A randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Defyne* in the chin for augmentation and correction of Chin Retrusion

NCT Number: NCT03624816

Protocol document date: 11Oct2019

[redacted]

A Randomized, No-Treatment Controlled, Evaluator-Blinded, Multi-Center Study to Evaluate the Effectiveness and Safety of *Restylane*® *Defyne* in the Chin for Augmentation and Correction of Chin Retrusion

Study product: *Restylane*® *Defyne*

Clinical trial number (CTN): 43USCH1702

Sponsor: Q-Med AB, a Nestle Skin Health affiliate

[redacted]

Investigators and Study Administrative Structure

Sponsor: Q-Med AB, a Nestle Skin Health affiliate

[redacted]

Medical Expert:

[redacted]

Clinical Project Manager:

[redacted]

Study Statistician:

[redacted]

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

Sponsor Signatures

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

[redacted]

[redacted]

[redacted]

[redacted]

Signed Agreement of the Clinical Investigational Plan

CTN: 43USCH1702

Title of the CIP: A Randomized, No-Treatment Controlled, Evaluator-Blinded, Multi-Center Study to Evaluate the Effectiveness and Safety of *Restylane*® *Defyne* in the Chin for Augmentation and Correction of Chin Retrusion

I, the undersigned, have read and understand the CIP specified above, and agree on the contents. The CIP, the clinical trial agreement (CTA) and the additional information given in the Instructions for Use (IFU) and Report of Prior Investigations (ROPI) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study site name and address

Study site number

Synopsis

Title of study:	A randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Defyne* in the chin for augmentation and correction of Chin Retrusion
Clinical Trial Number:	43USCH1702
Countries involved	United States
Number of sites	Approximately 12
Number of Subjects	A total of 140 subjects will be enrolled in the study. [redacted]
Target Indication	Injection into the chin for augmentation and correction of chin retrusion in subjects over the age of 21.
Primary Effectiveness Objective and Endpoint	1. The primary objective of the study is to evaluate the effectiveness of *Restylane® Defyne* versus a no-treatment control in the correction of chin retrusion by comparing response rates. [redacted]
Secondary Effectiveness Objectives and Endpoints	[redacted]

	[redacted]
Safety Objectives and Endpoints	• To evaluate all adverse events (AEs) and pre-defined, injection related events (IREs) reported during the first 4 weeks after treatment as recorded in the subject diary. • To evaluate the safety assessment at all visits, as assessed by a qualified staff member: [redacted]
Exploratory Objectives and Endpoints	[redacted]
Study Design	Randomized, evaluator-blinded, parallel group, no-treatment control, multi-center, US study
Subject Participation	A subject will be involved in the study for approximately 17.5 months from screening to final follow-up visit.
Enrollment	Written informed consent will be obtained before any study related procedure is performed. [redacted]

	[redacted]
Treatment	*Initial Treatment* The subjects will be randomized [redacted] to receive either *Restylane®* *Defyne* in the chin on Day 1 or to no-treatment-control. [redacted]
Study Procedures	*Evaluation of effectiveness* [redacted]

[redacted]

Evaluation of safety

Adverse Events (AEs) will be obtained from signs and symptoms reported by the subject or detected during each examination visit to obtain information about any medical occurrence that meets the definition of an AE. [redacted]

