	Title Clinical Study Protocol CTN 05DF1707 Midface	Doc id MA-36496
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A multi-centre, evaluator-blinded study to evaluate effectiveness and safety of HA fillers for lifting, contouring and correcting volume deficiency of the midface using an individualized treatment algorithm

Study products: Restylane® Volyme™
Restylane® Defyne™
Restylane® Lyft Lidocaine


Clinical trial number (CTN): 05DF1707

Sponsor: Q-Med AB



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



Medical expert:



Clinical Project Manager and
Study Director:



Scientific Writer:



Study statistician:




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

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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.

Head of Clinical Development, Q-Med AB

[Redacted signature]

Global Head of Medical Affairs, Q-Med AB


[Redacted signature]

Medical Expert, Q-Med AB

[Redacted signature]

Statistician, Q-Med AB

[Redacted signature]

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Signed Agreement of the Clinical Study Protocol

CTN: 05DF1707

Title of the CSP: A multi-centre, evaluator-blinded study to evaluate effectiveness and safety of HA fillers for lifting, contouring and correcting volume deficiency of the midface using an individualized treatment algorithm

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) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name

Signature

Date

Study site

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Exploratory Objectives and Endpoints	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Study Design	<p>This is a 24-week evaluator-blinded, multi-centre study to evaluate the safety and effectiveness of midface treatments with Restylane Volyme, Restylane Defyne, or Restylane Lyft Lidocaine, using an individualized treatment approach and treatment algorithm</p> <p>Approximately 90 subjects requiring volumization, lifting and/or contouring of midface and fulfilling all eligibility criteria will be enrolled in the study. Approximately 30 subjects should be allocated to each treatment group. The aim is to include 20% male subjects.</p> <p>Product selection for treatment of midface will be based on Investigator assessment of subject tissue coverage and main treatment goal; volumizing, lifting or contouring. Based on those parameters, one of the products Restylane Volyme, Restylane Defyne or Restylane Lyft Lidocaine will be used according to a defined treatment algorithm. After screening and first treatment there is a 24-week follow-up period [REDACTED]</p> <p>[REDACTED]</p> <p>Information about the subjects's tissue thickness and rationale for product choice will be collected. Details regarding the treatment procedure will also be collected, e.g. product used, injection technique, depth, injection volume, cannula/needle selection and anaesthesia used.</p> <p>Photographs will be taken before treatment and at follow-up visits to be used for effectiveness assessments.</p> <p>[REDACTED]</p> <p>Safety data, including AE reporting and device deficiencies, will be collected and reviewed throughout the study. A question regarding local tolerability will be asked 4 weeks after first treatment and touch-up, for collection of injection-related events.</p>
Inclusion criteria	<ol style="list-style-type: none"> 1. Male/Female 25 to 55 years old. 2. Subjects needing lifting, contouring or volumization of the midface. <p>[REDACTED]</p>

	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>5. Signed and dated informed consent to participate in the study.</p>
Exclusion Criteria	<p>1. Known/previous allergy or hypersensitivity to any injectable HA gel.</p> <p>2. Known/previous allergy or hypersensitivity to lidocaine [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>4. Previous use of any permanent (non-biodegradable) or semi-permanent (i.e., calcium hydroxylapatite or Poly-L-Lactic acid) facial tissue augmentation therapy or contouring with, lifting threads, permanent implants, or autologous fat in the treatment area.</p> <p>5. Previous use of any hyaluronic acid or collagen based facial tissue augmentation therapy in the facial area within 12 months before treatment.</p> <p>6. Previous use of any neurotoxin in the facial area within 6 months before treatment.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>8. Previous facial surgery (including aesthetic facial surgical therapy or liposuction) in the facial area.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>


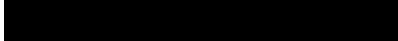





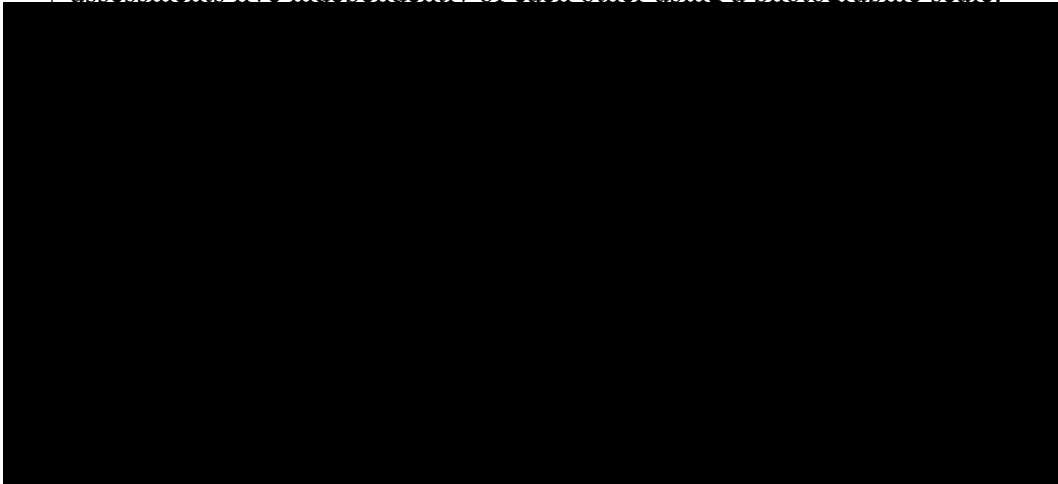

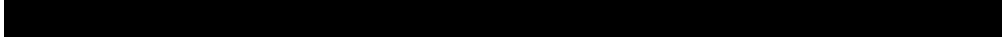
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	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
Investigational product, dose and mode of administration	<p>Restylane Volyme, Restylane Defyne, or Restylane Lyft Lidocaine will be used for midface treatment according to the Instructions For Use (IFU) in the applicable country.</p> <p>Midface is defined as the area inferior to the maxillary prominence, superior to the plane of nasal alae, including the area from the attachment of the ear to the face to the medial canthus and lateral to the nose on the subject's right and left sides. Product selection will be based on treatment algorithm.</p> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
Reference product, dose and mode of administration	Not applicable


3 months prior to screening; Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form or birth control).

