GALDERMA

Title Page

A randomized, controlled, evaluator-blinded, split face study to evaluate the performance and safety of GP0045 for correction of moderate to severe nasolabial folds

Study products: Investigational product: GP0045

Comparator product: [redacted]

Clinical trial number (CTN): 43FE1630

Principal Investigator: [redacted]

Sponsor: Q-Med AB

[redacted]

Confidentiality Statement

This study protocol contains confidential information belonging to Q-Med AB. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and neither disclose it to any third parties (except where required by applicable law) nor use it for any other purpose than in relation to the clinical study described herein.

GALDERMA

Summary of Changes in Clinical Study Protocol 43FE1630 from version 2.0 to version 3.0

[redacted]

[redacted]

Summary of Changes in Clinical Study Protocol 43FE1630 from version 1.0 to version 2.0

[redacted]

[redacted]

Effective date: 2018-04-24 16:03

Effective

3.0

Investigators and Study Administrative Structure

Principal Investigator:

[redacted]

Treating Investigator:

[redacted]

Investigational Site

[redacted]

Sponsor:

Q-Med AB

[redacted]

Medical expert:

[redacted]

GALDERMA		

Clinical Project Manager:	[redacted]
Statistician:	[redacted]
Clinical research organisation (CRO):	[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 study protocol (CSP) amendment.

Sponsor Signatures

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

Head of Clinical Development, Q-Med AB
[redacted]

Clinical Project Manager, Q-Med AB
[redacted]

Statistician, Q-Med AB
[redacted]

Medical Expert, Q-Med AB
[redacted]

GALDERMA

Signed Agreement of the Clinical Study Protocol

CTN:	43FE1630
Title of the CSP:	A randomized, controlled, evaluator-blinded, split face study to evaluate the performance and safety of GP0045 for correction of moderate to severe nasolabial folds

We, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the clinical trial agreement (CTA) and the additional information given in the Investigator's brochure (IB) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study site

GALDERMA

Synopsis

Title of study:	A randomized, controlled, evaluator-blinded, split face study to evaluate the performance and safety of GP0045 for correction of moderate to severe nasolabial folds
Clinical Trial Number:	43FE1630
Country, number of subjects	Sweden, Up to 20 subjects
Principal Investigator:	[redacted]
Treating Investigator	[redacted]
Primary Objective	**Objective** To evaluate the performance following injection of GP0045 in the treatment of NLF [redacted] at 6 months post treatment. Endpoint The response rate based on [redacted] live assessment by the blinded evaluator, at 6 months post treatment. The response rate is defined as percentage of subjects with at least 1 grade improvement [redacted]
Secondary Objectives	**Objective** To evaluate the performance following injection of GP0045 in the treatment of NLF [redacted] at 2 weeks, 3, 9, 12, 15 and 18 months post treatment. Endpoint The response rate based on [redacted] live assessment by the blinded evaluator, at 2 weeks, 3, 9, 12, 15 and 18 months post treatment. The response rate is defined as percentage of subjects with at least 1 grade improvement [redacted] [redacted] [redacted] [redacted] [redacted]
Safety Objective	**Objective** To evaluate the safety of GP0045 [redacted] Endpoints • Incidence, intensity, duration and onset of adverse events (AEs) collected during 18 months post treatment • Incidence, intensity, and duration of pre-defined expected post-treatment events collected using a subject diary during 2 weeks post treatment
Study Design:	This is an 18 months, randomized, evaluator-blinded, comparative, single-centre study to assess the performance and safety of GP0045 [redacted] in the treatment of NLF. A split face design will be used, i.e. subjects will be randomized to treatment with either GP0045 in the right NLF [redacted]; or [redacted] GP0045 in the left NLF.

	GP0045 [redacted] will be administered by the treating Investigator. For the initial injection, a maximum volume of 2.0 mL per NLF will be injected, and for the optional touch-up injection a maximum of 2.0 mL per NLF will be injected. [redacted] After the screening, eligible subjects are given the initial injection at the baseline visit and contacted by telephone on Day 3 following the injection. A second, optional injection (touch-up) may be given at Week 2 to subjects who have not achieved optimal correction from the initial injection. Subjects who receive a touch-up injection will be contacted by phone on Day 3 following the touch-up injection. Following the last injection (initial or touch-up), there is a follow-up period of 18 months. Subjects will be in the study for up to 20 months, including the screening period. At each physical follow-up visit, [redacted] assessments will be performed and photographs of the NLFs will be taken. The subjects will be provided with a 2-weeks diary in which to report pre-defined, expected post-treatment events daily, starting on the day of the injection (separate diaries are provided for each post-injection period). AEs will be recorded throughout the study and device deficiencies will be evaluated after each injection.
Inclusion criteria:	1. Ability to adequately understand the verbal explanations and the written subject information provided in local language and ability to give consent to participate in the study 2. Signed and dated informed consent to participate in the study, including photo consent [redacted] 5. Subjects with intent to undergo correction of both nasolabial folds [redacted]

	[redacted]
Exclusion criteria:	1. Known/previous allergy or hypersensitivity to any injectable HA gel 2. Known/previous allergy or hypersensitivity to local anesthetics, e.g. lidocaine or other amide-type anesthetics, [redacted] [redacted] 3 and Vitamin E are acceptable only as part of a standard multivitamin

