A Randomized, Controlled, Evaluator-Blinded, Multi-Center Study to Evaluate the Effectiveness and Safety of *Restylane*® *Kysse* versus a Control in the Augmentation of Soft Tissue Fullness of the Lip

Study product: *Restylane*® *Kysse*

Comparator product: [redacted]

Clinical trial number (CTN): 43USK1701

Sponsor: [redacted]

[redacted]

Investigators and Study Administrative Structure

Sponsor:

Q-Med AB, a Galderma affiliate

[redacted]

Galderma Research and Development, LLC

[redacted]

Medical Expert:

[redacted]

Clinical Project Manager:

[redacted]

Study Statistician:

[redacted]

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 investigational plan (CIP) amendment.

Sponsor Signatures

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

[redacted]

[redacted]

[redacted]

[redacted]

Synopsis

Title of study:	A randomized, controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Kysse* versus a control in the augmentation of soft tissue fullness of the lip
Clinical Trial Number:	43USK1701
Countries involved	United States
Number of sites	Approximately 15
Number of Subjects	Approximately 280 randomized subjects. [redacted]
Target Indication	Injection into the lips for lip augmentation and for correction of perioral rhytids in subjects over the age of 21.
Primary Effectiveness Objective and Endpoint	1. The primary objective of the study is to demonstrate non-inferiority of *Restylane® Kysse* versus a control in lip fullness augmentation by comparing change from baseline in the Blinded Evaluator assessment of Medicis Lip Fullness Scale (MLFS) in the upper and lower lip separately, at 8 weeks after last injection.
Secondary Effectiveness Objectives and Endpoints	1. To evaluate the effectiveness of *Restylane® Kysse* in lip fullness augmentation based on the Blinded Evaluator assessment of MLFS in the upper and lower lip, using the following endpoints: a. Change from baseline at 16, 24, 32, 40, and 48 weeks after last injection b. Response rates (defined as at least 1 point improvement from baseline) at 8, 16, 24, 32, 40, and 48 weeks after last injection. 2. To evaluate the aesthetic improvement of the upper perioral rhytids and oral commissures after treatment with *Restylane® Kysse,* based on the Blinded Evaluator assessment of Wrinkle Assessment Scale[1] (WAS), at 8, 16, 24, 32, 40, and 48 weeks after last injection using the following endpoints: a. Change from baseline b. Response rates (defined as at least 1 point improvement from baseline). 3. To evaluate the aesthetic improvement (overall appearance)

[1]Lemperle, G. A Classification of Facial Wrinkles. Plastic Reconstructive Surgery. 2001:1735-1750.

	after treatment with *Restylane® Kysse*, based on the Global Aesthetic Improvement Scale (GAIS) at Week 8, 16, 24, 32, 40, and 48 weeks after last injection using response rates (defined as at least "Improved"). 4. Subjects' satisfaction after treatment with *Restylane® Kysse* using the FACE-Q scales Satisfaction with Lips and Appraisal of Lines: Lips at Week 8, 16, 24, 32, 40, and 48 weeks. 5. Lip fullness compared to baseline, using Central Independent Photographic Reviewer's assessment of improvement in fullness of each (yes/no) by comparison of random, blinded pairings of the baseline and post-baseline photographs taken at Week 8, 24, 40, and 48.
Safety Objectives and Endpoints	1. To evaluate all adverse events (AEs) and pre-defined, expected, post-treatment events reported during the first 4 weeks after treatment as recorded in the subject diary. 2. To evaluate the safety assessment at all visits, as assessed by a qualified staff member: • Presence of any unexpected resistance by palpation of each lip at baseline and at each physical follow-up visit. • Lip texture and symmetry according to pre-defined methods, for each lip at baseline and at each physical follow-up visit. • Lip movement, function, and sensation (on three different locations per lip) according to pre-defined methods, at baseline and at each physical follow-up visit.
[redacted]	[redacted]