Number of treatments	A first treatment including an optional touch-up can be given during the study.												
Effectiveness Assessments	<p>  </p> <p> The 5-graded  Scale  will be used to assess the aesthetic improvement of midface. The Investigator, the blinded evaluator and the subject will, independently of each other, respond to the question: “How would you describe the subject’s/your aesthetic appearance of the midface, i.e. the treated area, compared to the photographs taken before treatment?” </p> <table border="1"> <thead> <tr> <th>Rating (for the subject)</th><th>Definition (for the Investigator and blinded evaluator)</th></tr> </thead> <tbody> <tr> <td>Very much improved</td><td>Optimal cosmetic result for the subject.</td></tr> <tr> <td>Much improved</td><td>Marked improvement in appearance from the original condition, but not completely optimal for this subject.</td></tr> <tr> <td>Improved</td><td>Obvious improvement in appearance from the original condition.</td></tr> <tr> <td>No change</td><td>The appearance is essentially the same as original condition.</td></tr> <tr> <td>Worse</td><td>The appearance is worse than the original condition.</td></tr> </tbody> </table> <p>  Midface Volume Scale  </p> <p>  is a 4-grade scale to assess the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4) as described below. The Investigator and blinded evaluator will rate the subject’s right and left midface for severity of volume deficiency  at baseline and at follow-up visits. The Investigator and blinded evaluator will conduct their MMVS assessments live independently of each other using a photographic scale.  </p> <p>  </p> <p>  </p>	Rating (for the subject)	Definition (for the Investigator and blinded evaluator)	Very much improved	Optimal cosmetic result for the subject.	Much improved	Marked improvement in appearance from the original condition, but not completely optimal for this subject.	Improved	Obvious improvement in appearance from the original condition.	No change	The appearance is essentially the same as original condition.	Worse	The appearance is worse than the original condition.
Rating (for the subject)	Definition (for the Investigator and blinded evaluator)												
Very much improved	Optimal cosmetic result for the subject.												
Much improved	Marked improvement in appearance from the original condition, but not completely optimal for this subject.												
Improved	Obvious improvement in appearance from the original condition.												
No change	The appearance is essentially the same as original condition.												
Worse	The appearance is worse than the original condition.												

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Safety Assessments	<ol style="list-style-type: none"> 1. A question to evaluate local tolerability profile asked 4 weeks after each treatment. 2. Adverse Event reporting through-out the study period to evaluate short- and long term safety.
Statistical Methods	<p><u>Effectiveness</u></p> <div data-bbox="491 1984 1482 2063" style="background-color: black; width: 621px; height: 35px;"></div> <p>the proportion of</p>


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	<p>improved subjects (improved, much improved and very much improved) will be calculated together with a 95% confidence interval.</p> <p>[REDACTED]</p> <p>[REDACTED] the proportion of improved subjects (decrease [REDACTED] of at least one grade compared to baseline) will be calculated together with a 95% confidence interval.</p> <p>[REDACTED]</p> <p>Evaluation of naturalness after treatment [REDACTED] [REDACTED] will be presented descriptively by treatment group and visit.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p><u>Safety</u></p> <p>Local tolerability and Adverse Events will be analyzed descriptively by treatment group.</p>
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Abbreviations and Definitions of Terms

AE	Adverse event
CE	French: <i>Conformité Européenne</i>
Coordinating Investigator	Investigator who is appointed by the Sponsor to coordinate work in a multicenter study
CRF	Case report form
CRO	Contract research organisation
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 treatment	Initial injection of study product
First subject in	First subject screened, i.e. who signs the informed consent form
First subject out	First subject who completed his/her last study visit
G	Gauge
GAIS	Global aesthetic improvement scale
GCP	Good clinical practice
HA	Hyaluronic acid
HIV	Human immunodeficiency virus
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”.
Blinded evaluator	An evaluator responsible for blinded evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject.
Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.
Investigator	The Principal Investigator (PI) or other qualified person, i.e. sub-investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log
Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
ISO	International Organization for Standardization
ITT	Intention-to-treat
Last subject in	Last subject who entered the study
Last subject out	Last subject who completed his/her last study visit
MedDRA	Medical dictionary for regulatory activities

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[REDACTED]	[REDACTED]
NLF	Nasolabial fold
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
Reference product	Medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a study
SAE	Serious adverse event
SOC	System organ class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
Study files	The Investigator file and the Sponsor file
Study products	The investigational product and the reference product under study
Study site	Institution or site where the study is carried out
Touch-up	Repeated injection to be performed 4 weeks \pm 3 days after first treatment if necessary to achieve optimal correction as assessed by the treating Investigator and subject.
U-HCG	Urinary human chorionic gonadotropin
WHO	World Health Organization
[REDACTED]	[REDACTED]



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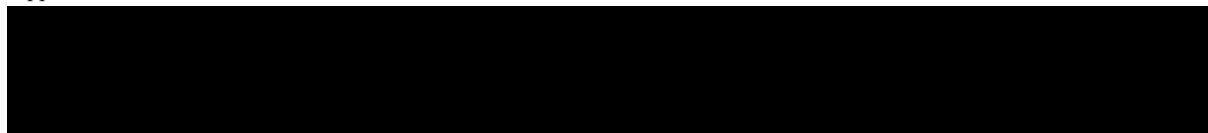
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1. Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2011 shall be followed. The International Conference on 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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

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[illegible]

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[REDACTED]

[REDACTED]

[REDACTED]

2.3 Reference product description

Not applicable.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

2.8 Objectives and endpoints

2.8.1 Effectiveness objectives and endpoints

1. To evaluate improvement of midface [REDACTED]

[REDACTED]

2. To evaluate midface fullness [REDACTED]

[REDACTED]

[REDACTED]

4. To evaluate naturalness of treatment result [REDACTED]

[REDACTED]

[REDACTED]


2.8.2 Safety objectives and endpoints

1. To evaluate local tolerability by direct questioning to subject at 4 weeks after first treatment and touch-up
2. To evaluate Adverse Events (AEs) collected throughout the study

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

3. Design of the Study

3.1 General outline

This is a 24-week evaluator-blinded, multi-center study to evaluate the safety and effectiveness of midface treatments with Restylane Volyme, Restylane Defyne, or Restylane Lyft Lidocaine, using an individualized treatment approach and treatment algorithm.

Approximately 90 subjects requiring volumization, lifting and/or contouring of midface and fulfilling all eligibility criteria will be enrolled in the study. Approx. 30 subjects should be allocated to each treatment group. The aim is to include 20% male subjects in the study.

Product selection for treatment of midface will be based on Investigator assessment of subject tissue coverage and main treatment goal; volumizing, lifting or contouring. Based on those parameters, one of the products Restylane Volyme, Restylane Defyne or Restylane Lyft Lidocaine will be used according to a defined treatment algorithm. Blinding will be accomplished by using a treating Investigator to administer the treatments and a blinded evaluator, to whom treatment allocation is concealed, to conduct assessments.

[REDACTED]


After screening and first treatment there is a 24-week follow-up period [REDACTED]

Information about the subject's tissue thickness and rationale for product choice will be collected as well as treatment procedure, e.g. product used, injection technique, depth, injection volume, use of cannula/needle and anaesthesia used.

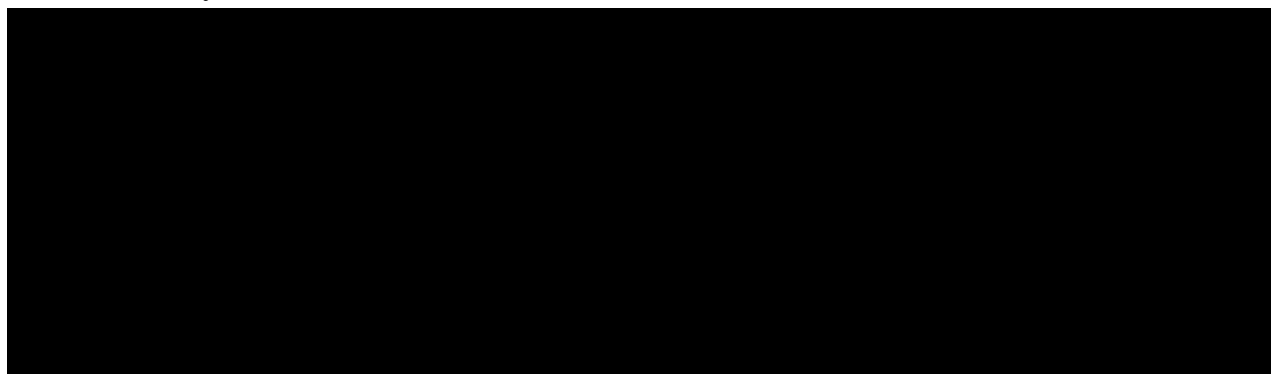
Photographs will be taken before treatment and at follow-up visits to be used for effectiveness assessments.

