A Randomized, Evaluator-Blinded Study to Evaluate Facial Harmony and Subject Satisfaction Using Restylane Defyne in a Stepwise Treatment Approach

Study products: Restylane® Defyne™

Clinical trial number (CTN): 05DF1910

Sponsor: Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala, Sweden
Telephone: +46 18 474 90 00
Facsimile: +46 18 474 90 01

Investigators and Study Administrative Structure

Coordinating Investigator: PPD

Sponsor: Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala, Sweden
Telephone: +46 (0)18 474 90 00

Senior Medical Expert: PPD

PPD

PPD

PPD

PPD

Clinical Project Manager: PPD

Statistician:

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.

Synopsis

Clinical Study Title:	A Randomized, Evaluator-Blinded Study to Evaluate Facial Harmony and Subject Satisfaction Using Restylane Defyne in a Stepwise Treatment Approach
Clinical Trial Number:	05DF1910
Region(s) / Country(ies) Involved and Planned Number of Study Sites:	Region/Country(ies): South America and Europe No. of Study Centres: 2 - 4
Total Number of Subjects (Planned):	Approximately 60 subjects will be enrolled (of which at least 20 males).
Clinical Study Design:	This is a 12-week, randomized, multi-centre, evaluator-blinded, on-label, post-market study. Approximately 60 subjects (of which at least 20 males) will be enrolled and randomized into two groups. Stratification for site and gender will be performed. Both groups will be stepwise treated in the chin and nasolabial folds (NLF)/marionette lines (ML). One group will start treatment in chin (at baseline), followed by treatment in NLFs and MLs at week 3. The other group will start treatment in NLFs and MLs at baseline, followed by treatment in chin at week 3. The two groups are referred to as down-up and top-down, respectively. An optional touch-up will be provided at week 6 for all subjects and treatment areas that have not obtained optimal aesthetic improvement as agreed between subject and Investigator. Subjects will be followed until week 9. Study assessments, such as questionnaires, must be completed before treatment if injection is planned at the visit (applicable for baseline, week 3 and week 6 [if touch-up will be performed]).
Clinical Study Duration:	First subject first visit to last subject last visit will be approximately 24 weeks: • 12 weeks enrolment • 3 weeks screening • 9 week follow up
Effectiveness Objectives and Endpoints:	Objective To evaluate aesthetic improvement after treatment in chin and NLFs/MLs, respectively, and in combination. Endpoint CCI and Treating Investigator assessment using the Global Aesthetic Improvement Scale (GAIS) at week 3, 6 and 9.

	Objective To evaluate naturalness of the treatment result CCI [redacted]. Endpoint Assessed by CCI and Treating Investigator using directed questions at week 3, 6 and 9.
	CCI [redacted]
	Objective To evaluate subject satisfaction treating chin versus treating NLFs/MLs, respectively, and in combination. Endpoint Subject assessment using subject satisfaction questionnaire and CCI at baseline, week 3, 6 and 9.
	CCI [redacted]

	CCI
Safety Objectives and Endpoints:	To evaluate Adverse Events (AEs) collected throughout the study. Device deficiencies will be assessed at treatment visits.
Inclusion Criteria:	1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent. 2. Subjects willing to undergo augmentation and correction therapy in the studied indications 3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures for the duration of the study (e.g., laser or chemical resurfacing, facelift, etc.). 4. Adult males or non-pregnant, non-breastfeeding females and women of non-child bearing potential over the age of 21. • Urinary pregnancy test must be negative for females of childbearing potential at screening and all injection visits. • Definition of non-child bearing potential: Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. Postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. 5. 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/enrolment visit and prior to treatment. Acceptable forms of effective birth control include: • Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository; • Bilateral tubal ligation; • Combined oral contraceptives (oestrogen and

	progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1; • Hormonal or copper intra uterine device (IUD) inserted at least 28 days prior to Day 1; • Vasectomized partner for at least 3 months prior to screening; • Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form of birth control).
Exclusion Criteria:	1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram-positive bacterial proteins. 2. History of allergy or hypersensitivity to lidocaine or other amide-type anaesthetics, or topical anaesthetics or nerve blocking agents (if such products are intended to be used for that subject). 3. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions. 4. Previous use of any permanent (non-biodegradable) treatment, lifting threads, permanent implants or autologous fat below the level of the horizontal line from the lower orbital rim. 5. Previous use of any semi-permanent treatment (e.g., calcium hydroxylapatite or Poly-L-Lactic acid) below the level of the horizontal line from the lower orbital rim within 24 months of the baseline visit. 6. Previous use of any HA based or collagen based biodegradable facial tissue augmentation therapy below the level of the horizontal line from the lower orbital rim within 12 months of the baseline visit. 7. History of other facial treatment/procedure in the previous 6 months that in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, e.g.: • Resurfacing (laser, photo modulation, intense pulsed light [IPL] radio frequency, dermabrasion, needling, chemical peel or other ablative/non-ablative procedures (such as ultrasound and cryotherapy)) • Mesotherapy • Lipolytic injections (e.g. deoxycholic acid or other lipolytic substances) • Botulinum toxin injections below the level of the horizontal line from the lower orbital rim 8. Previous facial surgery, within 12 months, below the level of the horizontal line from the lower orbital rim.

	9. History of cancer or previous radiation near or on the area to be treated. 10. Presence of any disease or lesions near or on the area to be treated, e.g.: • Inflammation, active or chronic infection (e.g., in mouth, head and neck region) • Perioral dermatitis, active herpes simplex or herpes zoster lesions, or outbreak within 4 weeks from baseline, or history of four outbreaks, or more, during the last year. • Scars or deformities • Cancer, or precancer such as actinic keratosis or actinic cheilitis 11. Presence of tattoo, piercing, beard or facial hair, which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment. 12. Presence of a dental, oral, or facial condition which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment, e.g. has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities. 13. An underlying known disease, a surgical or medical condition that would expose the subject to undue risk, e.g. active hepatitis, autoimmune disease, history of bleeding disorders, connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, or scleroderma. 14. Use of concomitant medication that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g. aspirin [except low dose aspirin] or other non-steroidal anti-inflammatory drugs [NSAIDs], Omega 3 or Vitamin E), within 14 days prior to injection. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation. 15. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies), systemic corticosteriods (inhaled corticosteroids are allowed) within 3 months prior to Baseline visit. 16. Use of topical facial corticosteroids or prescription retinoids (below the level of the horizontal line from the lower orbital rim) within 1 month of the Baseline visit or systemic retinoid treatment within 6 months of the Baseline visit. 17. Presence of any condition, which in the opinion of the Treating Investigator makes the subject unable to complete the study per protocol, e.g. • Subjects not likely to avoid other prohibited facial cosmetic treatments

