Open label Extension study

for 43USSA1705 (A randomized, evaluator-blinded, multi-center study to evaluate the safety and effectiveness of Sculptra Aesthetic for correction of nasolabial folds)

Study product: *Sculptra® Aesthetic*

Clinical trial number (CTN): 43USSA1705ext

Sponsor: Q-Med AB, a

Study Administrative Structure

Sponsor:	Q-Med AB, a Galderma Affiliate [redacted]
Global Head of Clinical Development:	[redacted]
Sponsor's Medical Expert:	[redacted]
Sponsor's Scientific Writer:	[redacted]
Sponsor's Clinical Project Manager:	[redacted]
Sponsor's 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 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]

Synopsis

Title of study	Open label Extension study *for 43USSA1705 (A randomized, evaluator-blinded, multi-center study to evaluate the safety and effectiveness of Sculptra Aesthetic for correction of nasolabial folds)*
Clinical Trial Number	43USSA1705ext
Countries involved	United States
Number of sites	Approximately 5 sites. [redacted]
Number of subjects	Approximately 60 subjects [redacted]
Safety Objective and Endpoint	The objective is to evaluate the long-term safety of *Sculptra Aesthetic* as a single regimen for correction of Nasolabial Fold (NLF) contour deficiencies [redacted] <u>Safety endpoint</u> • Incidence, intensity, time to onset and duration of adverse events collected throughout the study period.
Effectiveness Objective and Endpoints	The objective is to evaluate the long-term effectiveness of *Sculptra Aesthetic* as a single regimen for correction of NLF contour deficiencies [redacted]

Study Design	This is a prospective, long-term safety and effectiveness follow-up study. [redacted]
Subject Participation	A subject [redacted] may be involved in the extension of the study [redacted] from visit [redacted] to the final follow-up visit.
Enrollment	Written informed consent will be obtained before any study related procedure is performed.
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. [redacted]
Exclusion criteria	The presence of any of the following exclusion criteria will exclude a subject from enrollment in the study: 1. Any medical condition that, in the opinion of the Investigator, would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease that may interfere with the outcome of the study). 2. Other condition preventing the subject from entering the study in the Investigator's opinion, [redacted] subjects anticipated to be unavailable or incapable of understanding the study assessments. 3. Participation in any interventional clinical study throughout the duration of the study.
Investigational product, reference product, dose, mode of administration and location of treated area	[redacted]
Treatment	[redacted]
Study Procedures	<u>Effectiveness Assessments:</u> • [redacted]

	• [redacted] [redacted] Evaluation of Safety: • 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. [redacted] 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 [redacted] 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.
Schedule of Events	[redacted]
Statistical Methods	[redacted]

Abbreviations and Definitions of Terms

AE	Adverse event
Evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject.
CE	French: *Conformité Européenne*
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
CRF	Case report form
CRO	Contract research organization
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
DMP	Data management plan
eCRF	Electronic case report form
FDA	United States Food and Drug Administration
First treatment	Initial injection of study product
[redacted]	[redacted]
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFU	Instructions for use
[redacted]	[redacted]
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.
IP	Investigational Product
IPL	Intense Pulsed Light
IRB	Institutional Review Board
ISO	International Organization for Standardization
MedDRA	Medical dictionary for regulatory activities
Nasolabial Fold (NLF)	Lines between the nose and the corner of the mouth

[redacted]	[redacted]
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
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
SDV	Source Data Verification
[redacted]	[redacted]
SOC	System Organ Class
SOE	Schedule of Events
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 products and the reference product under study
Study site	Institution or site where the study is carried out
[redacted]	[redacted]
WHO	World Health Organization

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[redacted]

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1 Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the Clinical Trial Agreement (CTA), the Clinical Investigational Plan (CIP), Good Clinical Practice (GCP), and applicable regional or 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) insofar as such revisions are consistent with US treaty obligations and in accordance with US law (1).

The study shall follow the international standard for clinical study of medical devices for human subjects, International Organization for Standardization (ISO) 14155 2011 as applicable for US regulations and the International Conference on Harmonization (ICH) guideline for GCP (E6) as applicable for medical device.

1.2 Application to Institutional Review Board and/or Regulatory Authorities

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CIP/CIP amendment 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 regional or national regulations.