[REDACTED]

Safety will be followed by AE and device deficiency reporting throughout the study. A question regarding local tolerability will be asked 4 weeks after first treatment and touch-up, for collection of injection-related events.

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3.2 Study flow chart



3.3 Number of subjects

Approximately 90 subjects will be recruited at approximately 2-5 sites. The duration of enrolment is expected to approximately 3 months.

Approximately 15-45 subjects will be enrolled per site. The aim is to include 20% male subjects in the study.

3.4 Duration of subject participation

A subject will be involved in the study for 24-27 weeks.

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

3.5 Blinding

3.5.1 Treatment allocation

Treatment allocation will be assessed by the treating Investigator according to a treatment algorithm (see section 5.7.2).


All treatment information will be kept by the treating Investigator during the study not to be disclosed to the blinded evaluator.

3.5.2 Blinding

Due to the differences in the physical characteristics (viscosity) of the study products, it is not possible to truly double-blind the study, and the treatment assignment cannot be obscured from the treating Investigator.

The blinded evaluator shall not be allowed to retrieve study supplies or to be present during opening of the study supplies or be present during the injection procedure. The treating Investigator and the subjects are not allowed to discuss treatments with the blinded evaluator. All documents with information on study products shall be kept in a separate binder not available to the blinded evaluator.

The site personnel (except blinded evaluator), the subjects, Sponsor and the Sponsor representative shall not be blinded to treatment assignment during the study.

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3.5.3 Emergency unblinding

Not applicable as the treating Investigator is not blinded to treatment assignment.

3.6 Medical history

History of surgical events and medical conditions that are judged as relevant by the Investigator shall be documented in the electronic case report form (eCRF) using medical terminology.

3.7 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 are 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.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

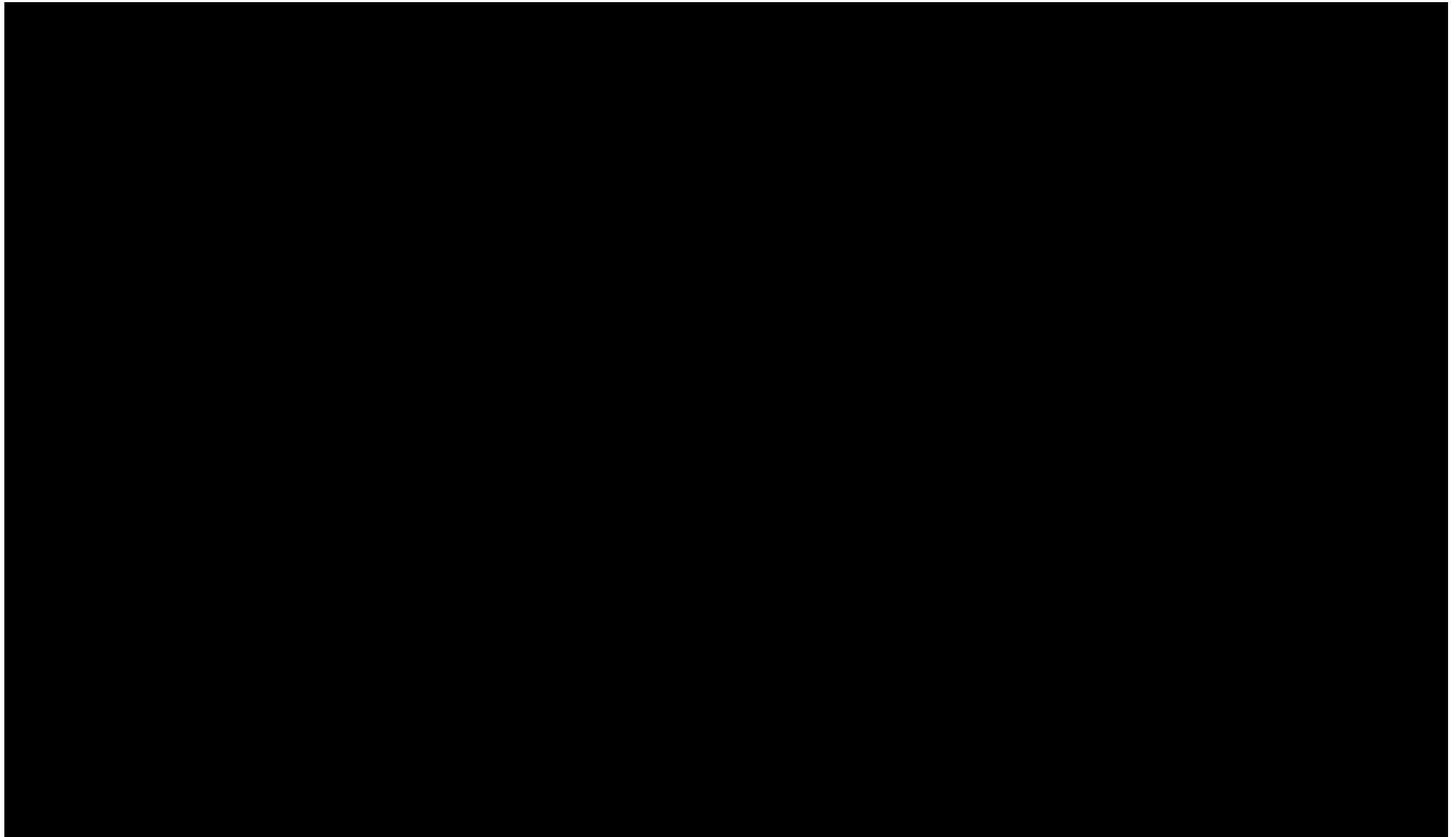
[REDACTED]

Participation in any other clinical study is prohibited.

If a subject receives prohibited therapy during the study, a protocol deviation should be documented. The subject shall continue in the study for the scheduled follow-up visits unless otherwise instructed by the Sponsor.