Study Design	Randomized, evaluator-blinded, controlled, parallel group, multi-center, US study
Subject Participation	A subject will be involved in the study for approximately 15 months from screening to final follow-up visit.
Enrollment	Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 30 days prior to injection. The screening visit and baseline visit may be performed on the same day. Subsequent to screening, eligible subjects will be randomized in the study. [redacted] At least 42 subjects will be Fitzpatrick skin type IV through VI. [redacted]
Treatment	*Initial Treatment* The subjects will be randomized (2:1) to receive either *Restylane*® *Kysse* or Juvéderm Volbella® XC in both lips on Day 1. [redacted] Treatment of the upper perioral lines, vermillion border, philtral columns, cupid's bow, and/or oral commissures may be performed to obtain optimal aesthetic result, as agreed by the Treating Investigator and subject. [redacted]

	[redacted]
Study Procedures	[redacted] [redacted] *Evaluation of safety* Adverse Events (AEs) will be obtained from signs and symptoms reported by the subject or detected during each examination visit to obtain information about any medical occurrence that meets the definition of an AE. In addition, all subjects will complete a Diary for 4 weeks after each treatment, to collect information about pre-defined, expected, post-treatment events at the treated area. Any subject with a treatment related AE that is ongoing at the time of study completion will be followed until that AE is resolved or stabilized. Any AE assessed as related to the study product or injection procedure with onset after subject participation in the study is over, and that the Investigator becomes aware of should be reported to the Sponsor.

	Study report A study report will be compiled at the conclusion of the study. This report will be included in the regulatory submission for marketing application.
Inclusion criteria:	1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent. 2. Males or non-pregnant, non-breastfeeding females, 22 years of age or older. 3. Subjects seeking augmentation therapy for the lips.

	[redacted]
Exclusion criteria:	1. Known/previous allergy or hypersensitivity to any injectable HA gel or to gram positive bacterial proteins. 2. History of allergy or hypersensitivity to lidocaine or other amide-type anesthetics, or topical anesthetics or nerve blocking agents (if such products are intended to be used for that subject). [redacted]

[redacted]

25. Participation in any interventional clinical study within 30 days of screening.

[redacted]

Investigational product:	*Restylane*® *Kysse* injectable gel. [redacted]
Reference therapy	Juvéderm Volbella® XC injectable gel. [redacted]
Therapy Dose	[redacted]
Schedule of Events	[redacted]
Efficacy Assessment:	[redacted]

[1] PMA P110033/S018: FDA Summary of Safety and Effectiveness Data

	[redacted]
Safety Assessment:	[redacted]
Statistical Methods:	Sample size A maximum of 280 subjects will be treated in the study. [redacted] Principles for the Analysis In general, all effectiveness, safety and baseline characteristics variables will be presented using descriptive statistics within each treatment group, and graphs as appropriate. Continuous endpoints will be summarized using descriptive statistics, e.g. mean, median, standard deviation, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level. The primary effectiveness analysis is test of non-inferiority of

	[redacted]

Abbreviations and Definitions of Terms

AE	Adverse event
BDDE	1,4-butanediol diglycidyl ether
CE	"Conformité Européenne" the quality and branding mark for products made or sold within the European Union.
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
Childbearing Potential	The ability of a pre-menopausal female to become pregnant. This includes women using oral, injectable or barrier contraception; women who have had a tubal ligation; women who are single; and women whose male partners have been vasectomized or utilize barrier contraceptive methods.
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
ET	Early termination
FDA	United States Food and Drug Administration
First subject in	First subject screened, i.e. who signs the informed consent form
First subject out	First subject who completed their last study visit
FST	Fitzpatrick Skin Type
G	Gauge
[redacted]	[redacted]
GCP	Good clinical practice
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IFU	Instructions for use
Investigational Product	Medical device being assessed for safety or performance in a study. "Investigational product" is the same as "study device", "investigational device", or "investigational medical device".

Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.
Investigator	The Principal Investigator (PI) or other qualified person, i.e. sub-investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log
Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
[redacted]	[redacted]
IRB	Institutional review board
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 their last study visit
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
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
ROPI	Report of Prior Investigations, i.e. compilation of the current clinical and non-clinical information on the investigational product, relevant to the clinical study
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
SOC	System Organ Class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
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
TC	Telephone Call

Touch-up	Repeated injection to be performed after treatment if necessary to achieve optimal correction
[redacted]	[redacted]
Tx	Treatment
WAS	Wrinkle Assessment Scale
WHO	World Health Organization

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Ethical Considerations

1.1 Statement of ethical compliance

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

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 CIP/CIP amendment(s) from the institutional review board (IRB). The study shall not begin until the required favorable opinion from the IRB has been obtained. The PI shall file all correspondence with the IRB in the Investigator file and copies of IRB approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the IRB or regulatory authorities (RA) shall be followed.