	[redacted] 16. Any condition (medical or other) 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) [redacted] 18. Participation in any other clinical study with an investigational product within 30 days before treatment
Investigational product, dose and mode of administration:	[redacted]
Reference therapy, dose and mode of administration	[redacted]
Duration of treatment and follow-up:	Following screening and treatment (initial and optional touch-up at 2 weeks) there is a follow-up period of 18 months, [redacted]

Performance Assessments:	[redacted]
Safety Assessments:	• Adverse Events • Subject Diary • Device deficiencies
Statistical Methods:	Statistical analysis will be descriptive and presented by study product and visit, as appropriate. Continuous data will be summarized using standard statistical measures such as n (number of subjects), mean, median, standard deviation, minimum, and maximum. Categorical data will be summarized in frequency tables presenting absolute (n) and relative (%) frequencies. All adverse events will be summarized and listed by system organ class (SOC) and preferred term (PT) assigned to the event using MedDRA.

Abbreviations and Definitions of Terms

AE	Adverse event
Blinded evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject. The evaluator must have a medical background and be trained in the scales used in the study.
CE	French: *Conformité Européenne*
CFR	Code of Federal Regulations
Comparator	Medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a study
CRF	Case report form
CRO	Contract research organisation
CSP	Clinical study protocol
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
DCF	Data clarification form
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
First subject in	First subject screened, i.e. who signs the informed consent form
First subject out	First subject who completed his/her last study visit
G	Gauge
[redacted]	[redacted]
GCP	Good clinical practice
GMP	Good manufacturing practice
HA	Hyaluronic acid
IB	Investigator's brochure, i.e. compilation of the current clinical and non-clinical information on the investigational product, relevant to the clinical study
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFU	Instructions for use
Investigational product	Medical device being assessed for safety or performance in a study. "Investigational product" is the same as "study device", "investigational device", or "investigational medical device".

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
Last subject in	Last subject who entered the study
Last subject out	Last subject who completed his/her last study visit
MedDRA	Medical dictionary for regulatory activities
NLF	Nasolabial fold
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
SAE	Serious adverse event
SAP	Statistical analysis plan
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
TW	Thin wall (needle)
WHO	World Health Organization
[redacted]	[redacted]

GALDERMA

Table of Contents

List of Tables

[redacted]

List of Appendices

[redacted]

1. Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical investigation of medical devices for human subjects – Good clinical practise, ISO 14155:2011, shall be followed. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for GCP (E6) shall be followed as applicable for medical device. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix 1).

1.2 Application to independent ethics committee and/or regulatory authorities

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CSP/CSP amendment(s) from the independent ethics committee (IEC). The study shall not begin until the required favourable opinion from the IEC has been obtained. The PI shall file all correspondence with the IEC in the Investigator file and copies of IEC approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the IEC or regulatory authorities (RA) shall be followed.

The study requires application for approval from the RA. The study will not be started until the Sponsor has received written approval. The Sponsor will provide the PI with a copy of the relevant document.

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

GP0045 is being developed as an injectable hyaluronic acid (HA) gel [redacted] In this study, GP0045 is intended for the correction of [redacted] nasolabial folds (NLFs) in men and women over the age of 18.

2.2 Study products description

[redacted]

[1] Greene JJ, Sidle DM. The Hyaluronic Acid Fillers; Current Understanding of the Tissue Device Interface. Facial Plast Surg Clin N Am 2015:23:423–32.

[2] Gold M. The science and art of hyaluronic acid dermal filler use in esthetic applications. J Cosmet Dermatol 2009 Dec;8(4):301-7.

[redacted]

2.2.2 Investigational product description

[redacted]

2.2.3 Comparator product description

The comparator product is [redacted] a CE-marked HA gel [redacted]

2.3 Previous experience

[redacted]

[3] Pons-Guiraud A. Classification des produits de comblement disponsible en France. Ann Dermatol Venerol 2008;135:I S27-34.

[4] Ascher B *et al*. Chapter 34: Hyaluronic acids. In: Ascher B ed. Injection Treatment in Cosmetic Surgery. Informa UK Ltd. 2009.

[redacted]

2.4 Study rationale and justification for design

[redacted]

[5] Cohen J, Dayan S, Brandt F, Nelson D, Axford-Gatley R, Theisen M and Narins R. Systemic review of clinical trials of small- and large-gel-particle hyaluronic acid injectable fillers for aesthetic soft tissue augmentation. Dermatol Surg 2013; 39:2015-231

[6] Day DJ, Littler CM, Swift RW, Gottlieb S. The wrinkle severity rating scale. Am J Clin Dermatol 2004;5(1):49-52

Effective date: 2018-04-24 16:03

Effective

3.0

2.5 Risks and benefits

[redacted]

[redacted]

3. Objectives and Endpoints

3.1 Objectives and endpoints

3.1.1 Primary objective and endpoints

The primary objective is to evaluate the performance following injection of GP0045 in the treatment of NLF [redacted] at 6 months post treatment.

Endpoint
The response rate [redacted], as assessed by the blinded evaluator, at 6 months post treatment.

The response rate is defined as percentage of subjects with at least 1 grade improvement [redacted]

3.1.2 Secondary objectives and endpoints

The secondary objectives are:

- To evaluate the performance following injection of GP0045 in the treatment of NLF [redacted] at 2 weeks, 3, 9, 12, 15 and 18 months post treatment.

