05DF2004: A Study Comparing Hyaluronic Acid Effectiveness & Evaluating Cheek Results with Restylane (CHEEKY Study)

NCT04638816

03Nov2020

[redacted]

A Study **C**omparing **H**yaluronic Acid **E**ffectiveness & **E**valuating Chee**k** Results with Rest**y**lane (CHEEKY Study)

Study products: Restylane® Volyme and Restylane® Lyft Lidocaine

Clinical trial number (CTN): 05DF2004

Sponsor: Q-Med AB, part of the Galderma Group

[redacted]

[redacted]

Effective

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Investigators and Study Administrative Structure

Sponsor:	Q-Med AB, part of the Galderma Group [redacted]
Medical expert:	[redacted]
Global Head of Clinical Development:	[redacted]
Clinical Project Manager:	[redacted]
Statistician:	[redacted]

Further details on all participating investigators and the complete administrative structure of the study are found in the study files.

[redacted]

[redacted]

Synopsis

Title of study:	A Study **C**omparing **H**yaluronic Acid **E**ffectiveness & **E**valuating Chee**k** Results with Rest**y**lane (CHEEKY Study)
Study population:	Adult women meeting inclusion/exclusion criteria.
Countries involved, number of sites/country:	3 sites in Canada.
Number of subjects:	60 female subjects [redacted]
Study Design	• Open-label, phase IV study. [redacted]
Primary Efficacy Objective and Endpoint:	To evaluate the aesthetic improvement (cheek appearance) with Restylane® Volyme and Restylane® Lyft Lidocaine compared to pre-treatment, assessed by the Treating Investigator week 4 after last treatment, [redacted]
[redacted]	[redacted]

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	[redacted]
Safety Objectives and Endpoints:	To evaluate the safety of Restylane® Volyme and Restylane® Lyft Lidocaine by assessment of adverse events (AEs) by the Treating Investigator throughout the study period. [redacted]
Clinical Study Duration:	First subject first visit to last subject last visit will be approximately 16 weeks [redacted]
Duration of Subject Participation:	[redacted]
Inclusion criteria:	1. Female adult subjects willing to comply with the requirements of the study and providing a signed written informed consent. [redacted] 5. Female of childbearing potential with a negative urine pregnancy test before treatment.
Exclusion criteria:	1. Subjects presenting with known allergy to hyaluronic acid (HA) filler or amide local anesthetics. [redacted]

[redacted]

	[redacted] 11. Participation in any other clinical study within three (3) months before treatment.
Study products:	Commercially available Restylane Volyme and Restylane Lyft Lidocaine
Reference therapy:	Not applicable
Treatment regimen and location of treated area:	[redacted]
Efficacy Assessments:	[redacted]

	[redacted]
Safety Assessments:	• AEs • Device deficiencies
Statistical Methods:	[redacted]

[redacted]

[redacted]

Abbreviations and Definitions of Terms

AE	Adverse event
CRF	Case report form
CRO	Contract research organization
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
ET	Early termination
FAS	Full analysis set
G	Gauge
[redacted]	[redacted]
GCP	Good clinical practice
HA	Hyaluronic acid
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFU	Instructions for use
[redacted]	[redacted]
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.
ISO	International Organization for Standardization
IPL	Intense pulsed light
MedDRA	Medical dictionary for regulatory activities
NSAID	Non-steroidal anti-inflammatory drug

[redacted]

[redacted]	[redacted]
OTC	Over-the-counter
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PIPEDA	Personal Information Protection and Electronic Documents Act
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
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.
Touch-up	Repeated injection to be performed after treatment, if necessary, to achieve optimal correction.
U-HCG	Urinary human chorionic gonadotropin
WHO	World Health Organization

[redacted]

[redacted]

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1. Ethical Considerations

1.1 Statement of ethical compliance

This clinical study shall be performed in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), good clinical practice (GCP) and applicable regional and national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study).[1]

The study shall follow the international standard for clinical study of medical devices for human subjects ISO14155 and the International Conference on Harmonisation (ICH) guideline for GCP (E6) as applicable for medical device and national regulations.

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 favorable 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 study does not require application for approval from the regulatory authority as it is a post approval phase IV study.

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

2. Background Information

2.1 Indication and population description

Restylane® Volyme is intended [redacted] to augment the volume of the cheeks [redacted]

Restylane® Lyft Lidocaine is intended to be used for facial tissue augmentation and is used for shaping the contours of the face. [redacted]

2.2 Study product profile

[redacted]

2.3 Study rationale and justification for design

The intended use in this post-market study will be in accordance with the approved IFU.