The study requires application for approval from the US Food and Drug Administration (FDA). The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

2. Background Information

2.1 Indication and population description

[redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2.3 Study rationale

The rationale of performing this study is to obtain evidence of safety and effectiveness of *Restylane® Kysse* to support a future US marketing application.

[redacted]

2.5 Risks and benefits

[redacted]

[redacted]

3. Objective(s) and Endpoint(s)

3.1.1 Primary objective and endpoint

The primary objective of the study is to demonstrate non-inferiority of *Restylane® Kysse* versus a control in lip fullness augmentation [redacted]

3.1.2 Secondary objectives and endpoints

The secondary objectives and endpoints are:

- To evaluate the effectiveness of *Restylane® Kysse* in lip fullness augmentation [redacted]
- To evaluate the aesthetic improvement of the upper perioral rhytids and oral commissures after treatment with *Restylane® Kysse,* [redacted]
- To evaluate the aesthetic improvement (overall appearance) after treatment with *Restylane® Kysse*, [redacted]

[1]Lemperle, G. A Classification of Facial Wrinkles. Plastic Reconstructive Surgery. 2001:1735-1750.

[redacted]

3.1.3 Safety objectives and endpoints

The safety objectives and endpoints are:

- To evaluate all AEs at all visits and pre-defined, expected, post-treatment events reported during the first 4 weeks after treatment as recorded in the subject diary.
- To evaluate the safety assessment at all visits, as assessed by a qualified staff member:

[redacted]

4. Design of the Study

4.1 General outline

This is a randomized, controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Kysse* for lip augmentation and correction of perioral rhytids. Approximately 280 subjects will be randomized in a 2:1 ratio of treatment to control and treated. Approximately 187 subjects will be treated with *Restylane® Kysse* and 93 subjects will receive the control in the lips and perioral rhytids for 48-weeks. All randomized subjects' lips will have a MLFS score of 1 (Very Thin) or 2 (Thin). The upper lip and lower lip scores do not have to be equal as long as each score is 1 or 2.

At least 42 subjects enrolled and treated will be FST IV through VI. This includes up to 21 subjects with FST V to VI who do not have to meet the inclusion criteria for MLFS.

Investigator blinding will be accomplished by using a Treating Investigator to administer the treatments and a Blinded Evaluator, to whom randomization and treatment are concealed, to conduct the blinded assessments. Safety assessments will be performed by non-blinded personnel.

Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. The method of injection is at the discretion of the Treating Investigator and will be recorded. Sufficient amount of product should be injected to achieve optimal correction of the lips, in the opinion of the Treating Investigator and subject. Optimal appearance is defined as at least 1 MLFS step improvement from Baseline and best correction that can be achieved as agreed by the Treating Investigator and the subject. Touch-up treatment may be administered after 4 weeks if deemed necessary to obtain optimal aesthetic result; this decision should be agreed upon by the Treating Investigator and the subject. Touch-up treatment will not be performed if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a touch-up. It is recommended that the dose should not exceed 1.5 mL in each lip (including vermillion, vermillion border and cupid's bow) per treatment session. The study product may also be injected for optimal correction of the upper perioral rhytids, philtral columns, and/or oral commissures. The recommended maximum injected volume per subject and treatment is 6 mL (i.e. 3 mL for lips and 3 mL for perioral area).

Subjects will have in-clinic follow up visits at 2, 4, 8, 16, 24, 32, 40, and 48 weeks after the last injection. If a touch-up is performed, a second 2-week and 4-week follow-up visits should be scheduled. At the 48-week visit after all study procedures for the visit are completed, subjects can receive an optional additional treatment if optimal aesthetic improvement is not maintained with *Restylane® Kysse*. If re-treatment is performed, a second 2-week and 4-week follow-up visits should be scheduled. In addition to the clinic visits, phone visits will also occur as specified in the study flow chart below.