  Endpoint
  The response rate [redacted], as assessed by the blinded evaluator, at 2 weeks, 3, 9, 12, 15 and 18 months post treatment.

  The response rate is defined as percentage of subjects with at least 1 grade improvement [redacted].

[redacted]

3.1.3 Safety objective and endpoints

The safety objective is to evaluate the safety of GP0045 [redacted]

Endpoints
- Incidence, intensity, duration and onset of adverse events (AEs) collected during 18 months post treatment
- Incidence, intensity, and duration of pre-defined expected post-treatment events collected using a subject diary during 2 weeks post treatment

4. Design of the Study

4.1 General outline

This is an 18 months, randomized, evaluator-blinded, comparative, single-centre study to assess the performance and safety of GP0045 [redacted] in the treatment of NLF. A split face design will be used, i.e. subjects will be randomized to treatment with either GP0045 in the right NLF [redacted] *or* [redacted] GP0045 in the left NLF. GP0045 and [redacted] will be administered by the treating Investigator.

After the screening, eligible subjects are given the initial injection by the treating Investigator at the baseline visit and contacted by telephone on Day 3 following the injection. A second, optional injection (touch-up) may be given by the treating Investigator at Week 2 to subjects who have not achieved optimal correction from the initial injection. Subjects who receive a touch-up injection will be contacted by phone on Day 3 following the touch-up injection. Following the last injection (initial or touch-up), there is a follow-up period of 18 months. [redacted]

Subjects will be in the study for up to 19.5 months, including the screening period.

At each physical follow-up visit, [redacted] assessments will be done and photographs of the NLFs will be taken (Section 7.4).

The subjects will be provided with a 2-weeks diary in which to report pre-defined, expected post-treatment events daily, starting on the day of the injection (separate diaries are provided for each post-injection period). AEs will be recorded throughout the study and device deficiencies will be evaluated after each injection (Figure 4-1).

[redacted]

4.2 Number of subjects

Up to twenty (20) subjects will be recruited at a single site in Sweden. The duration of the enrolment period is expected to be 4 weeks.

4.3 Duration of subject participation

The total duration of the study is expected to be approximately 20 months. Each subject will be involved in the study for up to 19.5 months, including the screening period.

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

4.4 Randomization

4.4.1 Randomization

Up to twenty (20) subjects will be randomized to treatment with either GP0045 in the right NLF [redacted]; *or* [redacted] GP0045 in the left NLF.

Before starting the study, a computer generated randomization list will be prepared under the supervision of a designated statistician from the Sponsor. Each subject will be assigned a consecutive subject number at the treatment visit when all inclusion criteria and exclusion criteria have been verified. Each subject number is linked to the specific treatment sequence to be administered according to the randomization list. All treatment information will be kept by the Investigator during the study.

4.4.2 Blinding

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

Because the method of administration is similar, the treatment can be masked from the subjects by simply preventing them from viewing the syringes during administration of the study products. This will be done by placing an opaque drape or patch over the subject's eyes during the injection procedure.

The blinded evaluator shall not be allowed to retrieve study supplies or to be present during opening of the study supplies or injections. The treating Investigator is not allowed to discuss treatments with the blinded evaluator or the subjects. All documents with information on study products shall be kept in a separate binder not available to the blinded evaluator. The blinded evaluator should not have access to CRF pages with study product information.

4.4.3 Emergency unblinding

Not applicable as the treating Investigator is unblinded.

4.5 Medical history

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

History of dermal fillers and other cosmetic procedures shall be documented in the CRF.

4.6 Concomitant therapies

4.6.1 Definition

Concomitant therapies are defined as follows:

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

4.6.2 Categories

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

- Drugs/therapies including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, herbal medicines/supplements, and homeopathic preparations
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers, X-rays, etc.

4.6.3 Recording

Concomitant therapies administered during the study are to be recorded on the dedicated forms in the CRF. Any concomitant therapies reported in the subject diary during the first 14 days shall be transferred into the concomitant therapies page/module in the CRF at the 2-week follow-up visit(s). Concomitant therapies are to be recorded, reviewed, and updated at each visit. The generic name or the trade name of all concomitant medication or a description of the procedure and the reason for its use shall be documented in the CRF. 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, dose modification for a chronic condition, etc.

4.6.4 Authorized concomitant therapies

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.

[redacted]

If a subject receives prohibited therapy during the study, a protocol deviation should be documented. The Sponsor must be notified to discuss the pertinence. The subject should, for safety reasons, continue in the study for the scheduled follow-up visits.

4.7 Schedule of events

[redacted]

Effective date: 2018-04-24 16:03

Effective

3.0

4.8 Visits

GALDERMA

Effective date: 2018-04-24 16:03

Effective

3.0

GALDERMA

Effective date: 2018-04-24 16:03

Effective

3.0

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. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries. The data will not contain any information that can be used to identify any subject.

Full face photographs collected during the study will be stored in a database by the Sponsor. The subjects are recognisable on the photographs, however 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

1. Ability to adequately understand the verbal explanations and the written subject information provided in local language and ability to give consent to participate in the study
2. Signed and dated informed consent to participate in the study, including photo consent

[redacted]

5. Subjects with intent to undergo correction of both nasolabial folds [redacted]

5.3 Exclusion criteria

1. Known/previous allergy or hypersensitivity to any injectable HA gel
2. Known/previous allergy or hypersensitivity to local anesthetics, e.g. lidocaine or other amide-type anesthetics, [redacted]

[redacted]

16. Any condition (medical or other) 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)

[redacted]

18. Participation in any other clinical study with an investigational product within 30 days before treatment

5.4 Screening and subject numbers

Each subject who has signed the informed consent form will be assigned a screening number and shall be listed on a subject screening and inclusion log. The screening number will consist of "SCR" followed by two (2) digits and start with 01 and followed by 02, 03, etc. in consecutive order.