Safety Assessments

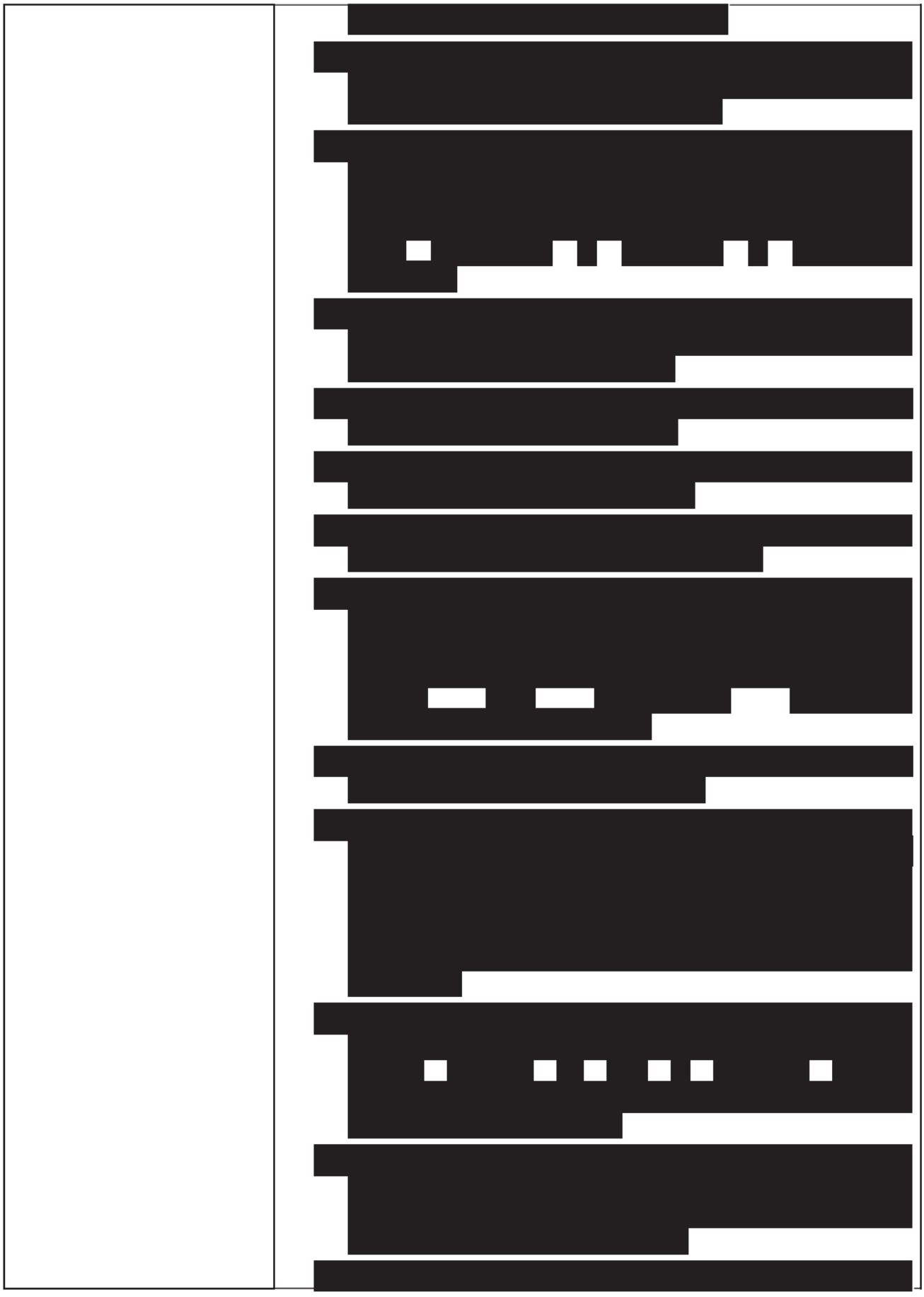
[redacted]

Study report

A study report will be compiled at the conclusion of the study. This report will be included in the regulatory submission for marketing application.

Inclusion criteria:	1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent. 2. Males or non-pregnant, non-breastfeeding females, over the age of 21. 3. Subjects seeking augmentation therapy for chin retrusion. 4. [redacted] 6. If the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test at the screening/enrollment visit and prior to treatment. [redacted] 7. Negative urinary pregnancy test for females of childbearing potential at screening and all injection visits.
Exclusion criteria:	1. Known/previous allergy or hypersensitivity to any injectable HA gel or to gram-positive bacterial proteins. [redacted]