A Study Flow Chart is provided on the next page.

4.2 Number of subjects

Subjects will be recruited from up to 15 study sites in the USA. Approximately 280 subjects will be included in the study.

4.3 Duration of subject participation

A subject may be involved in the study for approximately 15.0 months from screening to the final follow-up visit. "End of study" is defined as the time point when the last subject has completed the last study visit.

4.4 Randomization and blinding

[redacted]

4.4.2 Blinding

Investigator blinding will be accomplished by using a Treating Investigator to administer the treatments and a Blinded Evaluator, to whom randomization and treatment are concealed, to conduct the blinded assessments. The Blinded Evaluator is not allowed to discuss treatments with the Treating Investigator or subjects. All study related documents that contain information regarding the treatment of subjects should not be available to the Blinded Evaluator. Safety assessments will be performed by non-blinded personnel as treatment-related AEs are expected to occur during a few days after treatment, thereby revealing which subjects has received the study product.

4.4.3 Emergency unblinding

Not applicable as the Treating Investigator is unblinded.

4.5 Medical history

History of surgical events, medical conditions (including any prior dermatological procedures or implants), and medications taken prior to screening shall be documented using medical terminology.

4.6 Concomitant medications, treatments, and procedures

Except as noted below, concomitant medications or other treatments or procedures may be utilized when the Investigator or his/her authorized designee considers it medically necessary. Information regarding any use of concomitant medications, including prescription and over-the-counter medications administered during the investigation is to be recorded. 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:

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

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

If a treated subject has used any of the above prohibited medications or procedures he or she should, for safety reasons, continue in the study for the scheduled follow-up visits.

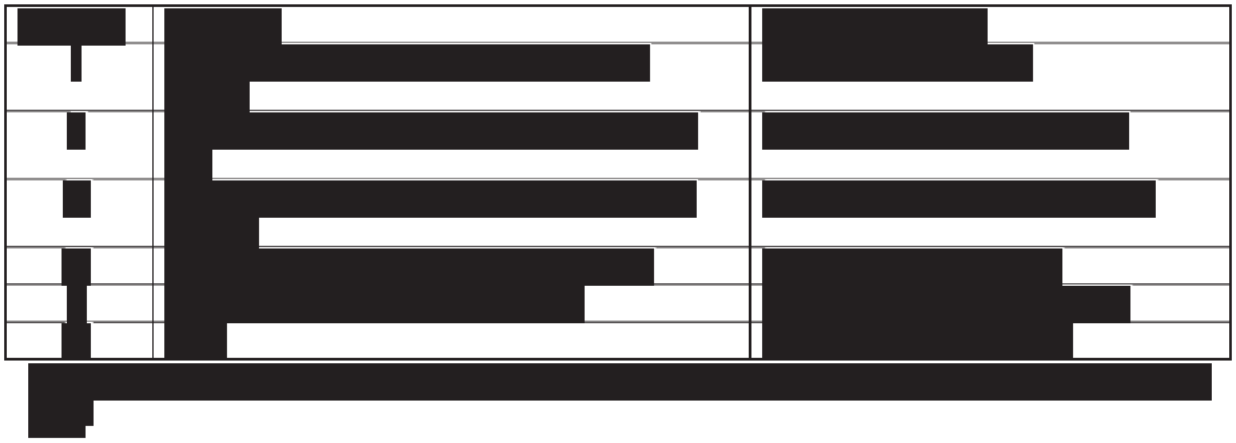
4.7 Schedule of events

[redacted]

GALDERMA

[redacted]

GALDERMA



[redacted]

[redacted]

[redacted]

5 [redacted]

[redacted]

4.8.18 Unscheduled Visits

- When necessary, unscheduled visits could take place (in particular because of an AE needing a specific treatment). Unscheduled visits related to the study should be documented and all adverse events captured.

5. Subjects

5.1 Subject information and informed consent

The Investigator or his/her authorized designee must always use the IRB-approved subject information and informed consent form and it must not be changed without prior discussion with the Sponsor and approval from the applicable IRB.