A “screening failure” is defined as a subject who does not fulfil the eligibility criteria. For screening failures, the CRF screening visit shall be completed to an extent that makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria. The reason for excluding a subject from entering the study shall also be specified in the subject screening and inclusion log. When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each subject will be assigned a subject number in a consecutive order, starting with 01.

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

5.5 Withdrawal of subjects

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

[redacted]

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

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

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

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

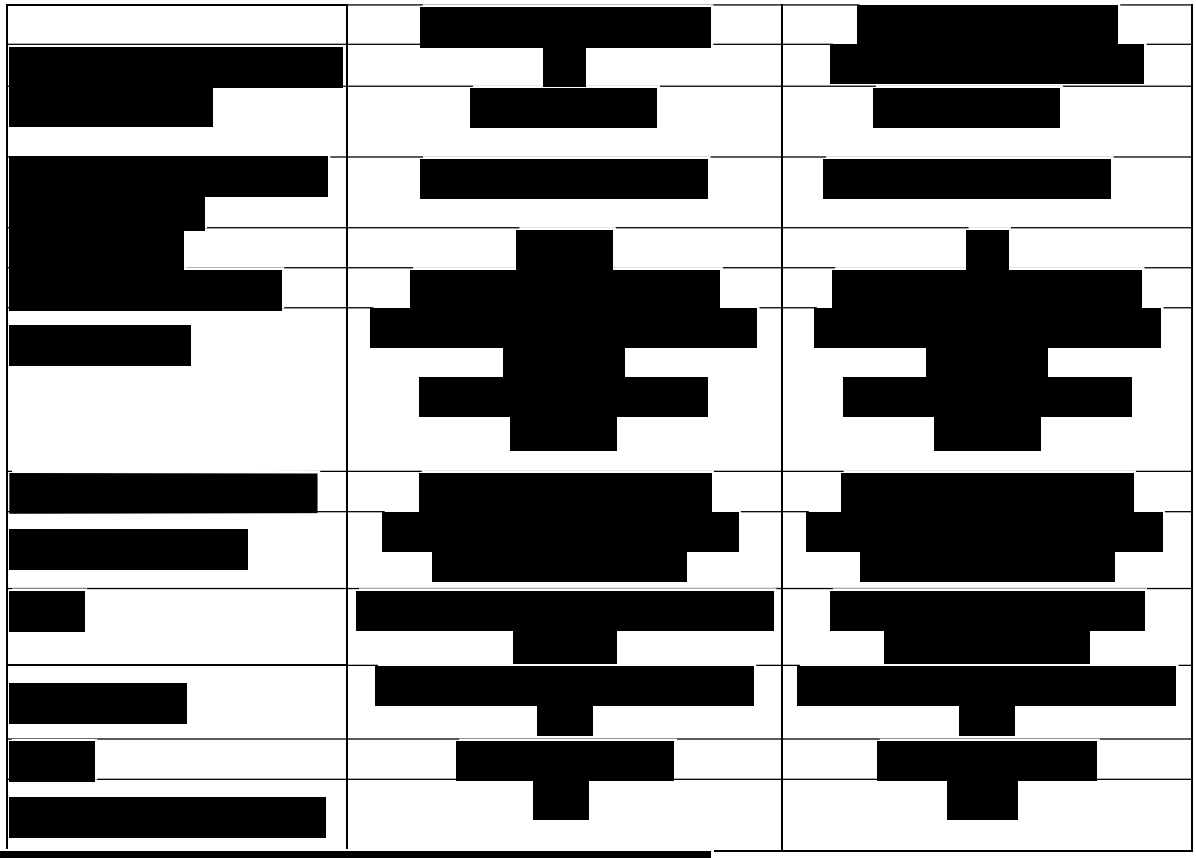
If reason for withdrawal is “subject request” or “other”, the subject shall be questioned to rule out the possibility of an AE.

If an AE which, according to the Investigator's assessment, is related to the use of any of the study products and is still ongoing at the time of the withdrawal, the Investigator shall follow up the subject until the AE resolves, is assessed as chronic or stable, or for three months (see Section 8.3.6).

6. Study Products

The term "study products" refers to both the investigational product (GP0045) and the comparator product [redacted] Study products are provided by the Sponsor.

[redacted]



[redacted]

6.1 Additional products and material

[redacted]

Effective date: 2018-04-24 16:03

Effective

3.0

6.2 Packaging, labelling, and storage

[redacted]

[redacted]

6.3 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 RA 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 disposal. It is therefore important that the PI maintains accurate product accountability records, i.e. documentation of the physical location of all study products and delivery 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, dispense date, the number of syringes used/amount dispensed, 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 destroyed locally at the site, with proper documentation, after agreement with the Sponsor. Any malfunctioning study products shall be reported as described in Section 8.4.3.