[redacted]

2.4 Risks and benefits

[redacted]

[redacted]

3. Objective(s) and Endpoint(s)

3.1 Objectives and endpoints

3.1.1 Primary objective and endpoint

To evaluate the aesthetic improvement (cheek appearance) with Restylane® Volyme and Restylane® Lyft Lidocaine compared to pre-treatment, assessed by the Treating Investigator week 4 after last treatment, [redacted]

3.1.2 Secondary efficacy objectives and endpoints

The secondary efficacy objectives and endpoints are:

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

[redacted]

3.1.3 Safety objective and endpoint

To evaluate the safety of Restylane® Volyme and Restylane® Lyft Lidocaine by assessment of adverse events (AEs) by the Treating Investigator throughout the study period.

[redacted]

4. Design of the Study

4.1 General outline

This is an 8-week, multi-center, phase IV, post-marketing study [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2 Number of subjects

Approximately 60 subjects will be enrolled at 3 sites in Canada. [redacted]

4.3 Duration of subject participation

The total duration of the study is expected to 16 weeks [redacted]

4.4 Randomization and blinding

Not applicable.

4.4.1 Randomization

Not applicable.

4.4.2 Blinding

Not applicable.

4.4.3 Emergency unblinding

Not applicable.

4.5 Medical history

History of relevant surgical events and medical conditions should be documented (including any prior dermatological procedures or implants) in the electronic case report forms (eCRF) using medical terminology.

4.6 Prior and concomitant therapies

4.6.1 Definition

Prior therapies include therapies that have been used within 30 days preceding the Screening visit or within the timelines specified in the Inclusion/Exclusion criteria, and then stopped prior to the Screening visit.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the Screening visit,
- any changes to existing therapies (such as change in dose or formulation) during the course of the study, or
- any new therapies received by the subject since the Screening visit

[redacted]

[redacted]

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[redacted]

Table 1 Schedule of events

[redacted]

[redacted]

5. Subjects

5.1 Subject information and informed consent

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

It is the responsibility of the PI or his/her 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 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 consequences to 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 authorized designee responsible for conducting the informed consent. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries.

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

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

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

5.2 Inclusion criteria

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

1. Female adult subjects willing to comply with the requirements of the study and providing a signed written informed consent.

[redacted]

5. Female of childbearing potential with a negative urine pregnancy test before treatment.

5.3 Exclusion criteria

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

1. Subjects presenting with known allergy to hyaluronic acid (HA) filler or amide local anesthetics.

[redacted]

[redacted]

11. Participation in any other clinical study within three (3) months before treatment.

5.4 Screening and subject number

Each subject who has signed the informed consent form will be assigned a subject number. [redacted]

5.5 Withdrawal of subjects

An Investigator may decide to discontinue a subject from the clinical study for safety reasons.

Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, any subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Early Termination (ET) visit should be completed for all subjects discontinuing the clinical study and the appropriate eCRF should be completed.

All discontinuations and the reason for discontinuation are to be documented by the Investigator.

For discontinuation due to an AE, the Adverse Event form is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

Pregnancies occurring during the screening period are considered as screening failures; they should be recorded as such in the eCRF and no pregnancy form is to be completed.

In case of a pregnancy occurring after the baseline visit, the procedures described in Section 8.2.8 should be followed. The subject may remain in the study, but no invasive procedure should be conducted.

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

[redacted]

[redacted]

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

[redacted]

6. Study Product

The term "study product" refers to Restylane Volyme and Restylane Lyft Lidocaine.

[redacted]

[redacted]

Table 2 Study product description

	Study Product	Study Product
Trade name or equivalent	Restylane® Volyme	Restylane® Lyft Lidocaine
[redacted]		

[redacted]

6.2 Reference product

Not applicable.

6.3 Additional products and materials

The sponsor Q-Med will provide pregnancy tests (urinary human chorionic gonadotropin [U-HCG]).

6.4 Packaging, labelling, and storage

[redacted]

6.4.2 Reference product

Not applicable.

6.5 Product accountability

The study products will be released to the PI or his/her authorized 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 authorized by the PI.

The study products must be traceable from the manufacturer 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 study products, deliveries, and return of study products between the Sponsor and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all study products received from the Sponsor; including the product name, date received, lot 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 study product, and number of syringes left in stock at the site.

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

Any malfunctioning study products shall be reported as described in Section 8.3.3.

Products deliberately or accidentally destroyed during shipment or at a study site shall be accounted for and documented. Used syringes, needles 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.

All study product(s) sent to the PI will be accounted for and no unauthorized use is permitted.

6.6 Treatment

6.6.1 Treatment procedure

[redacted]

[redacted]

[redacted]

7. Efficacy Assessments

[redacted]

[redacted]

[redacted]

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8. Safety Assessments

The methods for collecting safety data include laboratory assessments (pregnancy test) (Section 8.1), assessments of AEs (Section 8.2) and device deficiencies (Section 8.3).