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3.8 Schedule of events



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3.9 Visits

[REDACTED]	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
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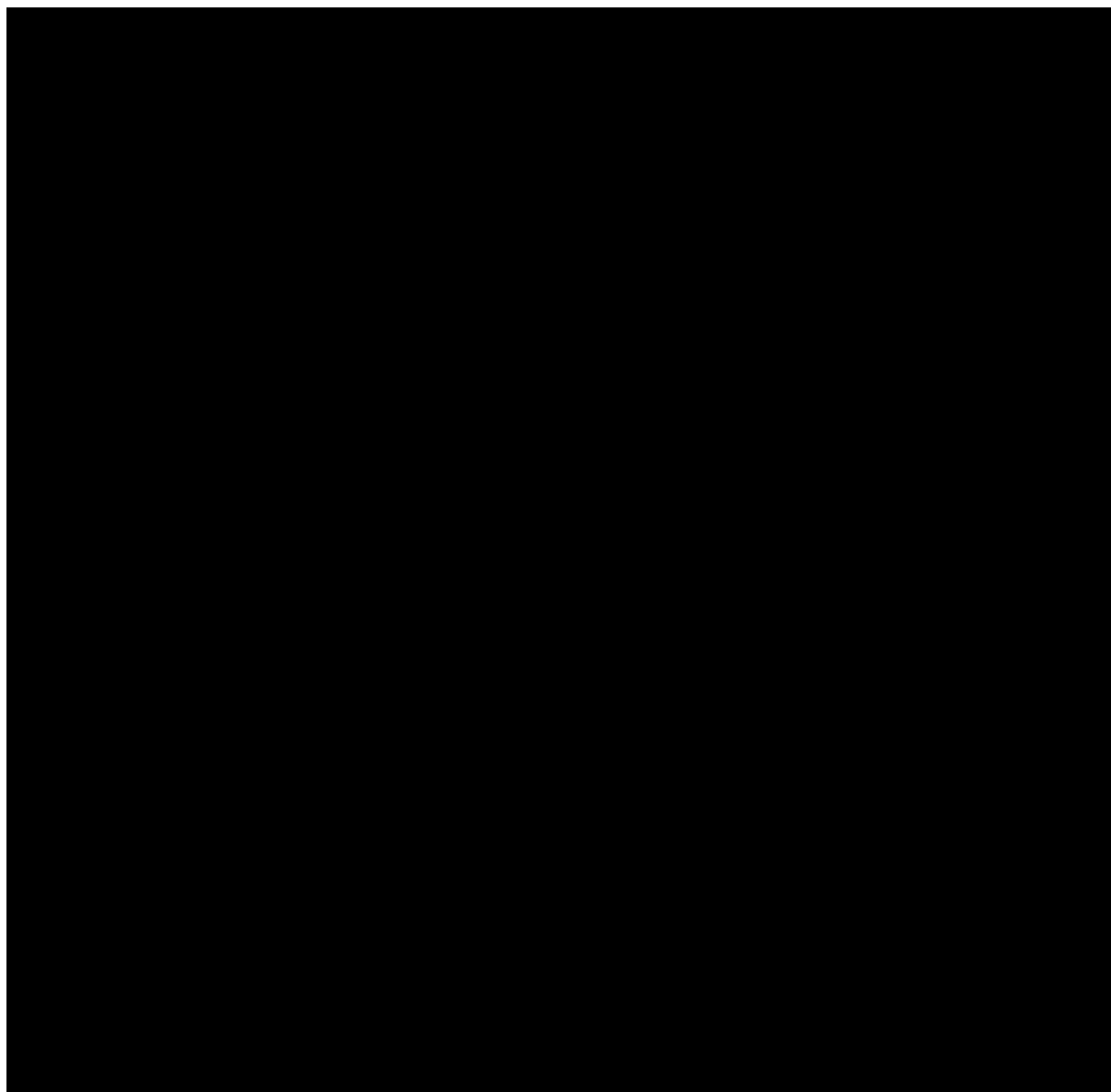
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4. Subjects

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.

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It is the responsibility of the PI or his/her authorised designee to give each subject, prior to enrolment 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 may be transferred to other, EU or non-EU, countries. 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.

4.2 Inclusion criteria

1. Male/Female 25 to 55 years old.
2. Subjects needing lifting, contouring or volumization of the midface.

■ [REDACTED]

■ [REDACTED]

5. Signed and dated informed consent to participate in the study.

4.3 Exclusion criteria

1. Known/previous allergy or hypersensitivity to any injectable HA gel.
2. Known/previous allergy or hypersensitivity to lidocaine or other amide-type anaesthetics, or topical anaesthetics or nerve blocking agents (if such products are intended to be used for that subject).


■ [REDACTED]

4. Previous use of any permanent (non-biodegradable) or semi-permanent (i.e., calcium hydroxylapatite or Poly-L-Lactic acid) facial tissue augmentation therapy or contouring with, lifting threads, permanent implants, or autologous fat in the treatment area.
5. Previous use of any hyaluronic acid or collagen based facial tissue augmentation therapy in the facial area within 12 months before treatment

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[illegible][illegible]

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affect the general condition or may require frequent medical treatment, any abnormal screening laboratory value or ECG, or psychiatric disorders).

[REDACTED]

4.4 Screening and subject numbers

Each subject who has signed the informed consent form will be assigned a subject number and 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 log.


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.

Screening will include ensuring that the subject is eligible based on product allocation and subject gender. Treatment assignment, i.e. product selection, will be based on a treatment algorithm as assessed by the treating Investigator.

- [REDACTED]
- [REDACTED]
- [REDACTED]

Once the product selection has been made, the study site must verify that the subject based on product selection is eligible to enroll.

[REDACTED]

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4.5 Withdrawal of subjects

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

[REDACTED]

- [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 endpoints. In these cases the eCRF for the next upcoming visit should be completed.

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

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

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

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5. Study Products

The term “study products” refers to Restylane Volyme, Restylane Defyne and Restylane Lyft Lidocaine.

5.1 Investigational products

Restylane Volyme is a sterile, biodegradable, transparent gel of non-animal cross-linked hyaluronic acid with the addition of lidocaine hydrochloride 3 mg/mL. The gel is supplied in a prefilled plastic syringe. The syringe contains 1 mL gel. The investigational product is for single use only.

Restylane Defyne is a sterile, biodegradable, transparent gel of non-animal cross-linked hyaluronic acid with the addition of lidocaine hydrochloride 3 mg/mL. The gel is supplied in a prefilled plastic syringe. The syringe contains 1 mL gel. The investigational product is for single use only.

Restylane Lyft Lidocaine is a sterile, transparent, biodegradable gel of stabilized hyaluronic acid of non-animal origin with the addition of 0.3% lidocaine hydrochloride. It is supplied in a glass syringe. The syringe contains 1 mL gel. The investigational product is for single use only.

Detailed product information is provided in the applicable instructions for use (IFU).

5.2 Reference product

Not applicable.

5.3 Additional products and material

The study site will provide pregnancy tests (urinary human chorionic gonadotropin; U-HCG) and needles/cannulas as needed

Local anaesthesia (topical or infiltration) may be used at the discretion of the treating Investigator before the treatment. If used, the anaesthesia shall be supplied by the study site. Type of anaesthesia, product name, and quantity used must be recorded in the eCRF.

The Investigator shall provide adequate equipment in case of emergency.

The sponsor will provide photo equipment as agreed when needed.

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.5 Reference product

Not applicable.

5.6 Product accountability

The investigational products 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 products are kept in a secure location, with access limited to those authorised by the PI.

The investigational products must be traceable from the manufacturer(s) to their use in subjects until return or disposal. It is therefore important that the PI maintains accurate product accountability records, i.e. documentation of the physical location of all investigational products, deliveries, and return of investigational products between the Sponsor and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all investigational 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, batch number, expiry date, dispense date, the number of syringes used, the subject receiving investigational product, and number of syringes left in stock at the site.