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

6.4 Treatment

[redacted]

GALDERMA

Effective date: 2018-04-24 16:03

Effective

3.0

[redacted]

[redacted]

7. PERFORMANCE ASSESSMENTS

7.1 General information

The methods for collecting performance data include assessment [redacted], and photography (Section 7.4).

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

7.2 [redacted] a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds (Table 3). Scoring of fold severity is based on visual assessment of the length and apparent depth of the NLF at a certain time-point and the result is not based on a comparison to the baseline or pre-treatment appearance. Each score [redacted] is exemplified by a photograph of NLFs (Appendix 3)

Live assessments will be performed through-out the study.

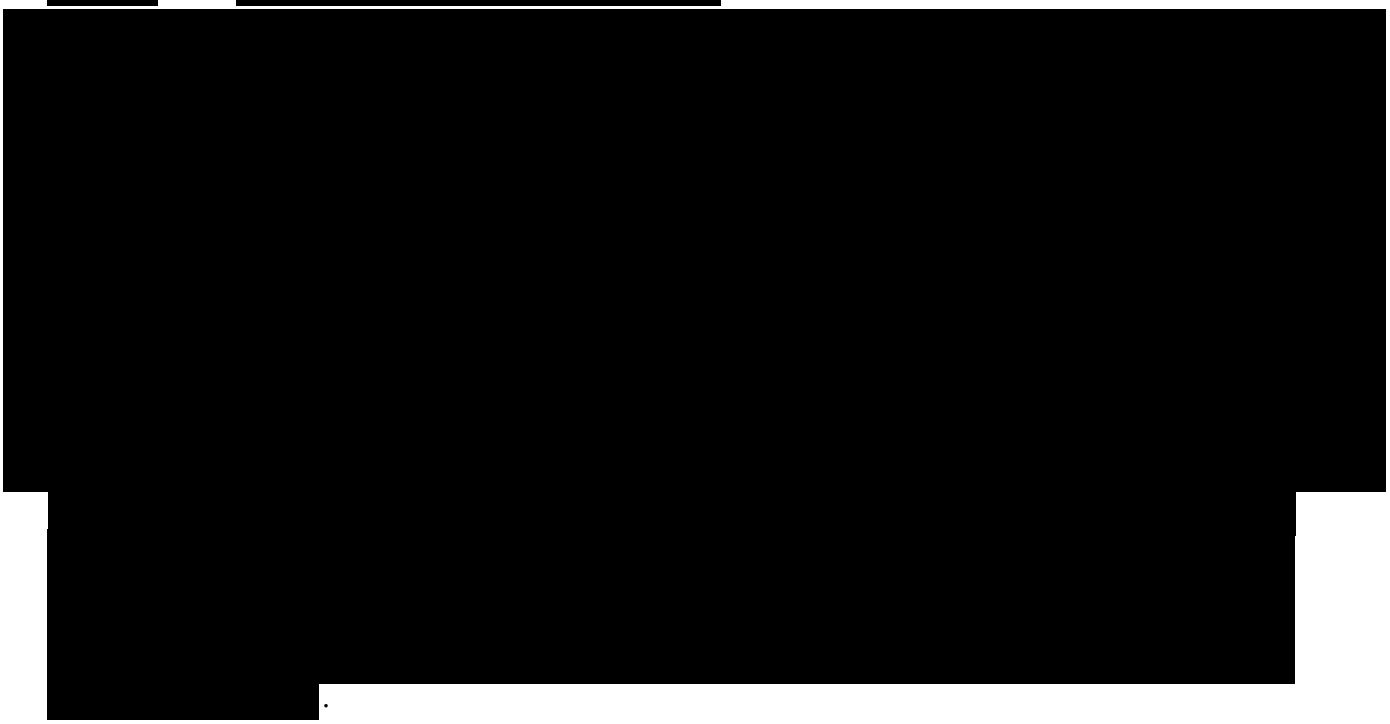
[redacted]

The blinded evaluator will evaluate [redacted] to verify the wrinkle severity inclusion criteria before the initial treatment. The [redacted] will also be assessed by the blinded evaluator at each follow-up visit for performance assessment. At the Week 2 follow-up visit after the initial treatment, the [redacted] assessment will be used for treatment guidance, e.g., to decide if touch-up treatment should be performed. A clinically significant improvement is defined as ≥1 grade improvement [redacted]

Each NLF (right/left) will be evaluated separately, thus generating two wrinkle severity score results per subject. A subject should preferably be assessed by the same blinded evaluator throughout the entire study.

When treatment is administered at the same visit as the [redacted] assessment, it is important to asses wrinkle severity prior to injection.

[redacted]



[redacted]

.

7.4 Photography

Photographs will be taken of each subject pre-treatment at visits when treatment is performed and at each follow-up visit. The photographs will be used to document condition at baseline, for [redacted] evaluation and to document AEs in the treated area. Note that no covering make-up should be used on the photographs.

The Investigator and other study site personnel designated to take photographs shall be thoroughly trained in the equipment and techniques before study start. The same photographic equipment and standardized setting must be used at each visit (e.g., distance, light, facial position and expression). For further details, please see the instruction of image procedures in the photo user guide

All photos should be taken from a straight frontal view with full face frame. The subject shall have a neutral facial expression.

Each photograph shall be labeled with:

- Study number (43FE1630)
- Subject number
- Visit number
- Date

In order to maintain confidentiality, the photographs must not include any information that may reveal the subject's identity.