It is the responsibility of the Investigator or his/her authorized 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 IRB. 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 Investigator or his/her authorized designee responsible for conducting the informed consent process.

All original signed informed consent forms shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated informed consent form and any other written information.

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

5.2 Inclusion criteria

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

1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent.
2. Males or non-pregnant, non-breastfeeding females, 22 years of age or older.
3. Subjects seeking augmentation therapy for the lips.

[redacted]

5.3 Exclusion criteria

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

1. Known/previous allergy or hypersensitivity to any injectable HA gel or to gram positive bacterial proteins.

2. History of allergy or hypersensitivity to lidocaine or other amide-type anesthetics, or topical anesthetics or nerve blocking agents (if such products are intended to be used for that subject).

[redacted]

25. Participation in any interventional clinical study within 30 days of screening.

[redacted]

5.4 Screening and subject numbers

Prior to any study procedures being conducted, the subject must sign the informed consent form. The subject number will be assigned at Baseline / Day 1. All study procedures performed should be documented in the subject's source documents and in the electronic Case Report Forms (eCRFs). 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.) should be recorded.

A screen failure is a subject who signed informed consent but never enrolled (i.e. received treatment) in the study. For screen failures, the subject's source documents should indicate which assessments have been made and the reason why the subject was discontinued.

A subject is considered enrolled when they have signed the informed consent and are randomized and/or treated.

During the study conduct, the Blinded Evaluators shall not have access to any subject's source documents that identify the subject.

5.5 Withdrawal of subjects

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

[redacted]

The reason and date for withdrawal should be documented in the subject's source documents and eCRFs. When possible, an explanatory comment should be added to further explain the reason for withdrawal. If withdrawal of a subject occurs during a regular investigational visit, the eCRF for that specific visit should be completed as far as possible.

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.

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

Subjects who receive product and are withdrawn or discontinued from the study will not be replaced.

For AEs still ongoing at the time of the withdrawal, see Section 8.7.6.

6. Study Products

6.1 Investigational product

The investigational device (i.e. the study product) is *Restylane*® *Kysse*, manufactured by Q-Med AB (a Galderma affiliate located in Uppsala, Sweden). The sterilized gel contains 20 mg/mL stabilized HA and 3 mg/mL lidocaine hydrochloride in a physiological buffer. Each syringe contains 1 mL gel. The investigational product is for single use only.

6.2 Packaging, labelling, and storage

[redacted]

6.3 Product accountability

The study products will be released to the Investigator or his/her authorized designee after study approvals have been received from the FDA and IRB and the CTA has been signed by all parties.

The Investigator must ensure that the study products are kept in a secure location, with access limited to those authorized by the Investigator.

The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the Investigator maintains accurate product accountability records, i.e. documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the Investigator, and documentation of administration of product to the subject.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor representative for destruction, or be destroyed locally at the site if documented as agreed with Sponsor.

Any malfunctioning study products shall be reported as described in Section 8.8.

Products deliberately or accidentally destroyed during shipment or at a study site shall be accounted for and documented. Used syringes, needles, and any unused material must be discarded immediately after the treatment session and must not be reused due to risk for contamination of the unused material and the associated risks including infections according to standard procedures at the site. Disposal of hazardous material, i.e. syringes and needles must conform to applicable laws and regulations. The study products must not be used outside the study.

6.4 Treatment

[redacted]

When injecting *Restylane® Kysse*, the following techniques may be used in the lip

[redacted]

[redacted]

[redacted]

6.4.9 Treatment compliance

Not applicable; the treatment will be administered by the injector at the investigational site.

7. Efficacy Assessments

7.1 General information

The methods for collecting efficacy data are described in the following sections. To minimize 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.