	• Subjects not likely to complete the study because of other commitments • Subjects anticipated to be unavailable for visits, incapable of understanding the investigational assessments or having unrealistic expectations of treatment result • Subjects who have a concomitant condition (e.g. acute viral or bacterial infection with fever) that might confuse or confound study treatments or assessments 18. Participation in any interventional clinical study within 30 days of screening. 19. Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.
Investigational Product:	Restylane Defyne Cross-linked hyaluronic acid 20 mg/mL Lidocaine hydrochloride 3 mg/mL Phosphate buffered saline pH 7 qs ad 1 mL The syringe is packaged with two 27 Gauge (G) x ½″ Ultra-Thin Wall (UTW) needles. At each treatment session, a maximum of 2 mL per treatment site is recommended per European Union (EU) label. Depending on the area to be treated and the tissue support, the product should be injected in the mid to deep dermis, subcutis or supraperiostic zone.
Treatment regimen:	Subjects randomized to down-up treatment (n=30 of which at least 10 males): **Baseline** - The chin and surrounding area to be treated with up to 2 mL of Restylane Defyne per treatment site with a maximum of 4 mL in total. **Week 3** – NLFs and MLs to be treated with up to 2 mL/line per NLF and up to 2 mL per ML of Restylane Defyne **Week 6** - Optional touch-up in any of the treated areas that have not obtained optimal aesthetic improvement. Up to 2 mL per facial half is recommended for NLF and MLs, and a total of 2 mL in the chin and surrounding area. Subjects randomized to top-down treatment (n=30 of which at least 10 males): **Baseline** – NLFs and MLs to be treated with up to 2 mL per NLF and up to 2 mL per ML of Restylane Defyne **Week 3** – The chin and surrounding area to be treated with up to 2 mL of Restylane Defyne per treatment site, with a maximum of 4 mL in total. **Week 6** – Optional touch-up in any of the treated areas that have not obtained optimal aesthetic improvement. Up to 2 mL per facial half is recommended for NLF and ML, and a total of 2 mL in the chin and surrounding area.

	Sufficient amount of study product should be injected to achieve optimal correction as agreed between the Treating Investigator and CCI. The method of injection is at the discretion of the Treating Investigator.
Blinded Evaluation:	CCI
Statistical Method:	CCI
Sample Size:	The sample size of approximately 60 subjects (30 per treatment group) is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of effectiveness and safety of the two treatment approaches when treating the chin, NLFs and MLs with Restylane Defyne.

Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	Adverse event
CA	Competent Authority
CE	French: *Conformité Européenne*
CFR	Code of Federal Regulations
Coordinating Investigator	Investigator who is appointed by the Sponsor to coordinate work in a multicentre study
CRO	Contract research organization
CSP	Clinical study protocol
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labelling)
DMP	Data management plan
eCRF	Electronic case report form
EU	European Union
G	Gauge
GAIS	Global aesthetic improvement scale
GCP	Good clinical practice
GDPR	General Data Protection Regulation
HA	Hyaluronic acid
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFU	Instructions for use
IUD	Intra uterine 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.

Abbreviation/Term	Definition
IPL	Intense Pulsed Light
IPR	Independent Photographic Reviewer
ISO	International Organization for Standardization
MDR	Medical Devices Regulation
MITT	Modified intention-to-treat
ML	Marionette lines
MedDRA	Medical dictionary for regulatory activities
NLF	Nasolabial fold
NSAID	Non-steroidal anti-inflammatory drug
OBT	Optimal Balance Technology
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PT	Preferred term
SAE	Serious adverse event
SDV	Source data verification
SOC	System organ class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
Study files	The Investigator file and the Sponsor file
Study products	The investigational product and the reference product under study
Study site	Institution or site where the study is carried out
Touch-up	Repeated injection to be performed after treatment, if necessary to achieve optimal correction
U-HCG	Urinary human chorionic gonadotropin
UTW	Ultra-Thin Wall
WHO	World Health Organization

Table of Contents

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE **2**

SYNOPSIS **3**

ABBREVIATIONS AND DEFINITIONS OF TERMS **10**

LIST OF TABLES **15**

LIST OF FIGURES **15**

LIST OF APPENDICES **15**

1. ETHICAL CONSIDERATIONS **16**

1.1 Statement of ethical compliance 16

1.2 Application to independent ethics committee 16

2. BACKGROUND INFORMATION **17**

2.1 Indication and population description 17

2.2 Study Product Profile 17

2.2.1 Investigational product description 17

2.3 Study rationale and justification for design 18

2.4 Risks and benefits 18

3. OBJECTIVE(S) AND ENDPOINT(S) **19**

3.1 Objectives and endpoints 19

3.1.1 Effectiveness objectives and endpoints 19

3.1.2 Safety objective and endpoints 20

4. DESIGN OF THE STUDY **20**

4.1 General outline 20

4.2 Number of subjects 21

4.3 Duration of subject participation 21

4.4 Randomization and blinding 21

4.4.1 Randomization 21

4.4.2 Blinding 22

4.4.3 Emergency unblinding 22

4.5 Medical history 22

4.6 Prior and concomitant therapies 22

4.6.1 Recording 23

4.7 Schedule of Events 24

4.8 Visits 25

4.8.1 Visit 1: Screening Visit 25

4.8.2 Visit 2: Baseline Visit (First Injection) 25

4.8.3 Visit 3: 3-Week Visit (Second Injection) 25

4.8.4 Visit 4: 6-Week Visit (Optional Touch-up) 26

4.8.5 Visit 5: 9-Week Visit (End of Study) 26

4.9 Demographics and baseline assessments 27

5. SUBJECTS 28

5.1 Subject information and informed consent 28

5.2 Inclusion criteria 28

5.3 Exclusion criteria 29

5.4 Subject number 31

5.5 Withdrawal of subjects 31

6. STUDY PRODUCTS 33

6.1 Investigational product 33

6.2 Additional products and materials 33

6.3 Packaging, labelling, and storage 33

6.3.1 Investigational product 33

6.4 Product accountability 33

6.5 Treatment 34

6.5.1 Treatment procedure 34

6.5.2 Treatment regimen (dose and interval) 34

6.5.3 Post-treatment care 35

6.5.4 Post-trial provisions 35

6.5.5 Electronic case report form recordings 35

6.5.6 Treatment compliance 36

7. EFFICACY ASSESSMENTS 37

7.1 General information 37

7.2 2D Photography 37

7.3 Global Aesthetic Improvement Scale (GAIS) 38

7.4 Naturalness, CCI [redacted] 38

CCI [redacted] 38

7.6 Subject Satisfaction Questionnaire 39

CCI [redacted] 39

39

39

8. SAFETY ASSESSMENTS 39

8.1 Adverse events 39

8.1.1 Definition of an adverse event (Medical Devices Regulation (MDR) article 2(57)) 39

8.1.2 Definition of a serious adverse event (MDR article 2(58)) 39

8.1.3 Recording instructions 40

8.1.4 Reporting of adverse events 42

8.1.5 Reporting of serious adverse events 43

8.1.6 Follow-up of unresolved events ongoing at termination of the study 44

8.1.7 Reporting and follow-up of events occurring after subject termination of the study 44
8.1.8 Pregnancy 44
8.1.9 Anticipated adverse events 45
8.2 Device deficiencies 45
8.2.1 Definition of a device deficiency 45
8.2.2 Recording instructions 45
8.2.3 Reporting of device deficiencies 45
9. DATA HANDLING AND MANAGEMENT 46
9.1 Data management 46
9.2 Electronic case report forms 46
9.2.1 Data entry 47
9.2.2 The query process 47
9.2.3 User identification 47
9.2.4 Audit trail 47
9.3 Source documents 47
9.4 Record keeping and access to source data 48
9.5 Document and data retention 48
10. STATISTICAL METHODS 49
10.1 Analysis populations 49
10.2 Demographics, baseline assessments, and subject characteristics 49
10.3 Efficacy analysis 49
10.4 Safety analysis 50
10.5 Handling of missing data 50
10.6 Interim analysis 50
10.7 Withdrawals and deviations 50
10.8 Sample size 50
11. PROTECTION OF PERSONAL DATA 50
12. QUALITY CONTROL AND QUALITY ASSURANCE 51
12.1 Quality control 51
12.2 Quality assurance 51
12.3 Changes to the clinical study protocol 52
12.3.1 Amendments 52
12.3.2 Deviations 52
13. FINANCING, INDEMNIFICATION, AND INSURANCE 52
14. PUBLICATION POLICY 52
15. SUSPENSION OR PREMATURE TERMINATION 53
16. SUMMARY OF CHANGES 53
17. REFERENCES 55