When the study is completed, all unused or expired investigational product at each study site shall be returned to the Sponsor for destruction, if not otherwise instructed by Sponsor in writing. Any malfunctioning investigational products shall be reported as described in section 7.4.3.

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

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5.7 Treatment

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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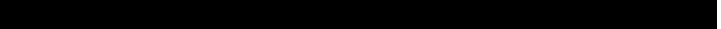
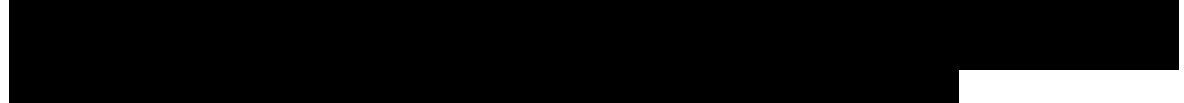



5.7.9 Treatment compliance

No other measurements of treatment compliance shall be made.

6. Efficacy Assessments

6.1 General information

The methods for collecting efficacy data include 2D photography (section 6.2), 

assessment of naturalness of
treatment results (section 6.6), 




To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial screening or baseline determinations completes all corresponding follow-up evaluations.


6.2 2D Photography

Photographs shall be taken prior to the first injection of the investigational product and at follow-up visits in order to document treatment effect.

Note that no covering make-up shall be used on the photographs

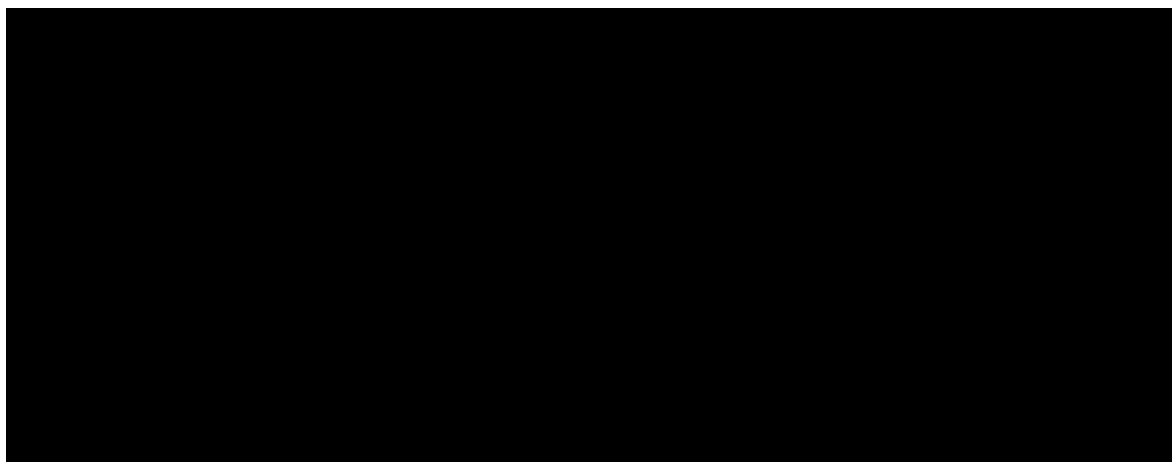
At visits where injections are performed the photographs shall be taken prior to the injections.

Instructions for photography are provided in a separate photography manual. Each photograph shall be labelled with the subject number, and the visit number at which the photograph was taken. In order to maintain confidentiality, the photographs must not include any information that may reveal the subject's identity. The photographs should be used in the assessment of  naturalness,  and to document AEs.. The photographs shall be presented on a computer monitor (preferably the same monitor throughout the study).

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6.3

The [REDACTED] is a qualitative 5-graded scale evaluating aesthetic improvement (Table 4). While [REDACTED] is neither an objective measurement tool nor a validated tool, [REDACTED] improvement has been commonly accepted by the medical community in Europe and the United States as clinical meaningful scale to assess visible aesthetic results. The [REDACTED] can be used not only by the Investigator and blinded evaluator, but is also a useful tool for subject's self-assessment.



The subject, Investigator and blinded evaluator shall, independently of each other, rate the midface for aesthetic change by comparing the appearance at follow-up against a photograph taken before treatment. The photographs shall be presented on a computer monitor (preferably the same monitor throughout the study). Live assessment may help the investigator and the blinded evaluator and a mirror may help the subject. The following question will be asked: **"How would you describe the subject's/your aesthetic appearance of the midface, i.e. the treated area, compared to the photographs taken before treatment?"** The subject shall rate according to the left column in Table 4 and the Investigator and blinded evaluator shall rate according to the right column in Table 4.

A clinically significant improvement is defined as a score of improved; much improved; or very much improved. The [REDACTED] assessments shall as far as possible be performed by the same Investigator or blinded evaluator throughout the study.

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6.4 [REDACTED]

[REDACTED] a 4-grade scale (Table 5) to assess the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4) as described below. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.6 Naturalness of treatment result

[REDACTED] assess naturalness of the treatment result based on review of baseline photographs and live assessment by responding to the question: “Are the subject’s treatment results natural looking?”

Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree ☐

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[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

7. Safety Assessments

7.1 Pre-defined, expected, post-treatment events


The subject shall evaluate local tolerability at the visit 4 weeks after the first treatment and touch-up. A question regarding the presence and maximum intensity of pre-defined expected post-treatment events, i.e. bruising, redness, swelling, pain (including burn), tenderness, and itching shall be assessed for the treated area (Table 7). These events shall not be reported as adverse events (AEs) if fully recovered during the first 2 weeks.

[REDACTED]

Any sign or symptom of pre-defined expected post-treatment events (as specified above) that are still ongoing 2 weeks post-treatment shall also be reported separately as AEs. The events shall be transferred to an AE page in the eCRF and thereafter followed as AEs. The start date of these events shall be the first time point when it was first experienced, and the intensity shall be the maximum intensity of the sign or symptom experienced.

7.2 Laboratory assessments

No laboratory assessments should be performed.

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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 persons³, whether or not related to the investigational product.

This definition includes:

- a) events related to the investigational product or the reference 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-threatening⁴ illness or injury, or
 - 2. a permanent impairment of a body structure or body function, or
 - 3. in-patient or prolonged hospitalisation⁵, 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 7.3.4).

7.3.3 Recording instructions

The study site personnel should question each subject about AEs at each study visit following the signature of informed consent. The following question should be asked at each visit: "Since your last clinical visit have you had any health problems?", and all AEs provided should be recorded. Information on AEs can also be obtained from signs and symptoms detected during each examination or from a laboratory test, observations made by the study site personnel, subject diaries, or spontaneous reports from the subjects or their relatives.

Exceptions from AE reporting are normal fluctuations in pre-existing diseases. However, pre-existing illnesses that deteriorates (in intensity or frequency) shall be reported as AEs.

³ For users or other persons, this definition is restricted to events related to the investigational product.

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).

⁵ 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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When an AE is related to a device deficiency (refer to section 7.4), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form.