Effective date: 2019-10-11 06:34
Effective
Version: 5.0



	[redacted]
Investigational product:	*Restylane*® *Defyne* injectable gel. [redacted]
Reference therapy	[redacted]
Therapy Dose	[redacted]
Schedule of Events	[redacted]

	[redacted]
Efficacy Assessment:	[redacted]
Safety Assessment:	1. Adverse Event reporting: AEs will be obtained from signs and symptoms reported by the Subject or detected during each examination. [redacted]
Statistical Methods:	<u>Sample size</u> [redacted]

	[redacted]

Abbreviations and Definitions of Terms

AE	Adverse event
BDDE	1,4-butanediol diglycidyl ether
CE	"Conformité Européenne" the quality and branding mark for products made or sold within the European Union.
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
Childbearing Potential	A female (including pre-menopausal subjects) capable of becoming pregnant. This includes women on oral, injectable or mechanical contraception; women who are single, women whose husbands have been vasectomized or whose husbands have received or utilizing mechanical contraceptive devices.
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labelling)
DMP	Data management plan
eCRF	Electronic case report form
EOS	End of Study
ET	Early termination
FDA	United States Food and Drug Administration
First subject in	First subject screened, i.e. who signs the informed consent form
First subject out	First subject who completed their last study visit
FST	Fitzpatrick Skin Type
G	Gauge
GAIS	Global aesthetic improvement scale
GCP	Good clinical practice
[redacted]	[redacted]
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ICF	Informed Consent Form

IFU	Instructions for use
IP	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.
IPR	Independent Photographic Reviewer
IRB	Institutional review board
ISF	Investigator Study File
ISO	International Organization for Standardization
ITT	Intention-to-treat
Last subject in	Last subject who entered the study
Last subject out	Last subject who completed their last study visit
MedDRA	Medical dictionary for regulatory activities
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
ROPI	Report of Prior Investigations, i.e. compilation of the current clinical and non-clinical information on the investigational product, relevant to the clinical study
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
SOC	System Organ Class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.

Study files	The Investigator file and the Sponsor file
Study products	The investigational product and the reference product under study
Study site	Institution or site where the study is carried out
TC	Telephone Call
Touch-up	Repeated injection to be performed after treatment if necessary to achieve optimal correction
TW	Thin wall
Tx	Treatment
WHO	World Health Organization

Table of Contents

List of Tables

List of Figures

List of Appendices

1. Ethical Considerations

1.1 Statement of ethical compliance

The study should be conducted in compliance with the clinical trial agreement, the clinical investigational plan, good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155 should be followed. The International Conference on Harmonization (ICH) guideline for GCP (E6) should be followed as applicable for medical device. The study should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki[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 CIP/CIP amendment(s) from the institutional review board (IRB). The study should not begin until the required favorable opinion from the IRB has been obtained. The PI should file all correspondence with the IRB in the Investigator Site File (ISF) and copies of IRB approvals should be forwarded to the Sponsor. Any additional requirements imposed by the IRB or regulatory authorities (RA) should 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 should be carried out in accordance with applicable regional or national regulations.

2. Background Information

2.1 Indication and population description

[redacted]

2.2 Investigational and comparator product descriptions

2.2.1 Clinical documentation

Please refer to the study *Restylane® Defyne* Instructions for Use (IFU). The study specific IFU summarizes the adverse effects experienced with HA injections along with precautions that can minimize these potential complications.[redacted]

[redacted]

[redacted]

2.3 Study rationale

The rationale of performing this study is to obtain evidence of safety and effectiveness of Restylane® Defyne in the chin for augmentation and correction of chin retrusion to support a future US marketing application.