List of Tables

Table 1. Schedule of events 24

Table 2. Fitzpatrick Skin Types (FST) 27

Table 3. Global Aesthetic Improvement Scale (GAIS) 38

List of Figures

Figure 1 Study Flow Chart 21

List of Appendices

Appendix 1 Declaration of Helsinki 1

Appendix 2 Investigator Signature Page 1

Appendix 3 Instructions for Use – Restylane Defyne (Version 3.0, Effective date: 2015-12-15) 1

Appendix 4 Global Aesthetic Improvement Scale (GAIS) 1

Appendix 5 Naturalness, CCI [redacted] **(Investigator's questionnaire)** 1

CCI [redacted] 1

..... 1

..... 1

Appendix 9 Subject satisfaction questionnaire 1

CCI [redacted] 1

1. Ethical Considerations

1.1 Statement of ethical compliance

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

The study shall follow the international standard for clinical study of medical devices for human subjects, International Organization for Standardization (ISO) 14155:2011, and the International Conference on Harmonisation (ICH) guideline for GCP E6 (R2) as applicable for medical device.

1.2 Application to independent ethics committee

It is the responsibility of the Principal Investigator (PI) to obtain approval of the 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 shall be followed.

As the study product is CE-marked for the intended use, application for approval from competent authority (CA) is not required.

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 (see further information in section 11).

2. Background Information

2.1 Indication and population description

Restylane Defyne is intended to augment the volume of facial tissues. It is recommended to be used for correction of severe wrinkles, or to redefine facial features. Depending on the area to be treated and the tissue support, the product should be injected in the mid to deep dermis, subcutis or supraperiostic zone. Lidocaine is added to the formulation to diminish the pain resulting from the injection during the treatment.

In this study, the investigational products will be used for stepwise treatment of the chin and nasolabial folds (NLF)/marionette lines (ML) within the approved indication.

Approximately 60 subjects, meeting all inclusion/exclusion criteria, will be enrolled to the study.

2.2 Study Product Profile

2.2.1 Investigational product description

Among the different materials used as raw materials in fillers, sodium hyaluronate, also denoted hyaluronic acid when found *in vivo* and hereinafter referred to as HA, is the most frequently used[1]. HA is a naturally occurring polysaccharide found in all vertebrates and in some bacteria. HA based fillers typically exhibit better biocompatibility and fewer adverse reactions than fillers made from other materials[1,2].

The chemical structure of HA is very simple with repeating disaccharide units of glucuronic acid and N-acetylglucosamine. As the chemical structure of HA is identical in all species and tissues, it is non-allergenic.

CCI [redacted]

Restylane Defyne is a sterile, biodegradable, transparent gel of non-animal cross-linked HA 20 mg/mL with the addition of lidocaine hydrochloride 3 mg/mL. The gel is supplied in a prefilled plastic syringe. The contents of the syringe are sterilized using moist heat. The syringe is packaged individually in a blister, with two 27G x ½" Ultra Thin Wall (UTW) needles. The needles have been sterilized using irradiation. Restylane Defyne was CE-marked 2010 with the previous name Emervel® Deep Lidocaine. Restylane Defyne is a product whose functional component, cross-linked HA, is obtained by using the CCI [redacted].

CCI

2.2.1.2 Clinical documentation

The first injectable OBT gel product was CE-marked in Europe in 2009. Several studies have been conducted to assess the safety and efficacy of OBT products in the treatment of e.g. cheeks, NLFs, and lips [6-10].

2.3 Study rationale and justification for design

CCI

This study aims to document the results of a stepwise treatment and determine if any of the two approaches to be used in this study, down-up and top-down, affects the studied endpoints. Results from the study will be the basis for future treatment guidelines used by aesthetic health care practitioners when injecting Restylane Defyne in the chin, NLF and ML.

Approximately 60 subjects (of which at least 20 males) will be enrolled and randomized into two groups with different treatment schedules. Comparison between the two groups will help to determine if the different treatment approaches affects the outcome, such as subject satisfaction.

2.4 Risks and benefits

After the injection of the study products, some common injection-related reactions might occur. These reactions include erythema, swelling, pain, itching, bruising or tenderness at the implant site. Typically, resolution is spontaneous within a few days after injection.

There is a risk that the subject will not gain the full aesthetic correction of the treated areas. There is also a risk for development of palpable HA lumps or displacement of the injected HA. Inflammation or infection has been reported in a few cases after treatment. There may be risk of bruising and/or damaging body structures such as nerves or blood vessels connected to the injection site, however these risks are minor.

Following facial aesthetic treatments isolated rare cases have been reported regarding ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction. Detailed information on reported adverse events (AE) relevant for the study product is provided in the instructions for use (IFU).

Lidocaine can in rare cases give allergic reactions, and therefore subjects with known allergy or hypersensitivity to local anaesthetics should not be included in the study.

Given the anticipated low level of transient and acceptable AEs in connection with the injection, the risk-benefit assessment of the use of the study products for lower face augmentation offers a potential clinical benefit, such as subject rated improvement of attractiveness and satisfaction, at reasonable risk.

3. Objective(s) and Endpoint(s)

3.1 Objectives and endpoints

3.1.1 Effectiveness objectives and endpoints

Objective

CCI [redacted]

Endpoint

CCI [redacted] and Treating Investigator assessment using the Global Aesthetic Improvement Scale at week 3, 6 and 9.

Objective

To evaluate naturalness of the treatment result CCI [redacted].

Endpoint

Assessed by CCI [redacted] and Treating Investigator using directed questions at week 3, 6 and 9.

CCI [redacted]

Objective

To evaluate subject satisfaction treating chin versus treating NLF/ML, respectively, and in combination.

Endpoint

Subject assessment using subject satisfaction questionnaire and CCI at baseline, week 3, 6 and 9.

CCI

3.1.2 Safety objective and endpoints

Objective:

To evaluate AEs collected throughout the study

Endpoint

Incidence, intensity, duration and onset of AEs collected from injection of study product to patient withdrawal or end of study (visit 5).

4. Design of the Study

4.1 General outline

This is a 12-week, randomized, male-female and site stratified, evaluator-blinded, multi-centre study to evaluate the effectiveness and safety of Restylane Defyne when using two different injection approaches, stepwise down-up vs. top-down, when treating the lower face.

Approximately 60 subjects requiring augmentation and correction therapy in the chin, NLFs and MLs fulfilling all eligibility criteria will be enrolled in the study. The subjects will be randomized to one of two treatment groups, the first treatment group will receive injections in the chin area at baseline and in the NLFs and MLs at the visit 3 (week 3), the second group will undergo the same treatment but in reverse order. The two groups are referred to as down-up and top-down. Male-female stratification will be applied in the randomization and the aim is to randomize 10 male subjects to each group.

Six weeks after the second treatment, at visit 4, an optional touch-up will be administered to subjects that have not obtained optimal aesthetic improvement as agreed between subject and Investigator.

The subject will return to the clinic for a final follow-up visit (visit 5) 9 weeks after the first treatment.