[redacted]

[redacted]

[redacted]

[redacted]

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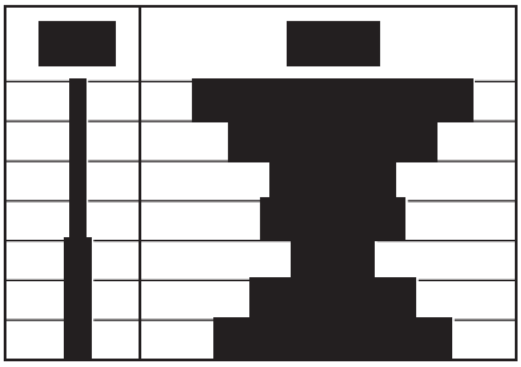

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8. Safety Assessments

8.1 Assessment of AEs by direct question to subject and evaluation of subject

Safety evaluations for this study include an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an AE. Each subject should be questioned about AEs at each study visit following the screening visit. Information on AEs can also be obtained from signs and symptoms detected during each examination by the Investigator or designee, which should include visual inspection of the treatment area.

AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product. If in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and eCRF.

It is the responsibility of the Treating Investigator to determine severity of the AE and relatedness of the event to the study product.

[redacted]

[redacted]

8.6 Laboratory Assessments

Pregnancy Test: For all women of childbearing potential, a urine pregnancy test will be performed at screening, all injection visits (prior to treatment) and at study exit. The test result will be documented.

8.7 Adverse events

8.7.1 Definition of an adverse event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons[1], whether or not related to the study product.

This definition includes:

a) events related to the investigational product or the reference product

b) events related to the procedures involved

8.7.2 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-threatening[2] illness or injury, or
2. a permanent impairment of a body structure or body function, or
3. in-patient or prolonged hospitalization[3], 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 fetal distress, fetal death, or a congenital abnormality or birth defect

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

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

8.7.3 Recording instructions

Each subject with an AE occurring after signing of the informed consent form through study exit should be fully recorded in the source document for further transcription to the eCRF. Each subject should be questioned about AEs at each study visit following the screening visit. The question asked should be: “Since your last clinical visit have you had any health problems?” Information on AEs can also be obtained from signs and symptoms detected during each examination.

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[1]For users or other persons, this definition is restricted to events related to the investigational 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 hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

When an AE is related to a device deficiency including technical device malfunction, the AE should be recorded in the AE eCRF and technical complaint should be reported separately on the study complaint form.

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

a) Event term (recorded in standard medical terminology and avoiding abbreviations)

b) Description of event and affected area

c) Start date (first day with symptoms)

d) Stop date (last day with symptoms)

e) Intensity (mild, moderate, or severe according to definition in Section 8.5.3.1)

f) Seriousness (serious or not serious, according to definition in Section 8.5.3.2)

g) Causal relationship to study product or study product injection procedure (yes or no)

h) Action taken (none, medication treatment, non-medication treatment, or other procedures/tests, subject withdrawn)

i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

The pre-defined, expected post-treatment events shall be assessed separately. These events shall be collected by subjects in a diary used daily for 30 days after the treatment.

8.7.3.1 Intensity

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

Mild: Awareness of symptoms or signs, but easily tolerated (acceptable*)*

Moderate: Enough discomfort to interfere with usual activity (disturbing)

Severe: Incapacity to work or to do usual activity (unacceptable)

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

8.7.3.2 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.

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 *e*CRF:

- "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.

8.7.4 Reporting of adverse events

Adverse event reporting on each subject shall start at screening visit after the signature of the ICF. 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.

[redacted]

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

Supporting documentation to be provided with the SAE report:

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

[redacted]

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 to the Sponsor. A copy of the fully completed SAE form shall be kept at the site.

In addition, the Investigator shall report SAEs to the responsible IRB without undue delay, if applicable according to national regulations. The Investigator is responsible for checking what reporting procedures are applicable for his/her IRB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period. For non-urgent complementary information not possible to send by e-mail or fax, please use surface mail.

[redacted]

8.7.7 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy after the subject has been treated, 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 after treatment must be reported by the Investigator on a pregnancy report form immediately upon acknowledgement and submitted to the Sponsor according to contact details specified in Section 8.7.5. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the exposure *in utero* report form to the Sponsor immediately but no later than 24 hours after the Investigators awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

[redacted]

8.8 Device deficiencies

8.8.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety[1], or performance.

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

8.8.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator or qualified designee. 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 or an SAE form shall be completed as applicable (refer to Section 8.7). 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.

