowed). 19. Any medical condition that, in the opinion of the Investigator, would make the subject unsuitable for inclusion (e.g. chronic, relapsing or hereditary disease that may interfere with the outcome of the study). 20. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g. subjects not likely to avoid other facial aesthetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result. 21. Study site personnel or close relatives of the study site personnel (e.g. parents, children, siblings and spouse) or employees at the Sponsor company. 22. Participation in any other clinical study within 3 months before study
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	treatment.
Study product, volume and mode of administration:	<p>Restylane Skinboosters Vital Lidocaine [REDACTED]</p> <p>If the subject prefers, topical anaesthetics, e.g. lidocaine or other amide-type anaesthetics, may be used prior to treatment at the discretion of the Investigator.</p> <p>The treatment site should be cleaned with a suitable antiseptic solution.</p> <p>[REDACTED]</p>
Reference therapy, dose and mode of administration	Not applicable
Duration of treatment:	<p>Two or three initial treatment sessions shall be scheduled [REDACTED]</p> <p>[REDACTED] An 18-month follow-up period shall follow after the completed initial treatment regimen.</p>
Efficacy Assessments:	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Superior facial aesthetic appearance of treated areas assessed by Independent Blinded Evaluator by comparing standardised photographs</p> <p>[REDACTED]</p>
Safety Assessments:	<p>AEs collected by asking direct questions at each study visit following the first treatment session.</p> <p>Local tolerability shall be assessed by collection of Subject Diaries</p> <p>[REDACTED]</p>

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Statistical Methods:	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
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Abbreviations and Definitions of Terms

AE	Adverse event
Blinded Independent Evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject.
CE	French: <i>Conformité Européenne</i>
CSP	Clinical study protocol
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors and inadequate labelling)
DMP	Data management plan
eCRF	Electronic case report form
First subject in	First subject treated with study product
First subject out	First subject who completed her last study visit
G	Gauge
	
GCP	Good clinical practice
GTW	Gauge thin walled (needles)
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFU	Instructions for use
Investigator	The Principal Investigator (PI) or other qualified person i.e. sub-Investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log.
Investigator File	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
ISO	International Organization for Standardization
Last subject in	Last subject who entered the study
Last subject out	Last subject who completed her last study visit
MedDRA	Medical dictionary for regulatory activities
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
SAE	Serious adverse event
SDV	Source data verification
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
	
Study files	The Investigator file and the Sponsor file
Study product	The investigational product under study
Study site	Institution or site where the study is carried out
U-HCG	Urinary human chorionic gonadotropin

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[REDACTED]

Device Type	Percentage of Respondents
Mobile Phone	100%
Tablet	95%
Smartphone	85%
Laptop	75%
Desktop Computer	65%
Smartwatch	55%
Smart TV	45%
Smart Speaker	35%
Smart Car	25%
Smart Home System	15%

[REDACTED] [REDACTED]


[REDACTED]

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2.7 Objectives and endpoints

2.7.1 Efficacy

The **efficacy objectives and endpoints** of the study are:

- To evaluate the aesthetic change from baseline of the treated areas [REDACTED] assessed by subject and Investigator individually [REDACTED] using standardised photographs.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.7.2 Safety

The **safety objectives and endpoints** are:


- To evaluate the safety of two different treatment regimens of Restylane Skinboosters Vital Lidocaine [REDACTED] by collecting AEs following treatment.
- To evaluate local tolerability, i.e. pre-defined, expected, post-treatment events [REDACTED] elicited by direct questioning to subjects in a diary [REDACTED]

3. Design of the Study

3.1 General outline

This is an 18-month, randomised, evaluator-blinded, multi-centre study of the efficacy and safety of Restylane Skinboosters Vital Lidocaine following two different treatment regimens. The subjects shall be randomised 1:1 to either Group A or Group B, i.e. to treatment with three or two initial treatment sessions of Restylane Skinboosters Vital Lidocaine. A Blinded Evaluator not working at the site, to whom randomisation and treatment are concealed, shall conduct assessment of the aesthetic change by using photographs [REDACTED]

[REDACTED]

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[REDACTED]

The subjects shall be followed 18 months after the initial treatment regimen has been completed.