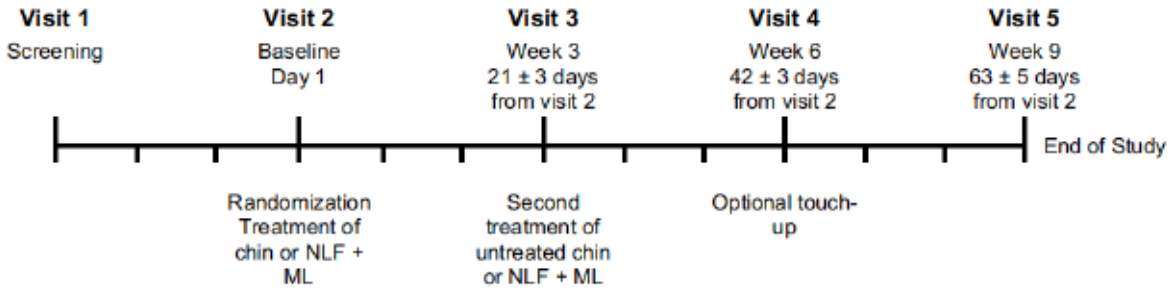
All efficacy study assessments will be performed before treatment and safety will be followed by AE and device deficiency reporting throughout the study.

The Investigator will assess, Global Aesthetic Improvement Scale (GAIS), naturalness/CCI [redacted], CCI [redacted] – CCI [redacted] and safety.

The subject assessments include, CCI [redacted] subject satisfaction questionnaire.

CCI [redacted].

Figure 1 Study Flow Chart



4.2 Number of subjects

Approximately 60 subjects, of which at least 20 males, will be enrolled at 2-3 study sites in South America and Europe. The duration of the enrolment period is expected to be around 12 weeks.

4.3 Duration of subject participation

The total duration of the study is expected to last approximately 24 weeks (6 months), or until 60 subjects have been successfully treated. A subject will be involved in the study for 9 – 12 weeks.

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 and blinding

4.4.1 Randomization

Approximately 60 subjects will be randomized in a CCI [redacted] ratio to either down-up or top-down treatment approaches. Before starting the study, a computer generated randomization list will be prepared under the supervision of a designated statistician from the Sponsor. The randomization list will be stratified by site and gender. Randomization numbers will be allocated in ascending sequential order within each strata. Randomization will be performed

using an Interactive Response System by assigning each subject to the two treatment groups according to the randomization list.

4.4.2 Blinding

The IPR will review blinded pairs of photographs from pre and post treatment. No information regarding treatment group or visit will be available to the photographic reviewer. The photographs will be coded and a separate key, not available to the IPR, will be used to pair the IPR evaluations to the correct subject and visit.

4.4.3 Emergency unblinding

Not applicable as the treating Investigator is not blinded to treatment.

4.5 Medical history

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

4.6 Prior and concomitant therapies

Except as noted below, concomitant medications or other treatments or procedures may be utilised when the PI or his/her authorised designee considers it medically necessary. Information regarding any use of concomitant medications, including over-the-counter medications administered during the study are to be recorded in the eCRF. 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 eCRF.

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

- Use of concomitant medication that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g. aspirin [except low dose aspirin] or other non-steroidal anti-inflammatory drugs [NSAIDs], Omega 3 or Vitamin E), within 14 days prior to injection. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.
- Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies,); systemic corticosteroids (inhaled corticosteroids are allowed) within 3 months prior to injection visits (visit 2, 3 and 4).
- Lidocaine should be used with caution in subjects receiving other local anaesthetics or agents structurally related to amide-type anaesthetics, e.g. certain antiarrhythmics, as the systemic toxic effects can be additive.
- Procedures involving an active dermal response in the facial area including the lips (e.g. tissue augmenting therapy, contouring or revitalisation treatment with permanent or non-permanent fillers, mesotherapy, fat-injection, neurotoxin (below the level of the horizontal line from the lower orbital rim), laser or light treatment, chemical peeling or dermabrasion) are prohibited.
- Facial surgery including liposuction, insertion of permanent implants in the facial area, planned sinus surgery or dental root surgery, or tattoo in the treatment area are prohibited.

- Use of topical facial corticosteroids or prescription retinoids or systemic retinoid treatment near or in the treatment area are prohibited.

Participation in any other clinical study is prohibited.

If a subject receives prohibited therapy during the study, a protocol deviation should be documented. The subject shall continue in the study for the scheduled follow-up visits unless otherwise instructed by the Sponsor.

4.6.1 Recording

Prior and concomitant therapies are to be recorded in the eCRF and reviewed, and updated if needed, at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition.

4.7 Schedule of Events

Table 1. Schedule of events

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening[1]	Baseline/ Day 1 (within 3 weeks after screening)	Week 3 (21 ± 3 days from visit 2)	Week 6 (42 ± 3 days from visit 2)	Week 9 (63 ± 5 days from visit 2)
Informed Consent	X	(X)[2]			
Demographic Data including, Fitzpatrick skin type, medical history & concurrent diseases, previous facial treatments/procedures	X	(X)[2]			
Weight and height	X	(X)[2]			X[3]
Inclusion /Exclusion Criteria	X	X			
Concomitant Medication/ Procedures	X	X	X	X	X
Urine Pregnancy Test		X	X	X[4]	
Photography 2D		X	X	X	X
Randomization		X			
Treatment[5]		X	X	X[6]	
Adverse Events[7]		X	X	X	X
Investigator Assessment					
GAIS			X	X	X
Naturalness/CCI around the chin CCI [redacted]		X[8]	X[8]	X	X
CCI [redacted]					
Subject Assessment					
CCI [redacted]					

1) The screening visit and baseline visit (visit 2) may be performed on the same day
2) Screening visit assessments should be performed on the same day as the baseline visit if no separate screening visit has been completed
3) Weight only
4) If touch-up treatment is planned
5) Treatment to be performed after all assessments have been completed.
6) Optional touch-up injection
7) AE reporting period starts at the baseline visit after randomization
8) Only applicable questions
9) CCI [redacted]
10) Assessments to be performed after end of study
11) CCI [redacted]

4.8 Visits

4.8.1 Visit 1: Screening Visit

The screening visit and baseline visit (visit 2) may be performed on the same day. The following activities and screening assessments will be performed within three weeks prior to baseline.

- Informed Consent
- Demographic Data including, Fitzpatrick skin type, medical history & concurrent diseases, previous facial treatments/procedures, see section 4.9.
- Weight and height
- Inclusion /Exclusion Criteria
- Concomitant Medication/ Procedures

4.8.2 Visit 2: Baseline Visit (First Injection)

Include screening visit assessments if screening and baseline is performed on the same day.

- Inclusion /Exclusion Criteria
- Concomitant Medication/ Procedures
- Urine Pregnancy Test
- Photography 2D
- Randomization
- Treatment (to be performed after efficacy assessments)
- Adverse Events

Investigator assessments

- CCI [redacted]

Subject assessments

- CCI [redacted]
- Subject satisfaction questionnaire (only applicable questions)

4.8.3 Visit 3: 3-Week Visit (Second Injection)

- Concomitant Medication/ Procedures
- Urine Pregnancy Test
- Photography 2D
- Treatment (to be performed after efficacy assessments)
- Adverse Events

Investigator assessments

- GAIS

- Naturalness/CCI [redacted] (only applicable questions)
- CCI [redacted]

Subject assessments

CCI [redacted]

- Subject satisfaction Questionnaire

4.8.4 Visit 4: 6-Week Visit (Optional Touch-up)

- Concomitant Medication/ Procedures
- Urine Pregnancy Test (if touch-up treatment is planned)
- Photography 2D
- Touch-up treatment (to be performed after efficacy assessments)
- Adverse Events

Investigator assessment

- GAIS
- Naturalness/CCI [redacted] around the chin/improvement in the submental area
- CCI [redacted]

Subject assessment

CCI [redacted]

- Subject satisfaction Questionnaire

4.8.5 Visit 5: 9-Week Visit (End of Study)

- Weight
- Concomitant Medication/ Procedures
- Photography 2D
- Adverse Events

Investigator assessments

- GAIS
- Naturalness/CCI [redacted]
- CCI [redacted]

Subject assessments

- Subject satisfaction Questionnaire

4.9 Demographics and baseline assessments

- Date of birth
- Gender
- Child bearing potential
- Race and ethnic origin
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino
  - Race: American Indian/Alaskan Native, Asian, Black, Native Hawaiian or other Pacific Islander, White, other
- Fitzpatrick skin type (FST), see Table 2 below.