2 Background Information

2.1 Indication and population description

Sculptra Aesthetic is indicated for use in immune competent people as single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles.

[redacted]

2.2 Study product Profile

2.2.1 Investigational product description

[redacted]

2.2.1.2 Clinical documentation

Please refer to the *Sculptra Aesthetic* Instructions for Use (IFU) document. [redacted]

[redacted]

2.3 Study rationale and justification for design

[redacted] The purpose of this extension of the study is to evaluate long-term safety and effectiveness data of *Sculptra Aesthetic* [redacted]

2.4 Risks and benefits

No treatment is administered in this study; hence, there are no risks to participate.

The benefit is better knowledge about the safety profile for Sculptra Aesthetic [redacted]

3 Objectives and Endpoints

3.1 Safety objective and endpoints

Safety Objective

The objective is to evaluate the long-term safety of *Sculptra Aesthetic* [redacted]

Safety endpoint

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

3.2 Effectiveness objective and endpoints

The objective is to evaluate the long-term effectiveness of *Sculptra Aesthetic* [redacted]

Effectiveness endpoints

[redacted]

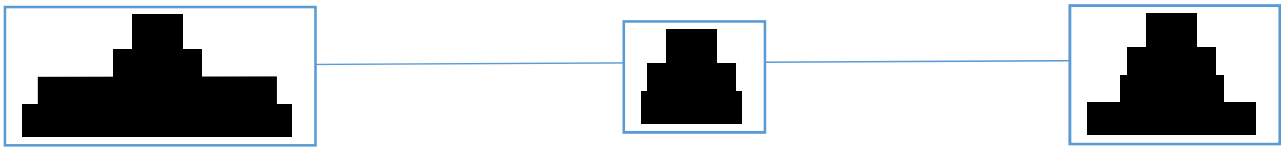
4 Design of the Study

4.1 General outline

This is a [redacted] prospective, open-label follow-up study, with aim to evaluate the long-term safety and effectiveness of treatment with *Sculptra Aesthetic* for correction of NLF contour deficiencies.

[redacted]

Figure 1. *Study Flow Chart*



4.2 Number of subjects

Approximately 60 [redacted]

4.3 Duration of subject participation

A subject may be involved in the study for approximately [redacted] the final follow-up visit.

End of study is when all enrolled subjects have completed all visits or were prematurely discontinued from the study.

4.4 Randomization and blinding

4.4.1 Randomization

No randomization is needed in this study.

4.4.2 Blinding

No blinding is needed in this study.

4.4.3 Emergency Unblinding

Not applicable as the Investigator is unblinded.

4.5 Medical history

Medical history is captured in the pivotal study, hence not applicable for this extension study.

4.6 Prior and concomitant therapies

4.6.1 Definition

Therapies are defined as medications, treatments and procedures.

Concomitant therapies are defined as follows:

[redacted]

4.6.2 Categories

The following three categories are to be considered for concomitant therapies:

- Drugs/therapies including but not limited to [redacted]
- Medical and surgical procedures including, but not limited to [redacted]
- [redacted]

4.6.3 Recording

Concomitant therapies are to be recorded in source documents and on the appropriate form in the eCRF. Concomitant therapies are to be recorded, reviewed, and updated at each visit. Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, or dose modification for a chronic condition.

4.6.4 Authorized concomitant therapies

[redacted]