[REDACTED]

Prior to treatment, local anaesthesia may be used.

Subsequent to screening and completed initial treatment regimen, there shall be an 18-month follow-up period [REDACTED]

[REDACTED] The purpose of the follow-up visits is to assess efficacy and safety of the treatment.

[REDACTED] ssessments shall be performed by the subjects and the Investigator as described in the respective section.

AEs and device deficiencies shall be recorded after treatment.

[REDACTED]

A subject that is withdrawn from the study shall not be replaced.

A data summary can be done during this open study.

3.2 Number of subjects

Approximately 50 female subjects (approximately 25 subjects in Group A and 25 in Group B) shall be recruited at two sites in Germany. Approximately 25 subjects shall be included per site and randomised in a 1:1 ratio to either Group A or Group B.

3.3 Duration of subject participation

A subject should be involved in the study for approximately 20 months.

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


3.4 Randomisation and blinding

3.4.1 Randomisation

Before starting the study, a statistician from Q-Med AB or designee will generate a randomisation list. Each subject will be assigned a consecutive subject number by the eCRF system at the treatment visit [REDACTED] when all inclusion criteria and exclusion criteria have been verified. Each subject number is linked to the specific number of treatment sessions to be administered according to the randomisation list.

3.4.2 Blinding

The subject shall be randomised to two or three initial treatment sessions of Restylane Skinboosters Vital Lidocaine, [REDACTED]. Due to the difference in the

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number of treatments, it is not possible to double-blind the study, and the treatment assignment cannot be obscured from the treating Investigator or the subject.

The Independent Blinded Evaluator shall not be allowed to retrieve study supplies or to be present during the treatment sessions.

The Sponsor will not be blinded to the number of treatment sessions.

3.4.3 Emergency unblinding

Not applicable as the treating Investigator is unblinded.

3.5 **Medical history and concurrent diseases**

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

3.6 **Concomitant medications, treatments and procedures**

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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 unless otherwise instructed by PI or Sponsor.

The subjects should also be informed that skincare products, make-up and cleansing of the face are not permitted within 12 hours before each study visit after screening. Sport activities and sauna are not permitted within 12 hours before each study visit after screening.

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3.7 Schedule of events

The assessments to be performed at each visit are presented in Table 1. The corresponding eCRFs shall be completed and signed by the Investigator for each visit. In case of a withdrawal (subject dropout before completion of the intended follow-up period), the study termination module in the eCRF shall be completed.

[REDACTED]

[REDACTED]

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[REDACTED]

1. [REDACTED]

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■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
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■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]

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4. Subjects

4.1 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 affect on 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 her authorised designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and may be transferred to non-EU countries. The data will not contain any information that can be used to identify any subject.


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


All signed 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.

4.2 Inclusion criteria

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


1. Provision of signed and dated informed consent to participate in the study.
2. Non-pregnant, non-breast feeding female aged 35-45 years.
3. Visible signs of aging in the face 
4. Intent to improve skin hydration, skin structure and the elasticity of the skin using Restylane Skinboosters Vital Lidocaine.

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4.3 Exclusion criteria

The presence of any of the following **exclusion** criteria shall exclude the subject from enrolment in the study:

1. Extensively photo damaged and aged skin [REDACTED]
2. Woman who plan to become pregnant during the course of the study.
3. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel.
4. Known/previous allergy or hypersensitivity to local anaesthetics, e.g. lidocaine or other amide-type anaesthetics.
5. History of severe or multiple allergies manifested by anaphylaxis.
6. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation [REDACTED]
Omega-3 or Vitamin E within 10 days before study treatment in order to avoid increased bruising or bleeding at injection sites.
7. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic or topical (facial) corticosteroids (inhaled corticoids are allowed) within three months before study treatment.
8. Previous tissue augmenting therapy or contouring with permanent filler or fat-injection in the face.
9. Previous tissue augmenting therapy, contouring or revitalisation treatment with non-permanent filler, neurotoxin or revitalisation preparations (e.g. Hyal System® or Restylane Skinboosters) in the face within 12 months before study treatment.
10. Previous tissue revitalisation treatment with laser or light, radiofrequency, focused ultrasound, chemical peeling, dermabrasion, mesotherapy or any other similar treatment with influence on skin quality in the face within 6 months before study treatment.
11. Previous aesthetic facial surgical therapy, liposuction or tattoo in the face.
12. Previous sinus surgery or dental root surgery within 3 months before study treatment.
13. Active skin disease, inflammation or related conditions, such as infection, perioral dermatitis, seborrheic eczema, rosacea, acne, psoriasis or herpes zoster in the face.
14. History of or active collagen diseases or autoimmune diseases such as systemic lupus erythematosus, rheumatic arthritis, skin or systemic sclerosis.
15. Tendency to form keloids, hypertrophic scars or any other healing disorder.
16. History of radiation of or cancerous or pre-cancerous lesions (e.g. actinic keratosis) in the face.
17. Use of systemic or facial topical retinoic acid within 12 months before study treatment.
18. Nicotine use within 6 months before study treatment. (Occasional smoking, such as 1-5 cigarettes per week, or similar amount of nicotine, is allowed).

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19. Any medical condition that, in the opinion of the Investigator, would make the subject unsuitable for inclusion (e.g. chronic, relapsing or hereditary disease that may interfere with the outcome of the study).
20. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g. subjects not likely to avoid other facial aesthetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.
21. Study site personnel or close relatives of the study site personnel (e.g. parents, children, siblings and spouse) or employees at the Sponsor company.
22. Participation in any other clinical study within 3 months before study treatment.

4.4 Screening and subject numbers

Each subject who has signed the informed consent form shall be assigned a screening number and shall be listed on a subject screening and inclusion log. [REDACTED]

A "screening failure" is defined as a subject who does not fulfil the eligibility criteria. For screening failures, the eCRF screening visit shall be completed to an extent that makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria. The reason for excluding a subject from entering the study shall also be specified in the subject screening and inclusion log. When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each subject shall be assigned a subject number consisting of the site number followed by a consecutive number starting with 01 at each site. The subject number shall consist of site number followed by subject number in consecutive order, e.g. 101, 102 etc.

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

4.5 Withdrawal of subjects

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

[REDACTED]

■

[REDACTED]

■

[REDACTED]

■ [REDACTED]

■ [REDACTED]

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 to further explain the reason for withdrawal. If withdrawal of a subject occurs during a regular study visit, the eCRF for that specific visit shall be completed as far as possible together with the study termination eCRF module.

If withdrawal of a subject occurs between regular study visits the subject should when possible (irrespective of the reason for withdrawal) be scheduled for a termination visit to document subject outcome for the primary and secondary endpoints. In these cases the eCRF for the next upcoming visit shall be completed.

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

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

If an AE which, according to the Investigator's assessment, is related to the use of any of the study products and is still ongoing at the time of the withdrawal, the subject shall be followed up until the AE resolves or is assessed by the Investigator to be "chronic" or "stable". Follow-up information for at least 3 months shall be provided to the Sponsor.

5. Study Product

The term "study product" refers to the injectable gel Restylane Skinboosters Vital Lidocaine. No reference product or comparator shall be used in this study.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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Detailed product information is provided in the IFU, Appendix 2.

5.1 Additional products and material

Pregnancy tests (U-HCG), transparent templates, if applicable, and silicone will be ordered by each clinic and the cost will be covered by the Sponsor.

The treating Investigator shall provide anaesthetics for the treatment session, if applicable at the discretion of the Investigator, and adequate equipment in case of emergency.

Type of anaesthesia, product name, and quantity used must be recorded in the eCRF.

5.2 Packaging, labelling and storage

In addition to the standard labelling of the device, a study-specific label will be attached to the box by Q-Med AB, Uppsala, Sweden containing the following information, in addition to applicable local labelling requirements:

- Exclusively for clinical investigation
- Clinical trial number: 05DF1404



Detailed product information is provided in the IFU, Appendix 2.