Table 2. Fitzpatrick Skin Types (FST)*

Skin type	Skin color	Skin characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

FST is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet light.†

* https://www.verywell.com/fitzpatrick-classification-scale-1069226

† Fitzpatrick T.B. (1988). The validity and practicality of sun-reactive skin types I through VI. Arch. Dermatol. 124, 869–871.

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 (ICF) 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 ICF and to consider participation in the study. Before any study-related activities are performed, the ICF shall be personally signed and dated by the subject and the PI or delegated Investigator. The consent includes information that data will be collected, recorded, processed, and may be transferred to both EU and non-EU countries. The data will not contain any information that can be used to identify any subject.

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

All signed ICFs shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated ICF and any other written information.

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

5.2 Inclusion criteria

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

1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent.
2. Subjects willing to undergo augmentation and correction therapy in the studied indications
3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures for the duration of the study (e.g., laser or chemical resurfacing, facelift, etc.).
4. Adult males or non-pregnant, non-breastfeeding females and women of non-child bearing potential over the age of 21.

    - Urinary pregnancy test must be negative for females of childbearing potential at screening and all injection visits.

Definition of non-child bearing potential: Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. Postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.

5. 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/enrolment visit and prior to treatment.

   Acceptable forms of effective birth control include:

   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository;
   - Bilateral tubal ligation;
   - Combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1;
   - Hormonal or copper intra uterine device (IUD) inserted at least 28 days prior to Day 1;
   - Vasectomized partner for at least 3 months prior to screening;
   - Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form of birth control).

5.3 Exclusion criteria

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

1. Known/previous allergy or hypersensitivity to any injectable HA gel or to gram-positive bacterial proteins.
2. History of allergy or hypersensitivity to lidocaine or other amide-type anaesthetics, or topical anaesthetics or nerve blocking agents (if such products are intended to be used for that subject).
3. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions.
4. Previous use of any permanent (non-biodegradable) treatment, lifting threads, permanent implants or autologous fat below the level of the horizontal line from the lower orbital rim.
5. Previous use of any semi-permanent treatment (e.g., calcium hydroxylapatite or Poly-L-Lactic acid) below the level of the horizontal line from the lower orbital rim within 24 months of the baseline visit.
6. Previous use of any HA based or collagen based biodegradable facial tissue augmentation therapy below the level of the horizontal line from the lower orbital rim within 12 months of the baseline visit.
7. History of other facial treatment/procedure in the previous 6 months that in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, e.g.:

- Resurfacing (laser, photo modulation, intense pulsed light [IPL] radio frequency, dermabrasion, needling, chemical peel or other ablative/non-ablative procedures (such as ultrasound and cryotherapy))
- Mesotherapy
- Lipolytic injections (e.g. deoxycholic acid or other lipolytic substances)
- Botulinum toxin injections below the level of the horizontal line from the lower orbital rim

8. Previous facial surgery, within 12 months, below the level of the horizontal line from the lower orbital rim.
9. History of cancer or previous radiation near or on the area to be treated.
10. Presence of any disease or lesions near or on the area to be treated, e.g.:
    - Inflammation, active or chronic infection (e.g., in mouth, head and neck region)
    - Perioral dermatitis, active herpes simplex or herpes zoster lesions, or outbreak within 4 weeks from baseline, or history of four outbreaks, or more, during the last year
    - Scars or deformities
    - Cancer, or precancer such as actinic keratosis or actinic cheilitis
11. Presence of tattoo, piercing, beard or facial hair, which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment.
12. Presence of a dental, oral, or facial condition which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment, e.g. has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities.
13. An underlying known disease, a surgical or medical condition that would expose the subject to undue risk, e.g. active hepatitis, autoimmune disease, history of bleeding disorders, connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, or scleroderma.
14. Use of concomitant medication that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g. aspirin [except low dose aspirin] or other NSAIDs, Omega 3 or Vitamin E), within 14 days prior to injection. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.
15. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies,), systemic corticosteriods (inhaled corticosteroids are allowed) within 3 months prior to Baseline visit.
16. Use of topical facial corticosteroids or prescription retinoids (below the level of the horizontal line from the lower orbital rim) within 1 month of the Baseline visit or systemic retinoid treatment within 6 months of the Baseline visit.
17. Presence of any condition, which in the opinion of the Treating Investigator makes the subject unable to complete the study per protocol, e.g.

- Subjects not likely to avoid other prohibited facial cosmetic treatments
- Subjects not likely to complete the study because of other commitments
- Subjects anticipated to be unavailable for visits, incapable of understanding the investigational assessments or having unrealistic expectations of treatment result
- Subjects who have a concomitant condition (e.g. acute viral or bacterial infection with fever) that might confuse or confound study treatments or assessments

18. Participation in any interventional clinical study within 30 days of screening.
19. Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.

5.4 Subject number

Each subject who has signed the ICF will be assigned a subject number The subject numbers will be allocated in ascending order within each centre. The reason for excluding a consenting subject from entering the study should be specified in each case. A screen failure should not be re-entered in the study.

For the duration of the clinical study, each subject will be identified using the subject number for all documentation and discussion.

5.5 Withdrawal of subjects

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

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

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

All discontinuations and the reason for discontinuation are to be documented by the investigator on the Exit form.

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

A subject who has been randomized and assigned a kit number/randomization number cannot be replaced by another subject if he/she discontinues the clinical study for any reason. Additional subjects could be enrolled (randomized/assigned to treatment) in order to attain the number of evaluable subjects.

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

In case of a pregnancy occurring after the baseline visit, follow the procedures described in section 8.1.8. The subject may remain in the study, but no invasive procedure should be conducted.

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

Potential reasons for discontinuation are defined below:

The withdrawal criteria are:

- **Medical reasons**: If the subject suffers from a medical condition that in the judgement of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons shall document the specific condition for withdrawing the subject.
- **Safety reasons**: If a subject suffers an AE, which in the judgment of the Investigator or the Sponsor presents an unacceptable consequence or risk to the subject.
- **Withdrawal of informed consent:** A subject can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorised representative at any time for any reason.
- **Lost to follow-up:** If a subject does not return for a scheduled visit, reasonable effort shall be made to contact that subject, e.g. call three times at different hours and leave messages if applicable before declaring the subject lost to follow-up.
- **Other:** Examples of other reasons for withdrawal may be failure to comply with protocol requirements or to complete the protocol-specified evaluations.

If reason for discontinuation is "withdrawal by subject" or "other", the subject will be questioned to rule out the possibility of an AE. If the AE led to discontinuation then "adverse event" should be chosen as the reason for discontinuation, rather than "withdrawal by subject" or "other".

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 by the Investigator to be "chronic" or "stable" or for at least 3 months.

Subjects who have received prohibited concomitant medications or therapies should be followed according to protocol.

6. Study Products

The term "study product" refers to Restylane Defyne.

6.1 Investigational product

Restylane Defyne is a sterile, biodegradable, transparent gel of non-animal cross-linked HA with the addition of lidocaine hydrochloride 3 mg/mL. The gel is supplied in a prefilled plastic syringe. The syringe contains 1 mL gel. The investigational product is for single use only.