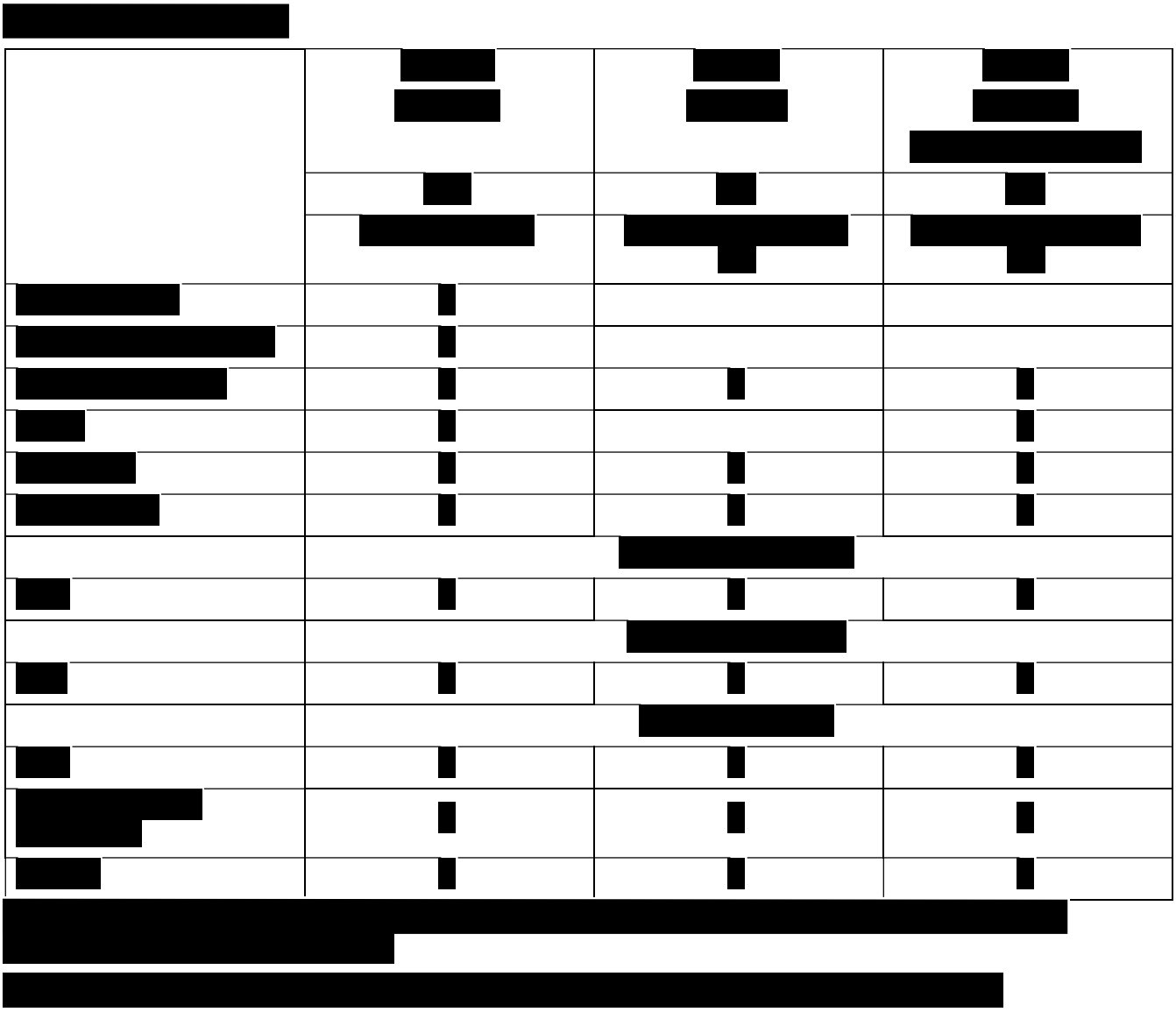
4.6.5 Prohibited concomitant therapies

[redacted]

[redacted]

[redacted]

4.7 Visits



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 (ICF) 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.

[redacted]

5.3 Exclusion criteria

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

1. Any medical condition that, in the opinion of the Investigator, would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease that may interfere with the outcome of the study).
2. Other condition preventing the subject from entering the study in the Investigator's opinion, [redacted]

5.4 Screening and subject number

Prior to any study procedures being conducted, the subject must sign the informed consent form. [redacted]

5.5 Withdrawal of subjects

Each subject shall be advised in the informed consent form that the subject has the right to withdraw from the study at any time, for any reason, without prejudice. Subjects may also be discontinued from

this study if the Investigator determines that it is in the subject's best interest to do so and may be withdrawn at the Investigator's discretion at any time.

The withdrawal criteria are:

[redacted]

The reason and date for withdrawal shall be documented in the eCRF. When possible, an explanatory comment shall be added to further explain the reason for withdrawal. If withdrawal of a subject occurs during a regular study visit, the eCRF for that specific visit shall be completed as far as possible.

If a subject is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses. Subjects who are withdrawn or discontinued from the study will not be replaced. For AEs still ongoing at the time of withdrawal, see section 7.2.6.

6 Study Products

No study products will be provided during this study.

6.1 Investigational product

No investigational product will be provided during this study.