Chin projection is an important component of facial appearance and affects the overall balance and harmony of the face. In clinical practice, surgical techniques, such as osteotomy or insertion of implants are commonly used for correction of chin retrusion. [redacted]

2.4 Justification for the design of the study

The purpose of this study is to evaluate the effectiveness of *Restylane® Defyne* in the treatment of chin augmentation and correction of retrusion [redacted]

2.5 Risks and benefits

[redacted]

[redacted]

3. Objective(s) and Endpoint(s)

3.1.1 Primary objective and endpoint

The primary objective of the study is to evaluate the effectiveness of *Restylane® Defyne* versus a no-treatment control in the correction of chin retrusion by comparing response rates [redacted]

3.1.2 Secondary objectives and endpoints

[redacted]

[redacted]

3.1.3 Safety objectives and endpoints

The safety objectives and endpoints are:

- To evaluate all adverse events (AEs) and

[redacted]

[redacted]

4. Design of the Study

4.1 General outline

This is a randomized, evaluator-blinded, parallel group, no-treatment control, multi-center study to evaluate the effectiveness and safety of *Restylane® Defyne* for chin augmentation and correction of Chin Retrusion. [redacted]

[redacted]

[redacted]

4.2 Number of subjects

Approximately 140 subjects will be included in the study.

4.3 Duration of subject participation

A subject may be involved in the study for approximately 17.5 months from screening to the final follow-up visit. "End of study" is defined as the time point when the last subject has completed the last study visit.

4.4 Randomization and blinding

[redacted]

[redacted]

4.5 Medical history

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

4.6 Concomitant medications, treatments, and procedures

Except as noted below, concomitant medications or other treatments or procedures may be utilized when the Investigator or his/her authorized designee considers it medically necessary. Information regarding any use of concomitant medications, including prescription and over-the-counter medications administered during the investigation should be recorded. Any concomitant medications taken prior to screening (within 30 days or as stated in the inclusion and exclusion criteria) should be documented using medical terminology.

The generic name or the trade name of all concomitant medication or a description of the procedure and the reason for its use should be documented:

[redacted]

[redacted]

GALDERMA	Title **43USCH1702 Protocol**	Doc id [redacted]

[redacted]

[redacted]

[redacted]

[6]For male subjects only

[redacted]

871.

[redacted]

[redacted]

Device Palpability Assessment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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 should 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 should be provided in a language clearly and fully understandable to the subject. The subject should 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 should 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 should be filed in the ISF. The subject should be provided with a copy of the signed and dated ICF and any other written information.

The Investigator should ensure that important new information is provided to all enrolled subjects throughout the study.

5.2 Inclusion criteria

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

1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent.
2. Males or non-pregnant, non-breastfeeding females, over the age of 21.

[redacted]

[redacted]

5.3 Exclusion criteria

[redacted]

[redacted]

[redacted]

5.4 Screening and subject numbers

Prior to any study procedures being conducted, the subject must sign the informed consent form. The subject number will be assigned at the screening visit. All study procedures performed should be documented in the subject's source documents and in the electronic Case Report Forms (eCRFs). The subject number, subject name and other information sufficient to link the eCRF to the medical records (e.g. national identification number, chart number, etc.) should be recorded.

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

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

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

5.5 Withdrawal of subjects

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

[redacted]

6. Study Products

6.1 Investigational device

The investigational device (i.e. study product) is *Restylane® Defyne* injectable gel. [redacted]

[redacted]

6.3 Product accountability

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

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

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

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

[redacted]