6.2 Additional products and materials

The study site will provide pregnancy tests (urinary human chorionic gonadotropin; U-HCG) and needles as needed.

Local anaesthesia (topical or infiltration) may be used at the discretion of the treating Investigator before the treatment. If used, the anaesthesia shall be supplied by the study site. Type of anaesthesia, product name, and quantity used must be recorded in the eCRF.

The Investigator shall provide adequate equipment in case of emergency.

The sponsor will provide photo equipment as agreed when needed.

6.3 Packaging, labelling, and storage

6.3.1 Investigational product

Standard commercially available products will be used.

In addition to the standard labelling of the device, a study-specific label will be attached to the box containing study specific information in addition to applicable local labelling requirements.

The investigational products syringes shall be stored in their original packaging at a temperature up to 25°C protected from sunlight and freezing. Opened packages or partially used devices shall not be reused. The expiry date is indicated on package.

Detailed product information is provided in the IFUs, which is delivered with each study product.

6.4 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, the CTA has been signed by all parties, site initiation visit has been performed and all essential documents are in place.

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(s) to their use in subjects until return or disposal. It is therefore important that the PI maintains accurate product accountability records, i.e. documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all study products received from the Sponsor; including product name, date received, batch or lot

number, expiration date, and amount received. In addition, dispensing logs shall be maintained including the product name, batch number, expiry date, dispense date, the number of syringes used, the subject receiving investigational product, and number of syringes left in stock at the site.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor for destruction or 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 8.2.3.

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

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

6.5 Treatment

6.5.1 Treatment procedure

Before treatment the subject will be informed about the potential risks involved with the treatment and when to contact the Investigator in case of emerging symptoms.

The investigational product is reserved for use by doctors who have been trained in the appropriate injection techniques.

Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections should be observed at all times including the use of disposable gloves during the injection procedure. All traces of make-up should be removed prior to any injection. The treatment site should be cleaned with a suitable antiseptic solution (extend at least five cm around the injection site).

Injection technique

The injection technique is important for the aesthetic effect of the treatment. The injection technique is at the discretion of the treating Investigator. The same predominant injection technique should be used for all subjects per site to limit variability due to technique.

6.5.2 Treatment regimen (dose and interval)

Down-up

Baseline - The chin and surrounding area to be treated with up to 2 mL of Restylane Defyne per treatment site with a maximum of 4 mL in total.

Week 3 – NLFs/MLs to be treated with up to 2 mL/line per NLF and up to 2 mL per ML of Restylane Defyne.

Week 6 - Optional touch-up in any of the treated areas that have not obtained optimal aesthetic improvement. Up to 2 mL per facial half is recommended for NLF and ML in combination, and a total of 2 mL in the chin and surrounding area.

Sufficient amount of study product should be injected to achieve optimal correction as agreed between the Treating Investigator and subject.

Top-down

Baseline - NLF and ML to be treated with up to 2 mL per NLF and up to 2 mL per ML of Restylane Defyne.

Week 3 – The chin and surrounding area to be treated with up to 2 mL of Restylane Defyne per treatment site with a maximum of 4 mL in total.

Week 6 - Optional touch-up in any of the treated areas that have not obtained optimal aesthetic improvement. Up to 2 mL per facial half is recommended for NLF and ML in combination, and a total of 2 mL in the chin and surrounding area.

Sufficient amount of study product should be injected to achieve optimal correction as agreed between the Treating Investigator and subject.

A total of up to 12 mL of study product is to be injected at the treatment visits (visit 2 and 3) and up to 6 mL during the optional touch-up at visit 4.

6.5.3 Post-treatment care

The injected sites could be gently moulded by the treating Investigator to conform to the contour of the surrounding tissues. Topical cooling may be applied to reduce initial swelling and bruising. After the injection, some common injection-related reactions might occur. These reactions include erythema, swelling, pain, itching, bruising or tenderness at the implant site. Typically, resolution is spontaneous within one week after injection into the skin.

The subject must avoid exposing the treated area to heat (sun bathing, sauna, steam baths, etc.) or extreme cold until any signs of initial swelling and redness have disappeared.

6.5.4 Post-trial provisions

In time the implant will be degraded in the body and additional treatments will be necessary to maintain the aesthetic result. After the study is finalised Q-Med AB will not supply any more treatments to the subjects, but the investigational products are commercially available if the subjects would like to have additional treatments.

6.5.5 Electronic case report form recordings

The treatment is a gel injected by the Investigator and the following details of the injection are to be recorded in the eCRF:

- Local anaesthetic used (product name, amount applied, application date, and concentration)
- Date for administration
- Administered volume
- Injection technique, see list below.
- Depth of injection
- Area of injection
- Post-treatment care (e.g. moulding, ice-pack)
- Use of needle
- Size of needle

In addition, any technical problems (device deficiencies) or clinical complications associated with the injection will be recorded in the eCRF.

Injection technique to be recorded in source data and the eCRF[‡]:

- Antegrade linear threading: also called push-ahead technique as some product is pushed ahead of the needle. Once the needle is in place, the product is injected ahead while inserting the needle in the tissue.
- Retrograde linear threading: the needle is threaded into the tissue at the appropriate depth, and the product in injected as a straight line on withdrawal of the needle
- Serial puncture: numerous small needle insertions to deliver a small amount of the product, repeated along a line or regions of the tissues
- Micro-bolus: small aliquots of the product is injected along a line or regions of the tissues
- Fanning: a number of linear threads to spread the product over a wider area
- Cross-hatching: combines multiple injections of linear threading that crisscross at right angle to provide volume in a square shape
- Other: at the choice of the treating Investigator

6.5.6 Treatment compliance

Treatment compliance is fulfilled if the treating Investigator has injected sufficient amount of study product to achieve optimal correction. Any deviations to the treatment procedure shall be recorded in the deviation log and might be reason to categorize the treatment as not compliant.

[‡] Van Eijk T, Braum M., A novel method to inject hyaluronic acid: the fern pattern technique. J Drugs Derm 2007;6:8.

7. Efficacy Assessments

7.1 General information

The methods for collecting efficacy data include 2D photography (section 7.2), GAIS (section 7.3), naturalness/CCI [redacted] (7.4), CCI [redacted], subject satisfaction questionnaire (7.6), CCI [redacted]. Assessments will be performed by the subjects, the Investigator, CCI [redacted] as shown in the schedule of events (section 4.7).

At treatment visits, all assessments must be performed before study treatment is administered.

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

7.2 2D Photography

Photographs shall be taken prior to the injections of the investigational product when applicable and at follow-up visits in order to document treatment effect.

Note that no covering make-up shall be used on the photographs.

At visits where injections are performed, the photographs shall be taken prior to the injections and should include a front, 45°-front lateral, and profile picture.

Instructions for photography are provided in a separate photography manual. Each photograph shall be labelled with the subject number, and the visit number at which the photograph was taken. In order to maintain confidentiality, the photographs must not include any information that may reveal the subject's identity. The photographs should be used in the assessment of GAIS, CCI [redacted] and to document AEs. The photographs shall be presented on a computer monitor (preferably the same monitor throughout the study).

Photographs shall be taken at the time points indicated in the schedule of events (section 4.7).

7.3 Global Aesthetic Improvement Scale (GAIS)

The GAIS is a qualitative 5-graded scale evaluating aesthetic improvement (Table 3). While GAIS is neither an objective measurement tool nor a validated tool, GAIS improvement has been commonly accepted by the medical community in Europe and the United States as clinical meaningful scale to assess visible aesthetic results. The GAIS can be used not only by the Investigator, but is also a useful tool for CCI .