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

- Event term (recorded in standard medical terminology and avoiding abbreviations)
- 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)
- Seriousness (serious or not serious, according to definition in section 7.3.2)
- Causal relationship to investigational product or investigational product injection procedure (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
- Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/stable, not recovered at the end of the study)

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

The pre-defined, expected post-treatment events shall be assessed separately. These events shall be collected by direct questioning to subjects at a visit 4 weeks after the first treatment, and touch-up. Any ongoing sign or symptom still persistent 2 weeks after treatment shall be recorded as an AE in the AE module for continued follow-up.

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


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

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

7.3.3.1 Causal relationship and seriousness

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

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

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- “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational 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

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

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


7.3.5 Reporting of serious adverse events

The Investigator shall report any **SAE** to the Sponsor **immediately but not later than 24 hours of awareness of the event**. This initial report shall be made via the eCRF system by completing the SAE module. Via the eCRF-system, the SAE-report will be automatically sent to Sponsor. If there are difficulties accessing the eCRF, an SAE paper form can be completed and sent via fax or e-mail to Sponsor (see contact details below).

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

- Clinical Trial Number
- Subject identification (age, gender, subject number)
- Adverse event description
- Date when AE occurred
- Date when AE became serious
- Name of PI and original reporter (if other than the PI)
- Name of investigational product
- Treatment specification

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

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Supporting documentation to be provided with the SAE report:

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

E-mail for SAE or pregnancy reporting:

Fax number for SAE reporting:

E-mail for device deficiency reporting:

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

Surface mail for providing complementary information:

The SAE form must be signed and dated by the Investigator. Information about investigational products must not be disclosed to the blinded evaluator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE module/form the fully completed and signed SAE module/form shall be sent 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 investigational 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. Follow-up information for at least three (3) months shall be provided to Sponsor. Follow-up information shall be reported on the AE follow-up form.

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7.3.7 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 delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge and be submitted to the Sponsor according to contact details specified in section 7.3.5. 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 (see contact details in section 8.3.5). These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalisation, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

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, safety⁶, 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 investigational product shall be reported as applicable. If an injury has occurred, an AE module or an SAE module/form 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.

⁶ Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

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7.4.3 Reporting of device deficiencies

The Investigator shall send the completed clinical study complaint form to the Sponsor via eCRF using the contact details specified in section 7.3.5. If there are difficulties accessing the eCRF, a paper form can be completed and sent via fax or e-mail to Sponsor. 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 investigational 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 if required by national regulations and the PI is responsible for reporting it to the IEC if required by national regulations.

The deficient investigational product shall be kept 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.

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 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 and the eCRF. 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 enrolled subjects (subsequent visits).

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The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data shall be entered directly from the source documents, which are to be defined at each site before enrolment 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 investigation site personnel prior to the study being initiated and any data being entered into the system for any subject.

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

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

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 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

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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 laboratory notes, memoranda, material dispensing records, subject files, etc.


The PI is responsible for maintaining source documents. These shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, shall be clearly identified with the CTN and subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

8.4 Record keeping and access to source data

The PI/Institution shall permit study-related monitoring, audits, IEC review, and RA inspections and shall provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed informed consent forms and detailed records of investigational product accountability). The records shall be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records shall be documented and the Sponsor shall be informed in writing.

The Sponsor shall verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record.

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

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8.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, informed consent forms, investigational 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 site(s) as to when these documents no longer need to be retained. Measures shall 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.

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.2 Analysis populations

The following populations will be defined:

- Safety
- Modified Intention-to-treat (MITT)

[REDACTED]


[REDACTED]

All effectiveness analyses will be based on the MITT population. Safety analysis will be performed based on the safety population set.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

9.3 Demographics, screening/baseline assessments, and subject characteristics

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

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9.4 Effectiveness analysis

the proportion of improved subjects (assessed as very much improved, much improved or improved) will be presented together with a 95% confidence interval (based on the binomial distribution).

the proportion of improved midfaces (1 grade decrease on the scale) and subjects (both midfaces improved) will be presented together with a 95% confidence interval (based on the binomial distribution).

Evaluation of naturalness after treatment will be presented descriptively by treatment group and visit.


9.5 Safety analysis

Adverse events will be summarised in frequency tables by study product, containing number of subjects with no AEs, number of subjects with at least one AE, and number of events, All AEs will be summarised and listed by system organ class (SOC) and preferred term (PT) assigned using MedDRA.

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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 Interim analysis

Not applicable.

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 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.

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



10. Protection of personal data

The study shall include collection and processing of personal data as specified in the Regulation (EU) 2016/679 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 than 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

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

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

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, address and place of work, and shall show the training, appointments and, for the PI, any other information that will confirm the suitability of the PI to be responsible for the study.

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the signature and delegation log.

11.3 Changes to the clinical study protocol

11.3.1 Amendments

The PI and other site personnel involved in the study must not implement any changes to the CSP without agreement with the Sponsor and prior review and documented approval from the IEC and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a dated and version controlled written protocol amendment. For non-substantial changes not affecting

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the rights, safety and well-being of the subjects or not related to the clinical objectives or endpoints, a simple notification to the IEC and RA, if applicable, can be sufficient.

11.3.2 Deviations

The PI is not allowed to deviate from the CSP. However, under emergency circumstances, deviations from the CSP to protect the rights, safety and well-being of the subjects may proceed without prior approval of the Sponsor and the IEC and RA. Such deviations should be documented and reported to the IEC and RA as soon as possible. Any CSP deviation shall be reported in the deviation log, which will be verified, discussed, and collected by the monitor and appropriate actions will be taken. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations will be performed as described in the monitoring manual. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor (within 24 hrs following detection) as well as the IEC if required.

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 resolved⁷. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

⁷ 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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14. Suspension or Premature Termination

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


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

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

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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.

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10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.
Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

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


Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

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

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for

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subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

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

Research Ethics Committees

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

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

Privacy and Confidentiality

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


Informed Consent

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

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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed

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

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

Use of Placebo

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

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

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

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

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

Post-Trial Provisions


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

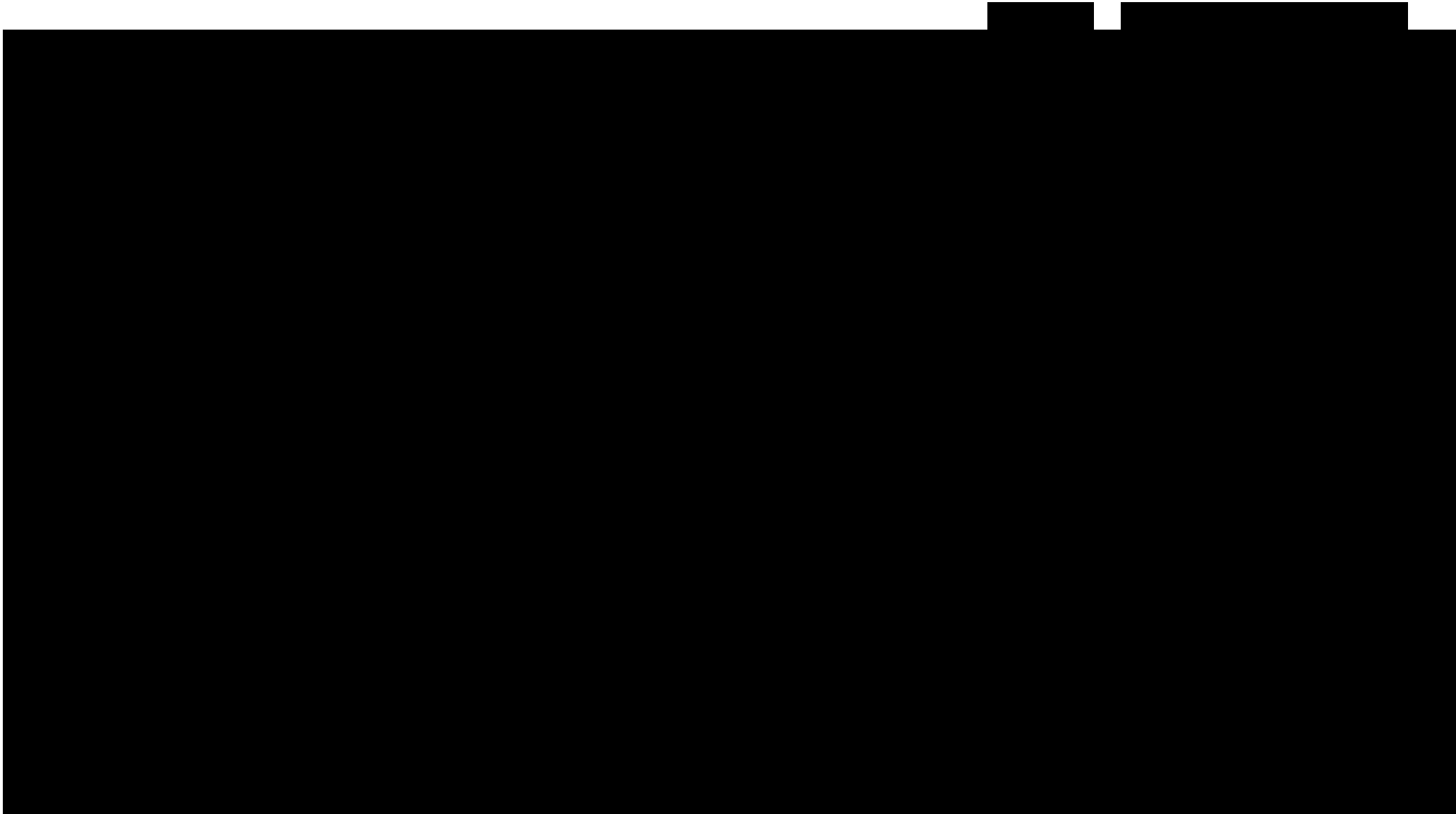
Research Registration and Publication and Dissemination of Results

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

Unproven Interventions in Clinical Practice

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

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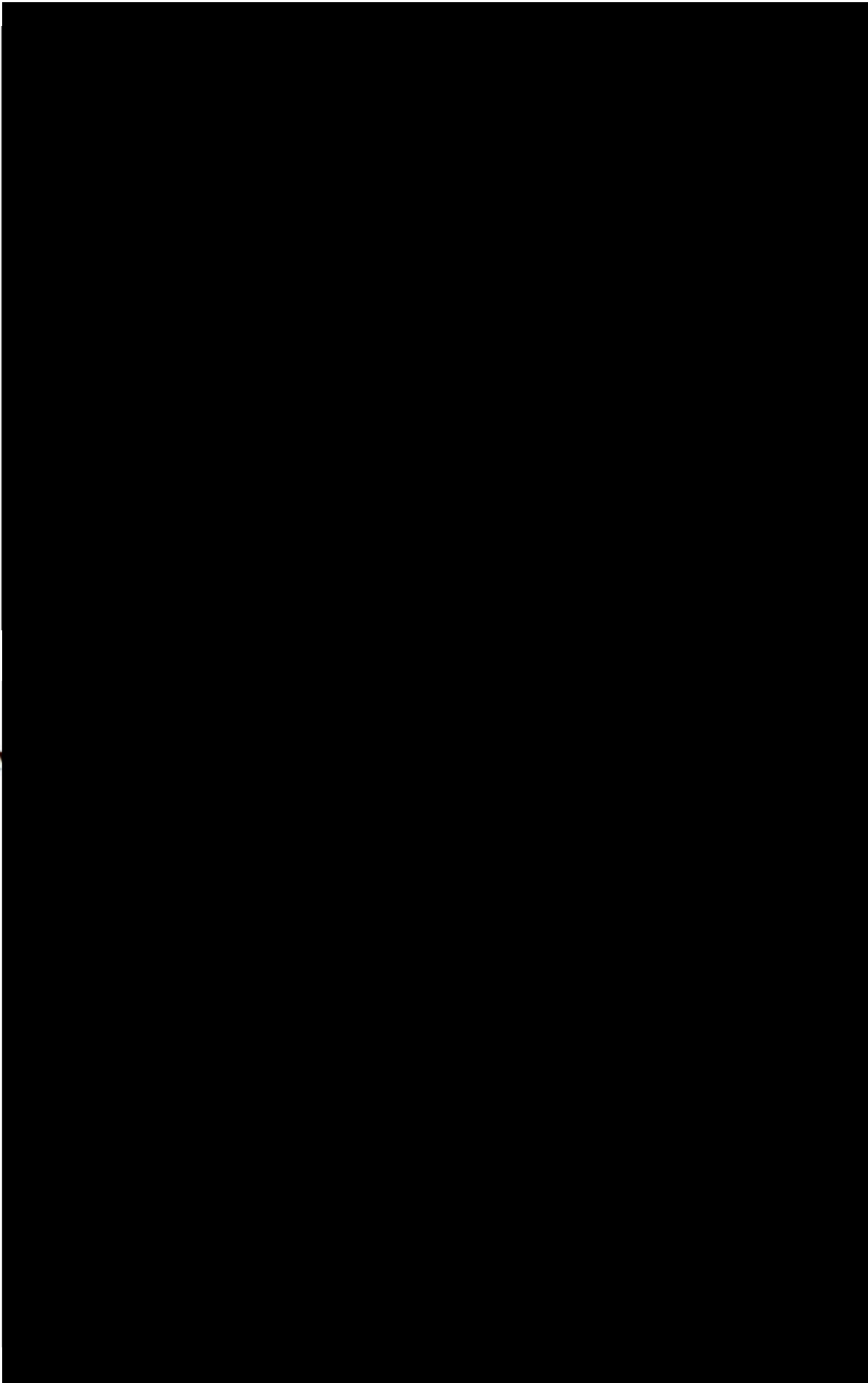