5.3 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 and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all study products received from the Sponsor; including the product name, date received, batch number, expiration date, and amount received. In addition, dispensing logs shall be maintained including the product name, dispense date, the number of syringes used, the number of syringes left in stock, and the subject receiving study product. A log for accountability procedure is provided by the Sponsor.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor for destruction. Any malfunctioning study products shall be reported as described in Section 7.4.3.

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

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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.

5.4 Treatment

5.4.1 Treatment procedure

Before treatment the subject shall be informed about the potential risks involved with the treatment and when to contact the Investigator in case of emerging symptoms.

A pregnancy test (U-HCG) shall be performed in subjects of childbearing potential before the treatment is performed. If the subject is pregnant, the treatment shall not be performed.

Restylane Skinboosters Vital Lidocaine shall be administered according to the IFU Appendix 2.

The study product is reserved for use by doctors who have been trained in the appropriate injection techniques.

The study product contains lidocaine hydrochloride, but if the subject prefers, additional local anaesthesia may be used at the discretion of the treating Investigator to further reduce pain on injection.


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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 treatment site should be cleaned with a suitable antiseptic solution (extend at least five cm around the injection site).

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5.4.2 Treatment regimen (dose and interval)


Initial treatment regimen

Group A shall be treated with three initial treatment sessions of Restylane Skinboosters Vital Lidocaine [REDACTED]

[REDACTED] he volume should be distributed evenly to both sides of the face.

Group B shall be treated with two initial treatment sessions of Restylane Skinboosters Vital Lidocaine [REDACTED]

[REDACTED] The volume should be distributed evenly to both sides of the face.

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5.4.5 Electronic case report form recordings

The treatment is an injectable gel administered by the Investigator and the following details of the injection shall be recorded in the eCRF:

- Local anaesthetic used (product name, amount applied and concentration)
- Date for administration
- Administered volume per side of the face (first treatment, second treatment etc.)
- Injection technique or procedure
- Depth of injection
- Area of injection per side of the face
- Post-treatment care (massage, cooling)

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

5.4.6 Treatment compliance


No other measurements of treatment compliance shall be made.

6. Efficacy Assessments

6.1 General information

The methods for collecting efficacy data include [REDACTED], photography (Section 6.3), [REDACTED] and evaluation of aesthetic change of the treated areas by blinded evaluation (Section 6.6). Assessments shall be performed by the subjects, the Investigator and a blinded independent 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.

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During the treatment visits, the efficacy assessments and photographs are performed prior to treatment.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

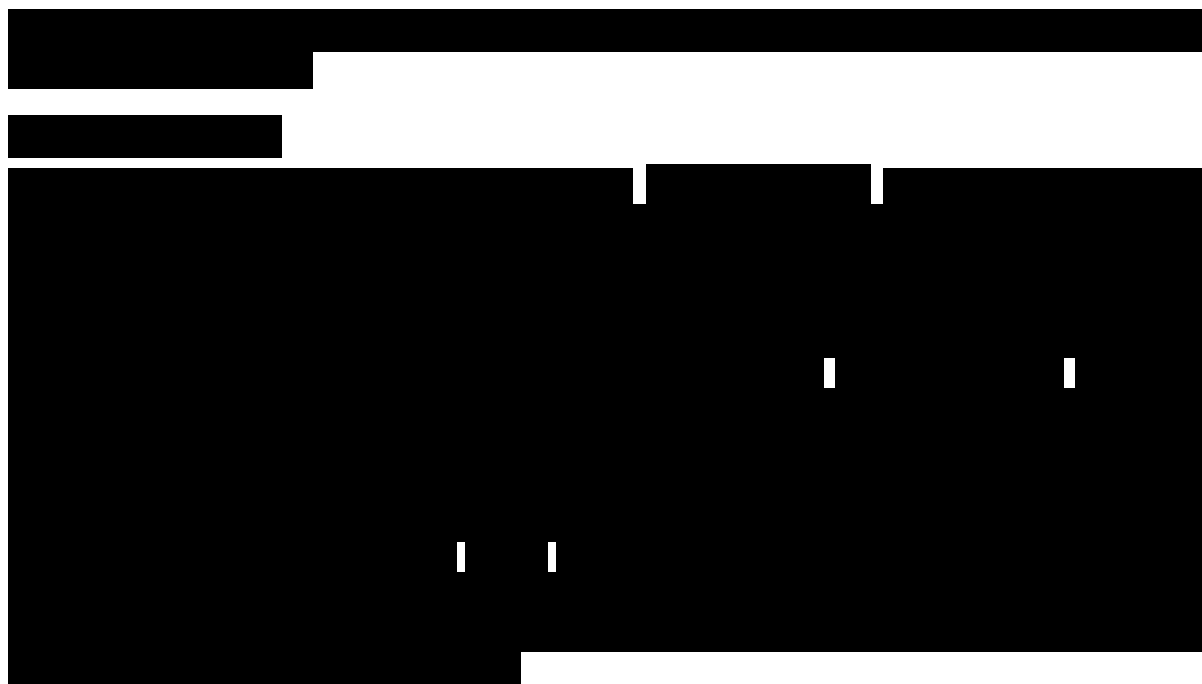
[REDACTED]