8.8.3 Reporting of device deficiencies

[redacted] A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported within 24 hours after the Investigator's awareness in accordance to Section 8.7.5.

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 IRB.

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

9. Data Handling and Management

9.1 Data management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for handling eCRFs, database set-up and

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

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 CIP and the eCRF. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. SAEs in the clinical database will be reconciled against the data in the safety database.

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

9.2 Electronic case report forms

A 21 Code of Federal Regulations 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 screen failure as well as enrolled subjects.

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data shall be entered directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorized study site personnel designated by the Investigator shall complete data collection. Appropriate training and security measures shall be completed with all authorized 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 authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study site as part of the Investigator file.

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

9.2.1 Data entry

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

9.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her authorized designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorized designee. The appropriate study site personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged.

9.2.3 User identification

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

9.2.4 Audit trail

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

9.3 Source documents

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 Investigator 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.

9.4 Record keeping and access to source data

The Investigator/Institution shall permit study-related monitoring, audits, IRB review, and RA inspections and shall provide direct access to the source data/medical record including

the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed informed consent forms and detailed records of study product accountability). The records shall be retained by the Investigator 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.

9.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, informed consent forms, study product accountability records, source documents, and other study documentation must be retained for as long as is specified in the CTA. Measures shall be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

It is the Investigator's responsibility to inform the Sponsor in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

10. Statistical Methods

10.1 General

[redacted]

10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the ITT analysis set using descriptive statistics by treatment, as appropriate.

10.4 Efficacy analysis

[redacted]

[redacted]

[redacted]

[redacted]

10.5 Safety analysis

Number and percentage of subjects reporting each pre-defined, expected, post-treatment symptoms, as collected in the 30 day diary, will be presented in total and by maximum severity. Number of days with the event will also be summarized using mean, SD, min, max, and median.

[redacted]

10.6 Handling of missing data

Number of missing values will be summarized and reported as appropriate. Missing data for the primary analysis will be handled using the hot deck imputation method. [redacted]

10.7 Interim analysis

There is no interim analysis planned.

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

Deviations from the statistical plan will be documented.

10.9 Sample size

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

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[1]PMA P040024/S072

[redacted]

11. Protection of personal data

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the Investigator are responsible for complying with all requirements pursuant to national legislation in which the Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the study subject should be made aware of this exception in the informed consent. The Institution and Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the investigation but the data collected until the consent was withdrawn may be used in the statistical analyses.

Authorized representatives from the Sponsor or a RA may visit the investigational site to perform audits/inspections, including source data verification, i.e., comparing data in the subjects' medical records and the eCRF. Data and information will be handled with strict confidentiality.

12. Quality Control and Quality Assurance

12.1 Quality control

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

Any CIP deviation shall be reported in the eCRF, which will be verified, discussed, and collected by the monitor and appropriate actions will be taken. The Investigator is responsible for promptly reporting any deviations from the CIP 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 IRB if required by national regulations. Deviations will be reviewed to determine the need to amend the CIP or to terminate the study. Handling of CIP deviations will be performed as described in the monitoring manual.

12.2 Quality assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the Investigator 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.

It is the responsibility of the Investigator 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 a signature and delegation log.

12.3 Changes to the clinical study protocol

The Investigator and other site personnel involved in the study must not implement any deviation from or changes to the CIP without agreement with the Sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CIP must be documented in a written protocol amendment. However, administrative changes are to be documented in the Sponsor file without requiring a protocol amendment. The Sponsor will assess if the changes require prior FDA approval, and inform the Investigator when such approval has been received.

13. Financing, Indemnification, and Insurance

The CTA outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CIP regarding certain rights and obligations, the CTA is the prevailing document.

The Sponsor'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/Investigator is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

14. Publication Policy

The Investigator's, Institution's, and Sponsor's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

This study will be displayed on clinicaltrials.gov in accordance with local regulations. The aim is to submit the results of this study for publication. Everyone who is to be listed as an author of the publication shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any

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

15. Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IRB or FDA, 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 enrollment or non-compliance with the CIP, GCP, or applicable regulatory requirements.

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

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

16. References

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17. Appendices

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