6.2 Additional study supplies

No additional study supplies will be provided during this study.

6.3 Treatment

No treatment will be given during this study.

7 Safety Assessments

7.1 Assessment of AEs by direct questioning of subject and evaluation of subject

Safety assessments for this study include [redacted]

It is the responsibility of the Investigator to determine severity of the AE and relatedness of the event to the study product and/or injection procedures. Adverse Events must be reported as outlined below in section 7.2.4.

[redacted]

7.2 Adverse events

7.2.1 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[I], whether or not related to the study product.

This definition includes:

- events related to the investigational product or the reference product
- events related to the procedures involved

7.2.2 Definition of a serious adverse event

A serious adverse event (SAE) is an AE that:

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
- a life-threatening[II] illness or injury, or
- a permanent impairment of a body structure or body function, or
- in-patient or prolonged hospitalization[III], or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- 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 (see Section 7.2.5).

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

[II] 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).

[III] 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).

7.2.3 Recording instructions

Each subject with an AE occurring after enrollment through study exit should be fully recorded in the source document(s) for further transcription to the eCRF. Each subject should be questioned about AEs at each study visit following study entry. The question asked should be: "Since your last clinical visit have you had any health problems?" Information on AEs can also be obtained from signs and symptoms

detected during each examination, observations made by the study site personnel, or spontaneous reports from the subjects or their relatives.

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

7.2.3.1 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.

7.2.3.2 Causal relationship and seriousness

[redacted]

7.2.4 Reporting of adverse events

Adverse event reporting on each subject shall start upon enrollment (singing of the informed consent) in the study.

The reporting shall continue during each follow-up visit (including any telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

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

7.2.5 Reporting of serious adverse events

The Investigator shall report any SAE to the Contract Research Organization (CRO) immediately but not later than 24 hours of awareness of the event. This initial report can be made via e-mail or submitted via the eCRF.

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

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

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

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the CRO 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 therapies form/list
- AE form/list
- Medical history form/list
- Study treatment CRF form
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

E-mail for SAE reporting: [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 as noted above. 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. 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, please use surface mail.

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

7.2.6 Follow-up of ongoing related events after termination of the study and events with onset after termination of study (subject last visit)

All serious as well as non-serious AEs with a causal relationship to the investigational product or treatment procedure and ongoing at study end, shall be followed-up after the subject's participation in the study is over. Such events shall be followed-up after the last study visit until resolved, assessed as chronic or stable or subject is lost to follow up. Follow-up information shall be reported on the AE follow-up form.

7.2.7 Reporting and follow-up of events occurring after subject termination of the study

All adverse events with a causal relationship to the study products or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor. [redacted]

7.2.8 Pregnancy

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9 Data Handling and Management

9.1 Data management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for handling eCRFs database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the 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

An electronic data capture application, compliant with regulatory requirements for software validation US FDA 21CFR11 will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and shall be completed electronically for each subject and all 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 has been completed with all authorized investigation site personnel prior to the pivotal study being initiated and any data being entered into the system for any subject. Appropriate training and security measures with any potential new investigation site personnel will be completed prior to their involvement in the study.

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, every effort should be made to complete the eCRFs within a reasonable time frame 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 within a reasonable timeframe Answered queries will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged. Answered queries will then be closed by the appropriate study personnel (i.e. data manager, site monitor, etc.)

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

[redacted]

[redacted]

10.6 Handling of missing data

All effectiveness endpoints will be evaluated based on observed cases.

10.7 Withdrawal 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 CIP deviations will be listed individually, including subject number and observed deviation.

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

10.8 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. 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.

The study shall include collection and processing of personal data as specified in the Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR) on the protection of individuals with regard to the processing of personal data. For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

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 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 CIP 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 IRB if required by national regulations. Deviations will be reviewed to determine the need to amend the CIP.

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 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 the signature and delegation log.

12.3 Changes to the Clinical Investigational Plan

The PI and other site personnel involved in the study must not implement any changes to the CIP without agreement with the Sponsor and prior review and documented approval from the IRB and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CIP must be documented in a dated and version-controlled written CIP amendment. However, administrative changes may be documented in the Sponsor file without requiring a CIP 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.

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15 Suspension or Premature Termination

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

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

16 References

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17 Appendices

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