[REDACTED]

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6.3 Photography

2D-photographs shall be taken prior to the first injection of the study product and at every follow-up visit by the Investigator or study staff in order to document treatment effect.


At visits when injections are performed, the photographs should be taken prior to the injections.

Note that no covering make-up should be used on the photographs. Standardised photographs should be achieved using 2D-photography. Each Investigator shall be thoroughly trained in the photographic equipment and techniques and how to upload photographs to the secured web portal or eCRF, if applicable, before study start.

Photographs shall be taken at the screening visit and a copy of the archival photographs should be included in the eCRF or the Investigator should upload these to the secured web portal. The quality of the uploaded photographs shall be assessed by the Investigator or other designated person; the photography shall be repeated if needed. If the photographs are considered as of good quality, the Investigator may proceed with treatment of the subject at the Day 1 visit/Baseline. If the photographs are considered not good enough, the photography shall be repeated.



Further details regarding image procedures will be specified in a separate user guide. Each photograph should be linked to subject number and the visit number at which the photograph was taken.

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The photographs should be used in the assessment [REDACTED] and by Independent Blinded Evaluator.

[REDACTED]

[REDACTED]	[REDACTED]								
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[REDACTED]

[REDACTED]


[REDACTED]

The diagram illustrates the relationship between the Constitution and the various branches of government. A horizontal bar at the top represents 'The Constitution'. Below it, six vertical columns represent the different branches: 'The People', 'The Government', 'The Judiciary', 'The Executive', 'The Legislature', and 'The Courts'. The columns are connected to the bar, indicating that all branches are subject to and derive their authority from the Constitution.

A black silhouette of a person standing at a podium, facing away from the viewer towards a large screen displaying a presentation slide. The person's arms are slightly raised as if gesturing during a presentation. The screen shows a dark background with several white plus signs arranged in a grid-like pattern, representing the content of the slide shown in the adjacent image.



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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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6.6 Superior Facial Aesthetic Appearance

Assessment of “Superior facial aesthetic appearance” is based on Blinded Evaluator assessment of the subject’s appearance [REDACTED]

An Independent Blinded Evaluator will retrospectively review photographs [REDACTED]


7. Safety Assessments

7.1 Pre-defined, expected, post-treatment events

The subject shall evaluate local tolerability in a [REDACTED] diary, [REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Any sign or symptom of pre-defined expected post-treatment events (as specified above) that is still ongoing [REDACTED] post-treatment shall also be reported separately as an AE. The event shall be transferred to the AE module in the eCRF and thereafter followed as an AE. The start date of this event should be the first time point when it was first recorded in the diary, and the intensity should be the maximum intensity of the sign or symptom recorded in the diary.

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7.2 Laboratory assessments

No laboratory assessments shall be performed.

7.3 Adverse events

7.3.1 Definition of an adverse event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons¹, whether or not related to the study product.