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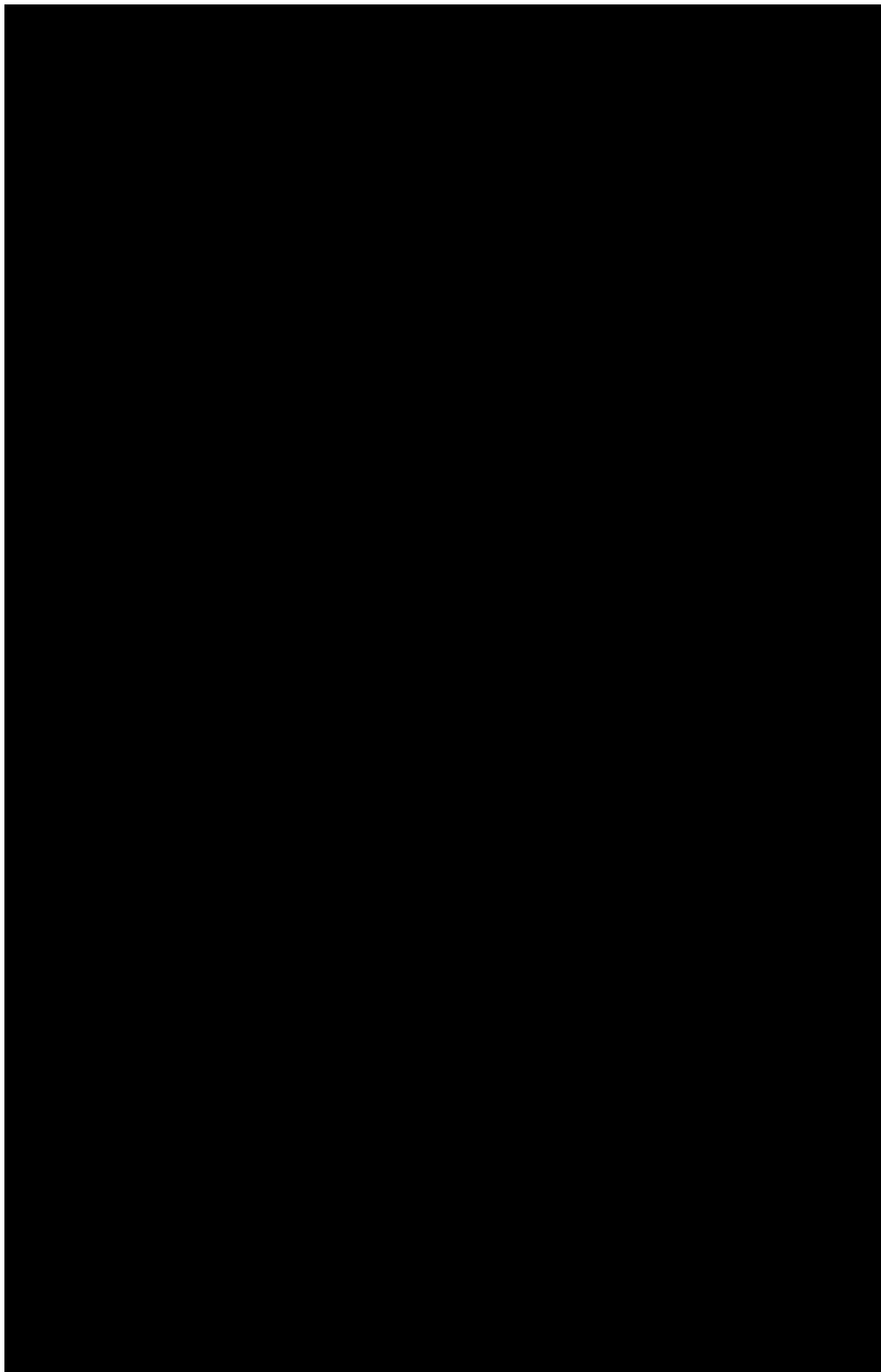
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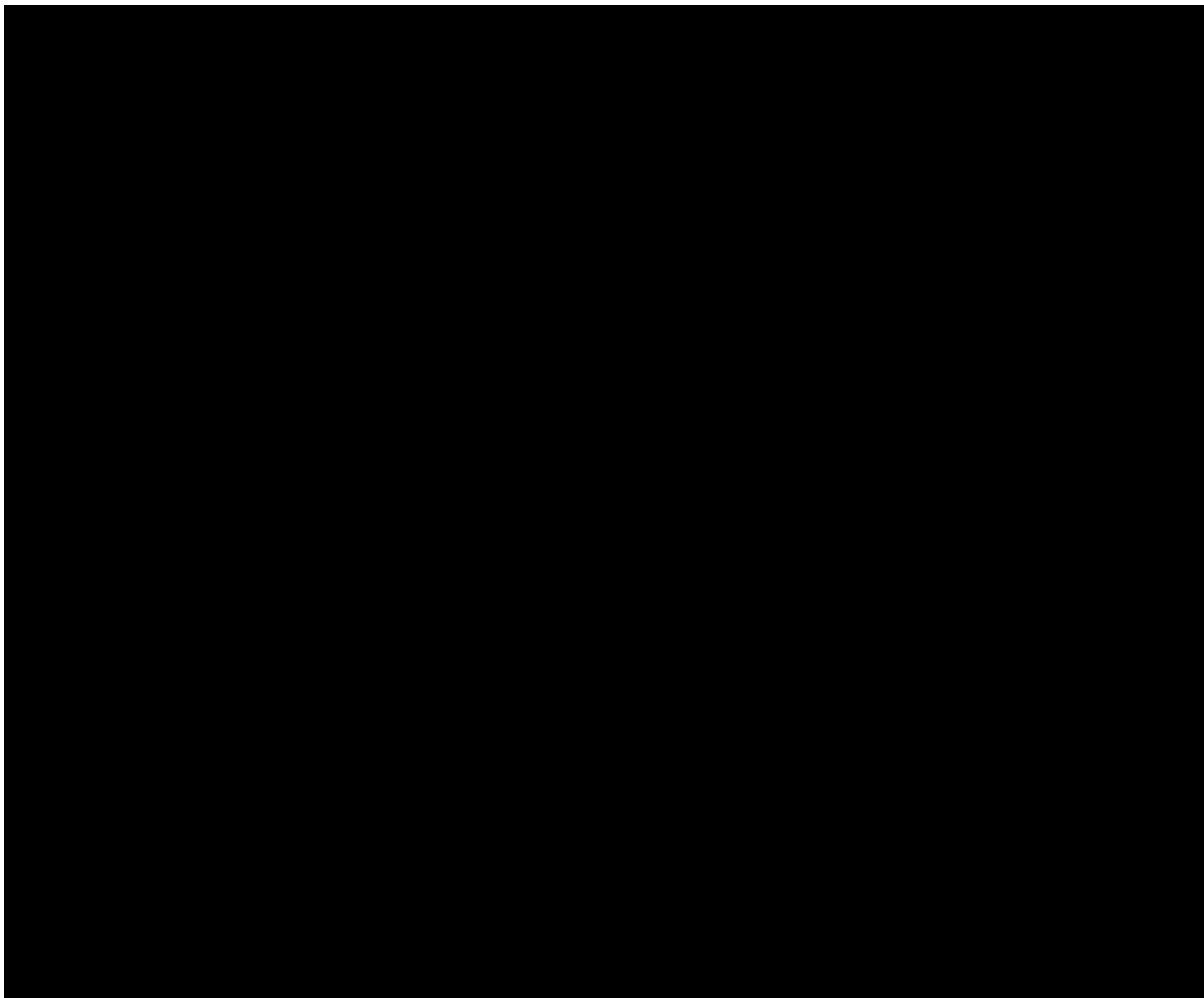


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SIGNATURES PAGE