8. Safety Assessments

8.1 Pre-defined, expected, post-treatment events

The subject shall evaluate pre-defined, expected, post-treatment events in a 14-day diary, starting on the day of treatment. The presence and maximum intensity of pre-defined expected post-treatment events, i.e. bruising, redness, swelling, pain, tenderness, and itching shall be assessed for each treated area individually (Table 5). AEs that have not been pre-defined as expected post-treatment events in the diary may also be recorded in the diary.

8.2 Laboratory assessments

No laboratory assessments are performed.

8.3 Adverse events

8.3.1 Definition of an adverse event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons[7], 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

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

8.3.2 Definition of a serious adverse event

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

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1. a life-threatening[8] illness or injury, or
2. a permanent impairment of a body structure or body function, or
3. in-patient or prolonged hospitalisation[9], or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to foetal distress, foetal death, or a congenital abnormality or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (see Section 8.3.4).

8.3.3 Recording instructions

[redacted]

[8] 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).

[9] Planned hospitalisation for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE. (Source: ISO 14155:2011).

[redacted]

8.3.3.1 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.

8.3.3.2 Causal relationship and seriousness

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

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 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 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.

8.3.4 Reporting of adverse events

[redacted]

8.3.5 Reporting of serious adverse events

[redacted]

[redacted]

8.3.6 Follow-up of unresolved events ongoing at termination of the study

[redacted]

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

[redacted]

8.3.8 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 for safety within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

[redacted]

8.4 Device deficiencies

8.4.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety[10], or performance.

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

8.4.2 Recording instructions

[redacted]

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

[redacted]

8.4.3 Reporting of device deficiencies

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

The database, the data entry screens and program will be designed in accordance with the CSP and the CRF. Data validation will be performed by computerised logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the CRFs 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 Paper case report forms

A CRF is required and shall be completed for each screened (screening visit CRF) and included subject (CRF sections for subsequent completed visits). The completed original CRFs are the sole property of the Sponsor and shall not be made available in any form to third parties, except for authorised representatives of appropriate RA, without written permission from the Sponsor. All original CRFs shall be kept in the Sponsor file. A copy of all CRFs shall be kept as a part of the Investigator file.

Any delegation of completion/entering of data shall be specified in a signature and delegation log. All information recorded by the Investigator (or delegated person) in the CRFs shall be in English. The CRFs must be signed and dated by the Investigator, who, by signing, takes responsibility for the accuracy, completeness and legibility of the data reported to the Sponsor in the CRFs. Forms to be completed by the subject, i.e. subject diary, shall be translated into local language.

The name and address of the subjects must not be registered in the CRFs or in the database. The subjects' identity must always remain confidential.

9.2.1 Correction of recorded data

Correction in the original CRF at site shall be made by crossing a single line through the incorrect data, leaving the wrong data clearly visible. The accurate data shall be recorded next to the inaccurate data and must be dated and signed (and explained if necessary). Correction fluid must not be used.

During the monitoring the monitor shall collect the original CRF at the study sites and leave a copy as a part of the Investigator file. Discrepant data identified after the original CRF has left the clinic is generally compiled in a query report generated in connection with data entry and printed from the database. Alternatively, a data clarification form (DCF) may be used e.g. when discrepant data is identified at the site. The query report/DCF shall state the question or data to be changed together with the correct data. Each query report/DCF shall be dated and signed by the Investigator. The original query report/DCF shall be handled as the original CRF and a copy of the query report/DCF shall be retained together with the copies of the CRF as a part of the Investigator file.

During data entry from the original CRF page the Sponsor may make corrections in the data in the clinical database if the corrections qualify as self-evident. A self-evident change (SEC) is defined as a change or correction made to discrepant data without requiring prior query/documentation from the study site. Self-evident changes permit the Sponsor to update or accept reported values in the clinical database according to agree upon data handling procedures. A summary of all such changes in the clinical database will be printed and sent to the PI at the end of the study for signature. The original SEC report shall be handled as the original CRF and be returned to the Sponsor and a copy of the report shall be retained together with the copies of the CRF in the Investigator file.

9.3 Source documents

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

The PI is responsible for maintaining source documents. These shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed CRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the CRF, 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 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. CRF, diaries, 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 CRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record.

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

9.5 Document and data retention

All records pertaining to the conduct of the study, including signed CRFs, 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 unauthorised access, preferably by storage in a fire-proof cabinet). Refer to the CTA.

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

10.1 General

[redacted]

10.2 Analysis populations

The following populations will be defined:

- Safety
- Full Analysis Set (FAS)
- Per Protocol (PP)

The FAS population is the primary population for all performance analyses. If there are any CSP deviations considered to have a substantial impact on the performance outcome at the 6 months follow-up visit, a PP population excluding those subjects will be defined. A detailed list containing such deviations will be included in the SAP. Safety analysis is performed based on the safety population set.

10.3 Demographics, baseline assessments, and subject characteristics

Demographic data, baseline assessments and subject characteristics will be presented using descriptive statistics.

[redacted]

10.6 Handling of missing data

No imputation of missing data will be performed.

10.7 Interim analysis

Not applicable.

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.

Deviations from the statistical analysis plan (SAP) will be documented in the Clinical Study Report.

10.9 Sample size

[redacted]

11. Protection of personal data

The study shall include collection and processing of personal data as specified in Directive 95/46 EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data. For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the PI are responsible for complying with all requirements pursuant to national legislation in the country in which the

Institution and the PI are located. The Sponsor will ensure that all requirements are complied with for data processing, which is carried out in Sweden by the Sponsor.