This definition includes:

- a) events related to the study product
- b) events related to the procedures involved

7.3.2 Definition of a 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-threatening² illness or injury, or
 - 2. a permanent impairment of a body structure or body function, or
 - 3. in-patient or prolonged hospitalisation³, or
 - 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to foetal distress, foetal death, or a congenital abnormality or birth defect

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 7.3.5).

7.3.3 Recording instructions


Each subject should be questioned about AEs at each study visit following the first treatment visit (visit 2a) the question asked should be: "Since your last clinical visit have you had any health problems?". Information on AEs can also be obtained from signs and symptoms detected during each examination, observations made by the study site personnel, subject diaries, or spontaneous reports from the subjects.

Exceptions from AE reporting are pre-defined, expected, post-treatment events that are resolved within ■ days after treatment. These events should be reported in the subject diary.

¹ For users or other persons, this definition is restricted to events related to the study product.

² 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).

³ 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).

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However, any pre-defined expected post-treatment event that deteriorates or is still ongoing at day ■ (Section 7.1) should be reported as an AE.

When an AE is related to a device deficiency (refer to section 7.4), including technical device malfunction, the AE should be recorded on the AE form/module in the eCRF and the technical complaint should be reported separately on the clinical study complaint form provided separately and not included in the eCRF.

Investigators, or other study site personnel, shall record all AEs, except the pre-defined expected post-treatment after the first initial treatment session and after the first maintenance treatment (Section 7.1), in the eCRF, including:

- Event term (recorded in standard medical terminology and avoiding abbreviations)
- Description of event and affected area
- Start date (first day with symptoms)
- Stop date (last day with symptoms)
- Intensity (mild, moderate, or severe according to definition in section 7.3.3.1)
- Seriousness (serious or not serious, according to definition in section 7.3.3.2)
- Causal relationship to study product or study product injection procedure (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
- Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable)

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

The pre-defined, expected post-treatment events shall be assessed separately (Section 7.1). These events shall be collected by direct questioning to subjects in a diary used daily for 14 days after the first treatment initial treatment session and after the first maintenance treatment. Any ongoing sign or symptom still persistent 14 days after treatment (i.e. Day 15) shall be recorded as an AE in the AE module for continued follow-up. Start date of the sign or symptom and maximum intensity shall be transferred from the subject diary by the Investigator.

7.3.3.1 Intensity


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

- | | |
|------------------|---|
| Mild: | Awareness of symptoms or signs, but easily tolerated (acceptable) |
| Moderate: | Enough discomfort to interfere with usual activity (disturbing) |
| Severe: | Incapacity to work or to do usual activity (unacceptable) |

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

7.3.3.2 Causal relationship and seriousness

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

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

- “Do you consider that there is a reasonable possibility that the event may have been caused by the study product?”, and
- “Do you consider that there is a reasonable possibility that the event may have been caused by the device 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.

7.3.4 Reporting of adverse events

AE reporting on each subject shall start after the first treatment session [REDACTED]. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

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

7.3.5 Reporting of serious adverse events

The Investigator is to report any SAE to the Sponsor **immediately but not later than 24 hours of awareness of the event**. The initial report will be made in the eCRF system. Telephone, fax and e-mail can be used if there are difficulties accessing the eCRF.


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

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

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

Supporting documentation to be provided with the SAE report:

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

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E-mail for SAE reporting:

Fax number for SAE reporting:

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

Surface mail for providing complementary information:

Q-Med AB

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

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

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

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

7.3.6 Follow-up of unresolved events after termination of the study

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure and ongoing at study end, shall be followed up after the subject's participation in the study is over. Such events shall be followed-up by the Investigator after the last study visit until resolved, assessed as chronic or stable. Follow-up information for at least three (3) months shall be provided to Sponsor. Final outcome after the end of the study shall be reported in the AE follow-up module in the eCRF or on a form as applicable.

7.3.7 Pregnancy


Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period the subject must be withdrawn from any following study treatment.

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 delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator in the eCRF Part A and B immediately upon acknowledge. The information can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information.

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

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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 shall not be reported as AEs.