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

6.4 Treatment

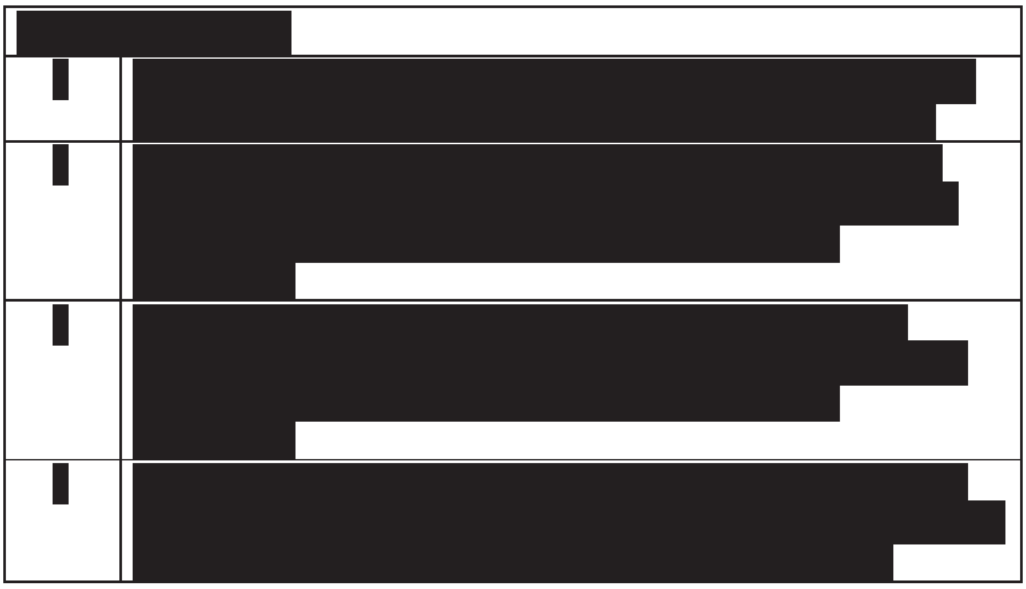
The investigational product is reserved for use by Treating Investigators who are experienced in chin augmentation procedures. Before treatment the subject will be informed about the expected post-treatment events that should be recorded in the Subject Diary and potential risks involved with the treatment and when to contact the Investigator in case of emerging symptoms.

[redacted]

6.4.1 Treatment compliance

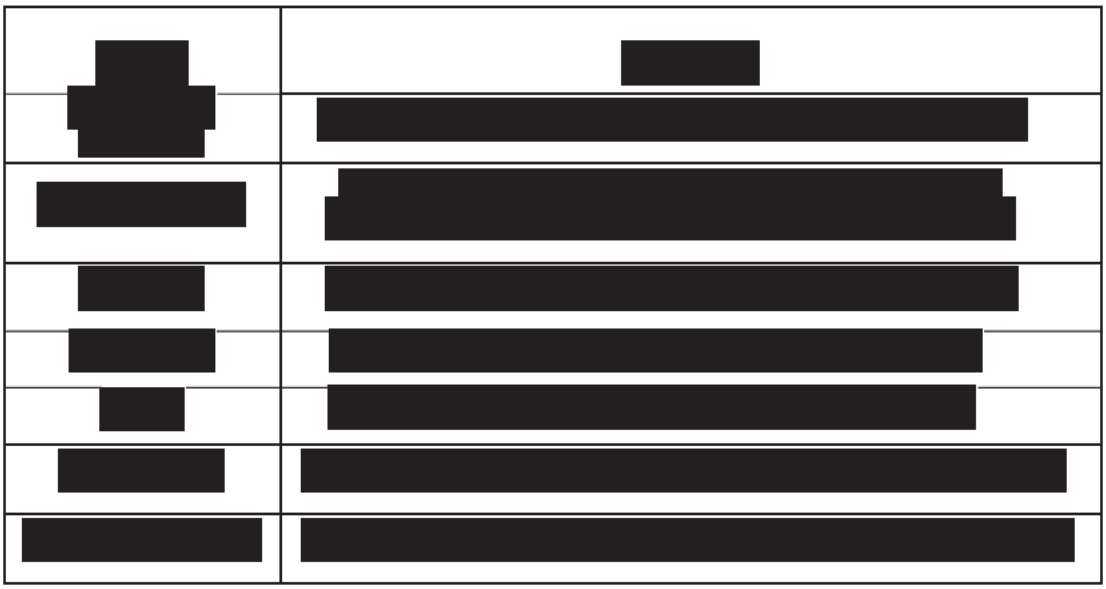
Not applicable; the treatment will be administered by the injector at the investigational site.