The informed consent form shall contain information about what personal data to be collected in the study and that this will be kept confidential. The provided information shall be sufficient to enable all subjects to give their consent not only to the participation in the study, but also to the processing of personal data. Such information includes information regarding the purposes of the collecting, processing, data transfer to countries not having same high level of security for processing of personal data than Sweden and EU, and the length of time during which personal data will be stored. The subject shall have the right of access to stored personal data, and the right to correction of incorrect information. If a subject decides to terminate the study prematurely, data collected before withdraw of consent will be used in the evaluation of the study, however no new data may be collected. Authorised representatives from the Sponsor, clinical research organisation (CRO) or a RA may visit the study site to perform audits/inspections, including source data verification, i.e. comparing data in the subjects' medical records and the CRF. 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.

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 PI and other relevant study site personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study site team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study. The CV shall give name, date of birth, address and place of work, and shall show the training, appointments and, for the PI, any other information that will confirm the suitability of the PI to be responsible for the study.

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

12.3 Changes to the clinical study protocol

12.3.1 Amendments

The PI and other site personnel involved in the study must not implement any changes to the CSP without agreement with the Sponsor and prior review and documented approval from the IEC and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a dated and version-controlled written protocol amendment. For non-substantial changes not affecting the rights, safety and well-being of the subjects or not related to the clinical objectives or endpoints, a simple notification to the IEC and RA, if applicable, can be sufficient.

12.3.2 Deviations

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

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 CSP 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/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

14. Publication Policy

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

The results of this study could be submitted to a medical journal for publication of the results. Everyone who is to be listed as an author of the results 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[11]. 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 the Sponsor 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 IEC or RA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons.

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

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

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

16. Appendices

Appendix 1 Declaration of Helsinki

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

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

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

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

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

General Principles

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

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

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

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

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

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

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The

responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

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

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

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

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

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

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

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

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

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

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

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

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

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

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

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

Unproven Interventions in Clinical Practice

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

GALDERMA

Effective date: 2018-04-24 16:03

[redacted]

Effective

3.0

GALDERMA

Effective date: 2018-04-24 16:03

Effective

3.0

[redacted]

GALDERMA

Effective date: 2018-04-24 16:03

[redacted]

Effective

3.0

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

GALDERMA

Effective date: 2018-04-24 16:03

[redacted]

Effective

3.0

GALDERMA

[redacted]

GALDERMA

Effective date: 2018-04-24 16:03

[redacted]