8.1 Laboratory assessments

Pregnancy Test: For all women of childbearing potential, a urine pregnancy test (U-HCG) will be performed prior to treatment at Visit 2 (Baseline and treatment, Day 1) and at Visit 3 (Optional touch-up treatment at 2 weeks), as applicable. The test result will be documented in the eCRF.

8.2 Adverse events

8.2.1 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 study product or the reference product

b) events related to the procedures involved

8.2.2 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

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (see Section 8.2.5).

8.2.3 Recording instructions

Each subject should be questioned about AEs at each study visit following signing of informed consent. 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

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

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

[3] Planned hospitalization 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).

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 deteriorate shall be reported as AEs.

When an AE is related to a device deficiency (refer to Section 8.3), 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:

a) Event term (recorded in standard medical terminology and avoiding abbreviations)
b) 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 8.2.3.1)
f) Seriousness (serious or not serious, according to definition in Section 8.2.3.2)
g) Causal relationship to study product or study product injection procedure (yes or no, according to definition in Section 8.2.3.2)
h) Action taken (none, medication treatment, non-pharmacological 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 AE form/module in the eCRF must be signed and dated by the Investigator.

8.2.3.1 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.

8.2.3.2 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 eCRF:

- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product?", and
- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

8.2.4 Reporting of adverse events

Adverse event reporting on each subject shall start after first treatment. The reporting shall continue during each follow-up visit (and any extra visits between planned visits) until the last scheduled visit in the study, Visit 5 (Follow-up at 8 weeks after last treatment).

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

8.2.5 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 submitted via the eCRF.

[redacted]

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

Supporting documentation to be provided with the SAE report:

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

E-mail for SAE reporting: [redacted]
Fax number for SAE reporting:

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

Surface mail for providing complementary information: [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 or faxed to the Sponsor or designee. 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. 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.

[redacted]

8.2.8 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period, the subject must be withdrawn from any following study treatment but should 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 be submitted to the Sponsor according to contact details specified in Section 8.2.5. 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.

8.2.9 Anticipated adverse events

Injection related AEs such as bruising, erythema, itching, swelling, pain and tenderness are anticipated. Information regarding anticipated AEs for Restylane Volyme and Restylane Lyft Lidocaine are included in the IFUs (co-packed with product).

8.3 Device deficiencies

8.3.1 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[4], or performance.

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

8.3.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to Section 8.2.4 and 8.2.5). 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.

8.3.3 Reporting of device deficiencies

[redacted]

E-mail for device deficiencies reporting: [redacted]

Fax number for device deficiencies reporting: [redacted]

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

A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the Sponsor within 24 hours after the Investigator's awareness (for contact information, see Section 8.2.5).

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

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

The database, the data entry screens and program will be designed in accordance with the CSP and the CRF template. 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. 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.

9.2 Electronic case report forms

An electronic data capture application, compliant with regulatory requirements for software validation will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and shall be completed electronically for each screened subject (screening visit) and included subjects (subsequent visits).

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data 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 PI 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 and recorded.

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 by 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

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

9.2.4 Audit trail

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

9.3 Source documents

The eCRF is essentially considered a data entry form and does not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

The PI is responsible for maintaining adequate and accurate source documents. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary.

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 clinical trial number (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 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 study 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 or other relevant source.

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 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 needs to be retained. 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 fireproof cabinet).

It is the PI'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

[redacted]

[redacted]

10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the FAS, using descriptive statistics.

10.4 Efficacy analysis

[redacted]

[redacted]

10.5 Safety analysis

[redacted] The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT, and maximum intensity. [redacted]

10.6 Handling of missing data

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

10.7 Interim analysis

Not applicable as this is an open study.

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

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

10.9 Sample size

[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, including the Personal Information Protection and Electronic Documents Act (PIPEDA). 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.

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 other countries. If a subject decides to terminate the study prematurely, data collected before withdrawal of consent will be used in the evaluation of the study, however no new data may be collected. Authorized representatives from the Sponsor, contract research organization (CRO) or a RA may visit the study site to perform audits/inspections, including SDV, i.e. comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

12. Quality Control and Quality Assurance

12.1 Quality control

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

Any CSP deviation shall be documented appropriately, 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 that 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.

12.2 Quality assurance

The study site may be subject to quality assurance (QA) 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.

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.

[redacted]

[redacted]

13. Financing, Indemnification, and Insurance

This is a Galderma fully sponsored study. The CTA between sponsor and Investigational sites 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.

[redacted]

15. 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, or for business reasons.

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

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

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.

[redacted]

16. References

1. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

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Effective

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