[redacted]

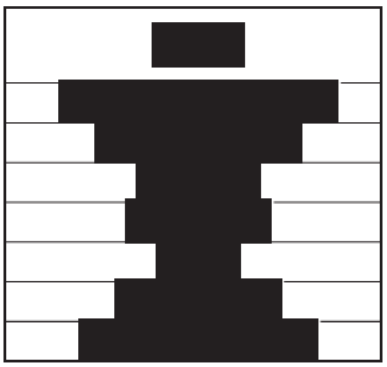


[redacted]

[redacted]



[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

documented.

8.9 Adverse events

8.9.1 Definition of an adverse event

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

This definition includes:

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

b) events related to the procedures involved

8.9.2 Definition of a serious adverse event

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

a) led to death,

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

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

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

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

---

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

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

[3]Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

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

8.9.3 Recording instructions

Each subject with an AE occurring after randomization and through study exit should be fully recorded in the source document for further transcription to the eCRF. Each subject should be questioned about AEs at each study visit following randomization. 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.

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

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

a) Event term (recorded in standard medical terminology and avoiding abbreviations)
b) Description of event and affected area
c) Start date (first day with symptoms)
d) Stop date (last day with symptoms)
e) Intensity (mild, moderate, or severe according to definition in Section 8.9.3.1)
f) Seriousness (serious or not serious, according to definition in Section 8.9.3.2)
g) Causal relationship to study product or study product injection procedure (yes or no)
h) Action taken (none, medication treatment, non-medication treatment, or other procedures/tests, subject withdrawn)
i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

The pre-defined, expected post-treatment events should be assessed separately. These events should be collected by subjects in a diary used daily for 28 days after the treatment.

8.9.3.1 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 should be recorded.

8.9.3.2 Causal relationship and seriousness

Each AE, serious as well as non-serious, should 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) should be used for the causality assessments. The Investigators should be asked to indicate a response to each of the following questions in the *e*CRF:

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

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

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

8.9.4 Reporting of adverse events

Adverse event reporting on each subject should start after the subject has been randomized. The reporting should continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

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

8.9.5 Reporting of serious adverse events

The Investigator should report any **SAE** to the Sponsor **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via e-mail.

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:

- CTN: 43USCH1702
- Subject identification (age, gender, subject number)
- Adverse event description
- Date when AE occurred
- Date when AE became serious
- Name of Investigator and original reporter (if other than the Investigator)
- Name of device: *Restylane® Defyne (investigational)*
- Treatment specification

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

Supporting documentation to be provided with the SAE report:

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

[redacted] [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 should be e-mailed to the Sponsor. A copy of the fully completed SAE form should be kept at the site.

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

8.9.6 Stopping Rule

Enrollment into the study will be temporarily halted if the Sponsor receives a SAE for a vascular embolic event that lead to skin necrosis, vison loss, or stroke and is determined by the Investigator to be directly or possibly related to the study device or injection procedure. The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes:

- The SAE was unanticipated, directly related to the study product or device injection procedure, and presents an unreasonable risk to study subjects, the study will be terminated and the Investigators notified. The IRB and RA will also be notified if the study is prematurely terminated due to safety concerns.
- If the SAE does not meet the above criteria, then enrollment in the study will continue.

8.9.7 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 study product or treatment procedure and ongoing at study end, should be followed up after the subject's participation in the study is over. Such events should be followed-up after the last study visit until resolved, or assessed as chronic or stable. All AEs assessed as related to the

study product or treatment procedure, serious as well as non-serious, with onset after the study termination (last subject study visit), and that the Investigator becomes aware of, should be reported to the Sponsor by email to [redacted]

8.9.8 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy after the subject has been treated, the subject must continue to be followed and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period after treatment must be reported by the Investigator on a pregnancy report form immediately upon acknowledgement and submitted to the Sponsor according to contact details specified in Section 8.9.5. The report can be prospective or retrospective. Follow-up should be conducted to obtain outcome information on all prospective reports.

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

8.9.9 Anticipated adverse events

Information regarding anticipated AEs for Restylane® Defyne (investigational) is included in the study specific IFU.