Effective

3.0

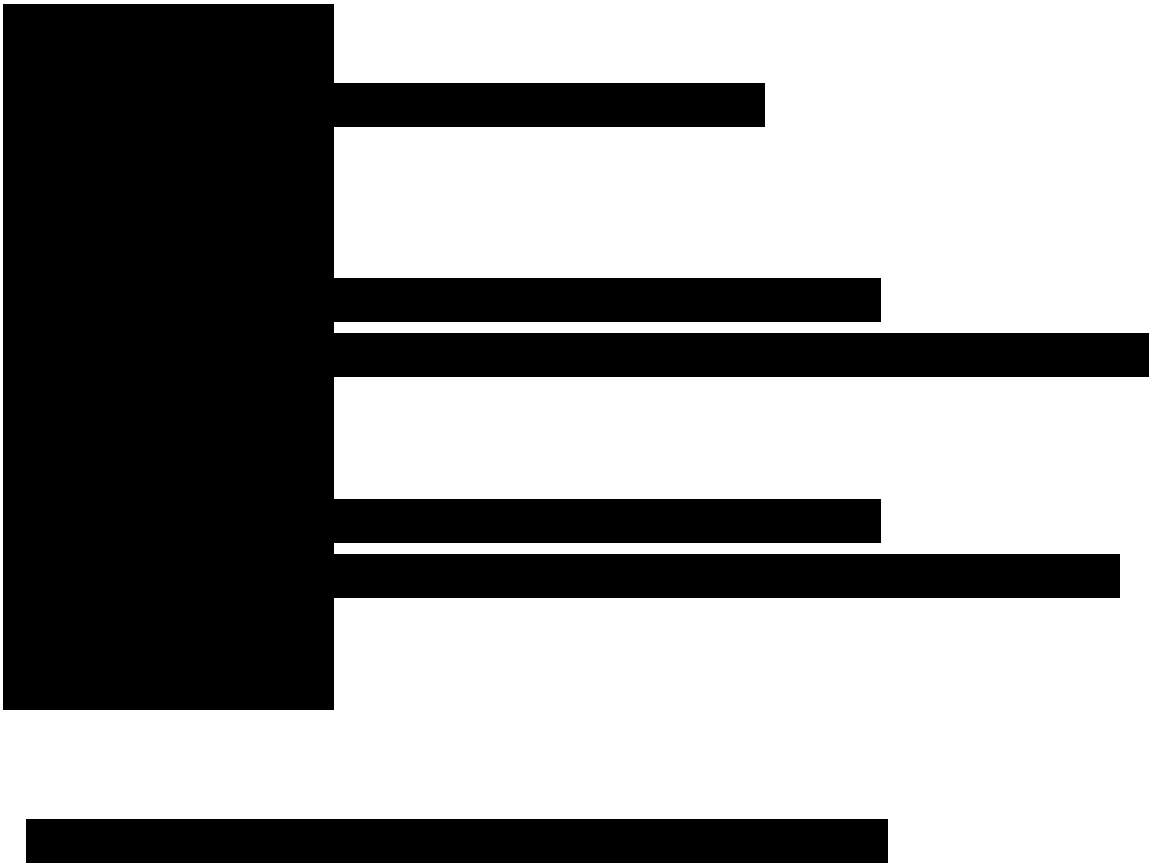
GALDERMA

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

Effective date: 2018-04-24 16:03

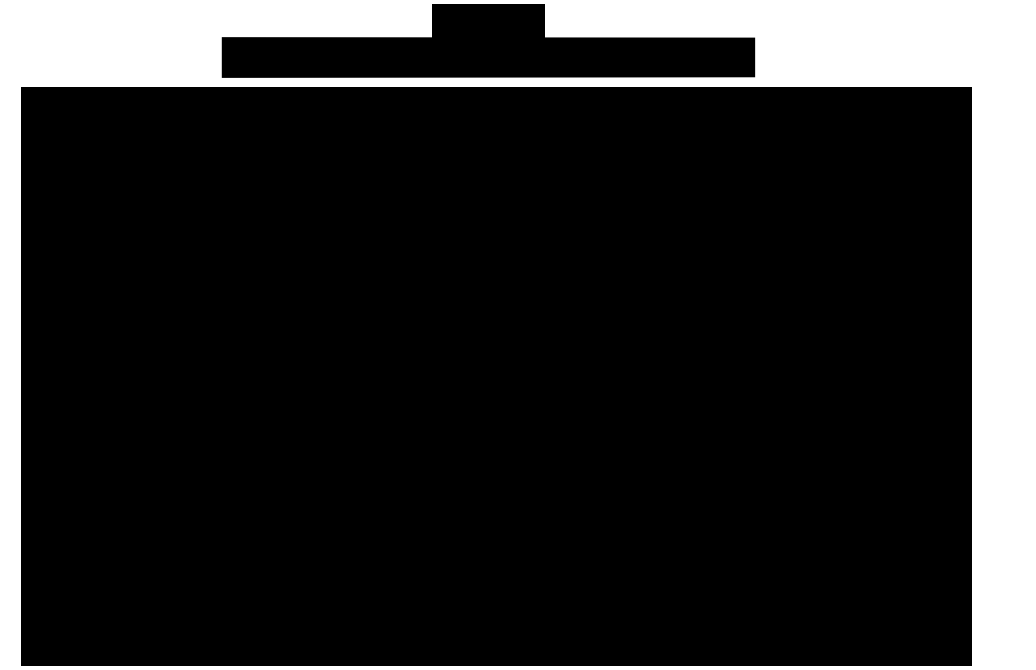
[redacted]

[redacted]

Effective

3.0

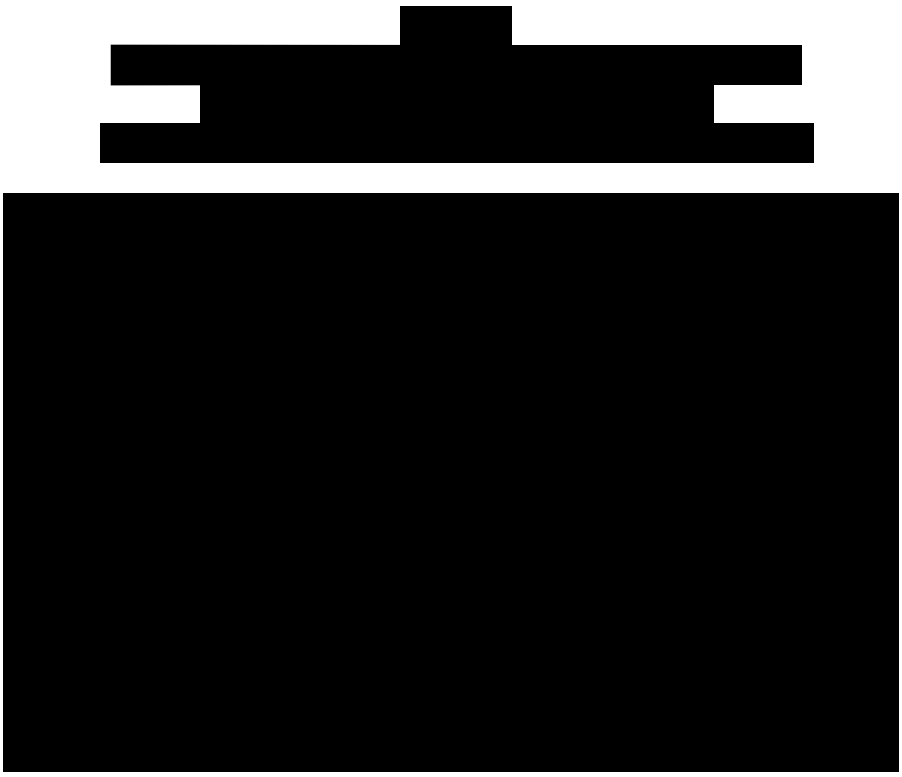
[redacted]



Effective date: 2018-04-24 16:03

Effective

3.0



GALDERMA		

Effective date: 2018-04-24 16:03

Effective

3.0

SIGNATURES PAGE