Table 3. Global Aesthetic Improvement Scale (GAIS)

Rating (for the CCI)	Description (for the Investigator and CCI)
Very much improved	Optimal cosmetic result for the subject.
Much improved	Marked improvement in appearance from the original condition, but not completely optimal for this subject.
Improved	Obvious improvement in appearance from the original condition.
No change	The appearance is essentially the same as the original condition.
Worse	The appearance is worse than the original condition.

Source: Adapted from Narins et al. 2003[11].

The CCI and Investigator shall, independently of each other, rate the lower face for aesthetic change by comparing the appearance at follow-up against a photograph taken before treatment. The photographs shall be presented on a computer monitor (preferably the same monitor throughout the study). The Investigator will perform a live assessment CCI . The following question will be asked: "**How would you describe the subject's/CCI aesthetic appearance of the lower face, i.e. the treated area, compared to the photographs taken before treatment?**" The CCI shall rate according to the left column in Table 3 and the Investigator shall rate according to the right column in Table 3, the scores for CCI and Investigator rating are comparable.

A clinically significant improvement is defined as a score of improved; much improved; or very much improved. The GAIS assessments shall as far as possible be performed by the same Investigator throughout the study.

7.4 Naturalness, CCI

Both the Investigator and CCI will answer the questions regarding naturalness, CCI according to Appendix 5 (Investigator's questionnaire) and Appendix 6 CCI respectively. CCI

CCI

7.6 Subject Satisfaction Questionnaire

The subjects will assess subject satisfaction, CCI [redacted] result at visit 2 – 5 (baseline, week 3, 6 and 9), before treatment with study product, when applicable (Appendix 9). Question 1, 2, 3 and 6 will be removed from the baseline questionnaire and question 2 from week 3.

CCI [redacted]

8. Safety Assessments

8.1 Adverse events

8.1.1 Definition of an adverse event (Medical Devices Regulation (MDR) article 2(57))

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[§], in the context of a clinical investigation, whether or not related to the investigational device.

This definition includes:

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

b) events related to the procedures involved

c) events that are anticipated as well as unanticipated

8.1.2 Definition of a serious adverse event (MDR article 2(58))

A serious adverse event (SAE) is any 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** illness or injury, or

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

2. a permanent impairment of a body structure or body function, or
3. hospitalization or prolonged hospitalization††, or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
5. chronic disease

c) led to fetal distress, fetal death, or a congenital physical or mental impairment 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 8.1.4).

8.1.3 Recording instructions

Each subject should be questioned about AEs at each study visit following signing of informed consent. The question asked should be: "Since your last clinical visit; have you had any health problems?". Information on AEs can also be obtained from signs and symptoms detected during each examination or from a laboratory test, observations made by the study site personnel, subject diaries, or spontaneous reports from the subjects or their relatives.

When an AE is related to a device deficiency (refer to section 8.2), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form eCRF.

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

a) Event term (recorded in standard medical terminology and avoiding abbreviations)
b) Affected area
c) Start date (first day with symptoms)
d) Stop date (last day with symptoms)
e) Intensity (mild, moderate, or severe according to definition in section 8.1.3.1)
f) Seriousness (serious or not serious, according to definition in section 8.1.3.2)
g) Causal relationship to study product or study product injection procedure (yes or no)
h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

The AE form/module in the eCRF must be signed and dated by the Investigator.

** 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).

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

8.1.3.1 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.

8.1.3.2 Causal relationship and seriousness

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

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

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

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

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

In addition, each SAE will be classified by both the Investigator and the Sponsor separately, according to four different levels of causality:

1. **Not related** – Relationship to the device, comparator or procedures can be excluded when:
   - the event has no temporal relationship with the use of the investigational device, or the procedures related to the investigational device;
   - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
   - the event involves a body-site or an organ that cannot be affected by the device or procedure;
   - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);

- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2. **Possible** – The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. **Probable** – The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. **Causal relationship –** the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt, when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on;
   - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/ exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
   - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   - harm to the subject is due to error in use;
   - the event depends on a false result given by the investigational device used for diagnosis, when applicable;

   In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

8.1.4 Reporting of adverse events

Adverse event reporting on each subject shall start at baseline (visit 2) after the subject has been randomized. The reporting shall continue during each follow-up visit (including

telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

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

8.1.5 Reporting of serious adverse events

The Investigator shall report any **SAE** to the Sponsor or via Sponsor's representative, **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via fax or e-mail or submitted via the eCRF.

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

- Subject identification (age, gender, initials, subject number)
- Adverse event description
- Date when AE occurred
- Name of PI
- Name of study product

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

Supporting documentation to be provided with the SAE report:

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

E-mail for SAE reporting: safety.q-med@galderma.com
Fax number for SAE reporting: +46 (0)18 474 91 75

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

Surface mail for providing complementary information:
Q-Med AB
Attn. Safety - Medical Affairs
Seminariegatan 21
SE-752 28 UPPSALA, Sweden

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed or faxed to the Sponsor. A copy of the fully completed SAE form shall be kept at the site.

In addition, the PI shall report SAEs to the responsible IEC without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her IEC regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor is responsible for reporting to the CA, if applicable and according to national regulations. For all SAEs which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by Sponsor.

For a description of the procedure regarding emergency unblinding, see section 4.4.3.

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

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

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

All AEs with a causal relationship to the study products or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor. The report should as a minimum include the information described in section 8.1.3. The report can be sent via fax or e-mail according to contact details specified in section 8.1.5. The events shall thereafter be followed-up until resolved or considered chronic or stable, or for at least three months. Final outcomes shall be reported.

8.1.8 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period the subject must be withdrawn from any following study treatment, but should continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge be submitted to the Sponsor according to contact details specified in section 8.1.5. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the exposure *in utero* report form to the Sponsor immediately but no later than 24 hours after the Investigators awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia

requiring hospitalization, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

8.1.9 Anticipated adverse events

Information regarding anticipated AEs for Restylane Defyne is included in the IFU.

8.2 Device deficiencies

8.2.1 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‡‡, or performance.

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

8.2.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE module or an SAE form shall be completed as applicable (refer to section 8.1). If no SAE was experienced as a result of the device deficiency the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,
- Circumstances had been less fortunate

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

8.2.3 Reporting of device deficiencies

The Investigator shall send the completed clinical study complaint form to the Sponsor.

E-mail for device deficiencies reporting: complaints.q-med@galderma.com

Fax number for device deficiencies reporting: + 46 18 474 91 01

A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the Sponsor within 24 hours after the Investigator's awareness (for contact information, see section 8.1.5).

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

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

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

9. Data Handling and Management

9.1 Data management

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

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

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

9.2 Electronic case report forms

An electronic data capture application , compliant with regulatory requirements for software validation complying with US FDA 21CFR11 will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and shall be completed electronically for each screened subject (screening visit) and enrolled subjects (subsequent visits).

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

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

The study data is the sole property of the Sponsor and shall not be made available in any form to third parties, except for authorized representatives of appropriate CA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study site as part of the Investigator file.

Any delegation of collection of data shall be specified and recorded.

9.2.1 Data entry

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

9.2.2 The query process

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

9.2.3 User identification

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

9.2.4 Audit trail

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

9.3 Source documents

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

subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

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

These shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, shall be clearly identified with the 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 CA inspections and shall provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed ICF and detailed records of study product accountability). The records shall be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records shall be documented and the Sponsor shall be informed in writing.

The Sponsor shall verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record or other relevant source.