8.10 Device deficiencies

8.10.1 Definition of a device deficiency

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

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

8.10.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form should be completed by the Investigator or qualified designee. The type of complaint should be described and injury to the subject or user or unintended exposure to study product should be reported as applicable. If an injury has occurred, an AE or an SAE form should be completed as applicable (refer to Section 8.9.4 and 8.9.5). If no SAE was experienced as a result of the device deficiency the Investigator should assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,

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

- Circumstances had been less fortunate

In Part B of the clinical study complaint form the Sponsor will make the same assessment.

8.10.3 Reporting of device deficiencies

The Investigator should send the completed clinical study complaint form to the Sponsor by email to [redacted] A device deficiency that led to a SAE and any device deficiency that is assessed as it could have led to a SAE should be reported within 24 hours after the Investigator's awareness in accordance to Section 8.9.5.

In order to fulfil regulatory reporting requirements, all deficiencies with the study product must be assessed by both the Investigator and the Sponsor to determine if it could have led to a SAE.

If a SAE has resulted from a device deficiency or if either the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the IRB.

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

9. Data Handling and Management

9.1 Data management

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

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

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

9.2 Electronic case report forms

A 21 Code of Federal Regulations Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and should be completed electronically for each screen failure as well as enrolled subjects.

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

be entered directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorized study site personnel designated by the Investigator should complete data collection. Appropriate training and security measures should be completed with all authorized investigation site personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and should 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 should be specified in a signature and delegation log.

9.2.1 Data entry

All data should be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator should 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 should review the eCRFs and evaluate them for completeness and consistency. Each eCRF should be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations should 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 should be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or its representatives, the responsible data manager or monitor should raise a query in the electronic data capture application. The query should state the question or data to be changed and should be resolved in the system by the PI or his/her authorized designee. The appropriate study site personnel should answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged.

9.2.3 User identification

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records should 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 should 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 should 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 should 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, should be clearly identified with the CTN and subject number. Any personal information, including name, should be removed or rendered illegible to preserve individual confidentiality.

9.4 Record keeping and access to source data

The Investigator/Institution should permit study-related monitoring, audits, IRB review, and RA inspections and should 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 should be retained by the Investigator as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records should be documented and the Sponsor should be informed in writing.

The Sponsor should 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 should be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

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

10. Statistical Methods

10.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical [redacted]

[redacted]

10.5 Safety analysis

Number and percentage of subjects reporting each pre-defined, expected, post-treatment symptoms, as collected in the 28-day diary, [redacted]

All AEs will be coded according to MedDRA and summarized by system organ class (SOC), preferred term (PT) and treatment.

A summary of all AEs will be provided, which will include:

- number of subjects with at least one AE and number of events (in total as well as serious AEs)
- number of subjects with at least one related TEAE and number of events (in total as well as serious AEs)
- number of subjects with at least one un-related TEAE and number of events (in total as well as serious AEs)
- number of subjects who did not have an AE

The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT, and severity. In addition, for related AEs the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized. Serious AEs will be listed.

Non-related AEs will be summarized by SOC, PT, and intensity.

To evaluate consistency of AEs across different subgroups, AEs will also be summarized by subgroups defined as described in Section 3.1.4.

Palpation, movement, function and sensation assessments will be presented in frequency tables by visit.

[redacted]

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.

[redacted]

control group.

11. Protection of personal data

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

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

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

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

12. Quality Control and Quality Assurance

12.1 Quality control

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

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

12.2 Quality assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the Investigator and other relevant study site personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study site team should 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 should be listed together with their function in the study on a signature and delegation log.