7.3.8 Anticipated adverse events

Information regarding anticipated AEs is included in the IFU, Appendix 2.

7.4 **Device deficiencies**

7.4.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety⁴, or performance.

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

7.4.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE module or an SAE module shall be completed as applicable (refer to section 7.3). If no SAE was experienced as a result of the device deficiency the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

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

In Part B of the clinical study complaint form the Sponsor will make the same assessment.

7.4.3 Reporting of device deficiencies


The Investigator shall send the completed clinical study complaint form QMS-8134 to the Sponsor using the contact details specified on the printed form. A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported within 24 hours after the Investigator's awareness in accordance to section 7.3.5.

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 a SAE has resulted from a device deficiency or if either the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the IEC.

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

⁴ Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

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8. Data Handling and Management

8.1 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 database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the CSP and the CRF. 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 and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

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

8.2 Electronic case report forms

A 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and 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 entered directly from the source documents, which are to be defined at each site before inclusion of the first subject.


Authorised study site personnel designated by the PI shall complete data collection. Appropriate training and security measures shall be completed with all authorised study site personnel prior to the study being initiated and any data being entered into the system for any subject.

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

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

8.2.1 Data entry

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. 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

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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.

8.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her 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.

8.2.3 User identification

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


8.2.4 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.

8.3 **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 hospital records and photographs, should be clearly identified with the CTN and subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

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8.4 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.

8.5 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 for 15 years (after study completion or longer if required by national legislation. 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.

9. Statistical Methods

9.1 General

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

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

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9.2 Analysis populations

The following populations will be defined:

- Safety [REDACTED]
- Intention-to-treat (ITT) [REDACTED]

Intention-to-treat is the primary population for all efficacy analyses. If there are any CSP deviations considered to have substantial impact on the efficacy outcome, a per protocol (PP) population excluding those subjects may be defined. Safety analysis is performed based on the safety population set.

[REDACTED]

9.3 Demographics, baseline assessments, and subject characteristics

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

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

9.6 Handling of missing data

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

9.7 Data summary

Since this is an open study, available data may be analysed prior to study completion.

9.8 Withdrawals and deviations

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

Subjects with CSP deviations will be listed individually, including group, subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which should be documented in the clean file document and prior to statistical analyses.

Deviations from the statistical plan will be documented in the statistical report.

[REDACTED]


[REDACTED]

10. Protection of personal data

The study will include collection and processing of personal data as specified in Directive 95/46 EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data. For the purposes of the study, Sponsor will be considered the data controller, and institution and 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 not having same high level of security for processing of personal data as Sweden and EU, 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, contract research organisation (CRO) or a RA may visit the study site to

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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.

11. Quality Control and Quality Assurance

11.1 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 actions shall be taken. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor as well as the IEC if required by national regulations. Deviations shall be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations shall be performed as described in the monitoring manual.

11.2 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.

11.3 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.

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12. 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.

13. Publication policy

The PI's, institution's, and Q-Med AB's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

The aim is to submit the results of this study for publication in the public database ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved⁵. 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.


14. 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.

⁵ Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (<http://www.icmje.org>).

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16. Appendices

Appendix 1	Declaration of Helsinki
Appendix 2	Instructions for Use Restylane Skinboosters Vital Lidocaine

Effective

Effective date: 2014-12-02 09:19

Version: 1.0

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Appendix 1 Declaration of Helsinki

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

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:

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

Preamble

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

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

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

General Principles

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

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

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

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


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

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

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

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

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

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

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

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

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

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

All vulnerable groups and individuals should receive specifically considered protection.

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


Scientific Requirements and Research Protocols

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

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

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

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

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Research Ethics Committees

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

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

Privacy and Confidentiality

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

Informed Consent

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

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

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


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

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

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

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

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

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Appendix 1 Declaration of Helsinki

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
 - Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
- Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions


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

Research Registration and Publication and Dissemination of Results

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

Unproven Interventions in Clinical Practice

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

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Appendix 2

Instructions for Use Restylane Skinboosters Vital Lidocaine

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SIGNATURE PAGE

Date	Signed by
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