[redacted]

15. Suspension or Premature Termination

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

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

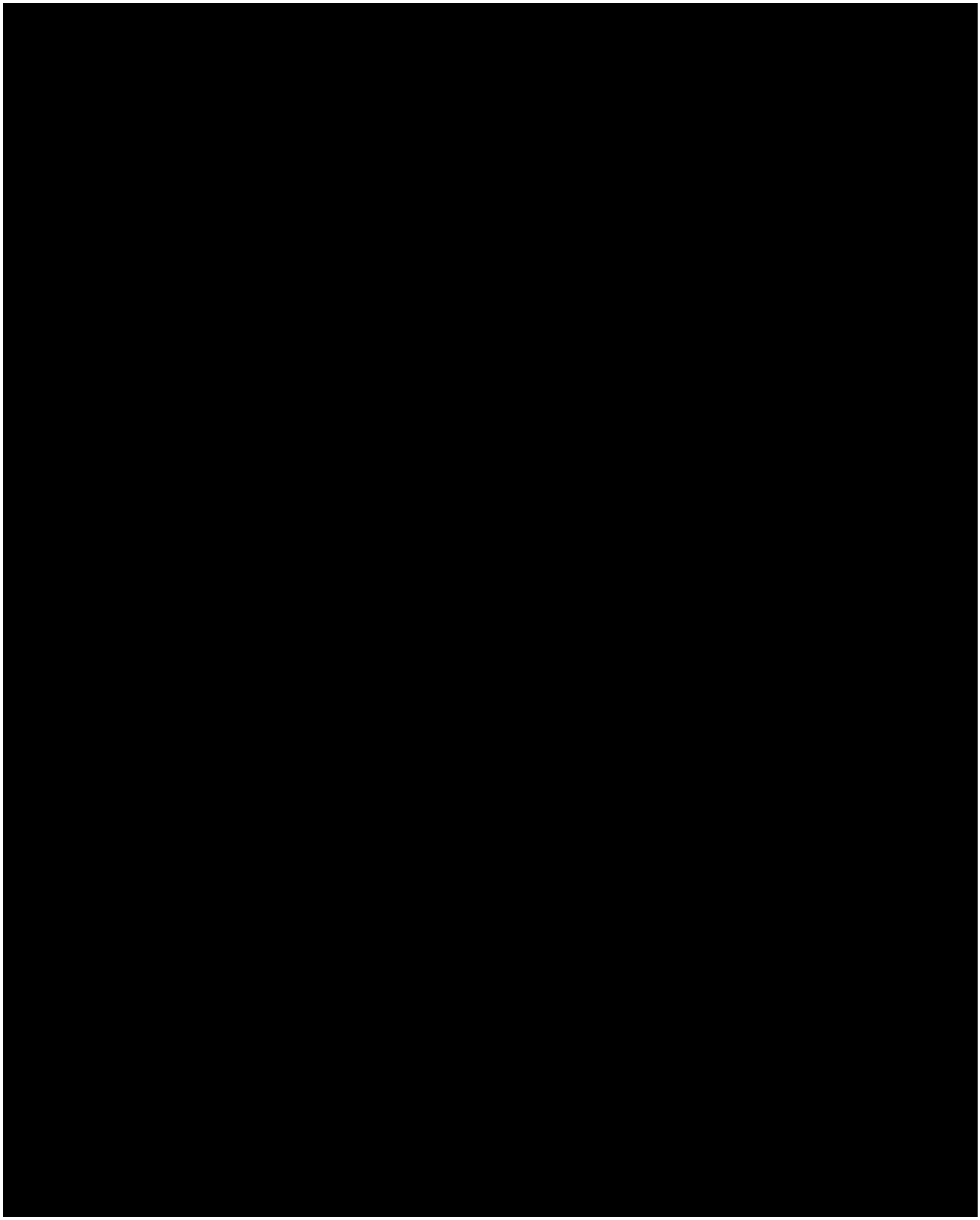
In the event of premature termination, the Sponsor will provide information on the handling of currently enrolled subjects who have not completed the study.

[redacted]

nd Consensus Recommendations. Plast Reconstr Surg. 2016 Jun; 137(6):961e-71e.

17. Appendices

[redacted]



SIGNATURES PAGE

Date	Signed by
2019-10-11 06:34	[redacted]
Justification	Approved by Owner