9.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, ICF, study product accountability records, source documents, and other study documentation must be retained for 15 years after study completion or longer if required by national legislation. Sponsor will inform the site(s) as to when these documents no longer needs to be retained. Measures shall be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fireproof cabinet).

After study completion and database lock, a security sealed CD with electronic study data shall be provided by the eCRF vendor for archiving.

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 Analysis populations

The following populations will be defined:

- Safety — Includes all subjects who were injected with study product.
- Modified Intention-to-treat (MITT) — Includes all treatment compliant subjects, i.e. subjects treated at both baseline and 3 weeks.

All efficacy analyses will be based on the MITT population. Safety analysis is performed based on the safety population set.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

10.2 Demographics, baseline assessments, and subject characteristics

Demographic endpoints and subject characteristics will be presented by investigational product using descriptive statistics.

10.3 Efficacy analysis

All analyses will be performed by treatment group and in total.

The GAIS assessment will be presented in frequency tables at each follow-up visit and for each evaluator separately (CCI /Investigator). In addition, the proportion of improved subjects (assessed as very much improved, much improved or improved) will be presented together CCI .

CCI [redacted]

The subject satisfaction questionnaire assessments will be presented in frequency tables at each applicable visit. For the questions where the answer is given using an agreement scale the number and percentage of subjects agreeing (Definitely agree/Somewhat agree) to the assessment will also be presented.

The evaluation of naturalness, CCI [redacted] will be presented in frequency tables at each follow-up visit and for each evaluator separately (CCI /Investigator). CCI [redacted]

10.4 Safety analysis

Adverse events will be summarised in frequency tables by study product, containing number of subjects with no AEs, number of subjects with at least one AE, and number of events, subdivided by related/unrelated, serious/non-serious. All AEs will be summarised and listed by system organ class (SOC) and preferred term (PT) assigned using MedDRA. Furthermore, AEs will be summarised by causality, and both related and unrelated events will be summarised separately by maximum intensity. For related AEs, i.e. AEs judged by the Investigator or Sponsor to be related to the study product and/or study product injection procedure, the number of days to onset and the duration of the event will be summarised by PT.

10.5 Handling of missing data

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

10.6 Interim analysis

Since this is an open study, available data may be analysed prior to study completion.

10.7 Withdrawals and deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with CSP deviations will be listed individually, including subject number and observed deviation.

Deviations from the statistical plan will be documented in the statistical report or the Clinical Study Report.

10.8 Sample size

The sample size of approximately 60 subjects (30 per treatment group) is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of effectiveness and safety of the two treatment approaches when treating the chin, NLFs and MLs with Restylane Defyne.

11. Protection of personal data

The study shall include collection and processing of personal data as specified in the Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR) on the protection of

individuals with regard to the processing of personal data. For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

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.

The ICF 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 withdrawal of consent will be used in the evaluation of the study, however no new data may be collected. Authorized representatives from the Sponsor, contract research organization (CRO) or a CA may visit the study site to perform audits/inspections, including source data verification, i.e. comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

12. Quality Control and Quality Assurance

12.1 Quality control

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

Any CSP deviation shall be documented appropriately, verified, discussed, and collected by the monitor and appropriate actions will be taken. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those that occur under emergency circumstances, to the Sponsor as well as the IEC if required by national regulations. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study.

12.2 Quality assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate CA. 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, 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 CA, 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 CA, 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 CA. Such deviations should be documented and reported to the IEC and CA 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. Q-Med AB's obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The Institution/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

14. Publication Policy

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

The aim is to submit the results of this study for publication in the public database ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study 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[§§]. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

15. Suspension or Premature Termination

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

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

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

16. Summary of Changes

Section in the clinical study protocol	Rational for changes	Description of changes
Throughout the protocol	Administrative and editorial changes	Correction of spelling mistakes and change of address to investigational site
8.1.1 Definition of an adverse event	MDR article 2(57)	The definition of an adverse event has been updated according to MDR article 2(57)
8.1.2 Definition of a serious adverse event	MDR article 2(58)	The definition of a serious adverse event has been updated according to MDR article 2(58)

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

Section in the clinical study protocol	Rational for changes	Description of changes
8.1.3.2 Causal relationship and seriousness	MDR article 2(58)	The definition of a serious adverse event has been updated according to MDR article 2(58) to include four different levels of causality
Appendix 3 Instructions for Use	Incorrect IFU in version 1.0 of the CSP **NOTE:** The incorrect IFU was replaced in an intermediate version of the CSP between version 1.0 and 2.0. This intermediate CSP version has been used for all submissions to ECs and CAs. The IFU can be replaced without changing the CSP version as stated in Appendix 3 (page 1), the change was therefore not considered to require a CSP version update.	*Instructions for Use – Restylane Defyne (Version 4.0, Effective date: 2019-12-09)* was replaced by: *Instructions for Use – Restylane Defyne (Version 3.0, Effective date: 2015-12-15)*
Appendix 4 Global Aesthetic Improvement Scale (GAIS)	Incorrect GAIS table and instruction	Appendix 4 was updated to match section 7.3 in the CSP

17. References

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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 AEs. 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.

Appendix 2 Investigator Signature Page

Signed Agreement of the Clinical Study Protocol

CTN: 05DF1910

Title of the CSP: A Randomized, Evaluator-Blinded Study to Evaluate Facial Harmony and Subject Satisfaction Using Restylane Defyne in a Stepwise Treatment Approach

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 instructions for use (IFU) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study site

Appendix 3 Instructions for Use – Restylane Defyne (Version 3.0, Effective date: 2015-12-15)

Note: New versions of the IFU might be released during the trial. These changes will not result in protocol amendments and the Investigators will be informed of the updates through other means.

Table of contents

1	INTRODUCTION	1
2	PURPOSE	1
3	SCOPE	1
4	REQUIREMENTS FOR APPROVAL	1
5	RESULTS	2
6	CONCLUSION	9

1. Introduction

This report compiles the information given in the Instructions for Use for Restylane® Defyne™. The information is written in 22 languages:

English, Bulgarian, Croatian, Czech, Danish, Dutch, Finnish, French, German, Greek, Hungarian, Italian, Norwegian, Polish, Portuguese, Rumanian, Russian, Serbian, Slovak, Spanish, Swedish and Turkish. (Article No. 90-98003)

The article number and version of the Instructions for Use together with the revision date expressed by month and year, and the CE marking with Dekra Notified Body number, shall be inserted in the printed Instructions for Use.

2. Purpose

The purpose of the Instructions for Use is to ensure that the user gets the information needed to handle the device safely.

3. Scope

The Instructions for Use is supplied with Restylane Defyne, 1 ml in EU.

4. Requirements for approval

The contents of the Instructions for Use must be in accordance with Medical Device Directive, Council Directive 93/42/EEC, SS-EN 1041 and ISO 15223.

Relevant parts from Summary of Product Characteristics for medicinal products containing lidocaine should be included.

5. Results

Front page:

Restylane® (logotype)

DEFYNE™

THE Emervel® COLLECTION

Injectable Gel with Lidocaine

Information pages (English presented below):

INSTRUCTIONS FOR USE (EN)

I. COMPOSITION

Cross-linked hyaluronic acid	20 mg/mL
Lidocaine hydrochloride	3 mg/mL
Phosphate buffered saline pH 7	qs ad 1 mL

II. DESCRIPTION

Restylane® Defyne™ is a sterile, biodegradable, transparent gel of non-animal cross-linked hyaluronic acid with the addition of lidocaine hydrochloride 3 mg/mL. The gel is supplied in a prefilled plastic syringe. The contents of the syringe are sterilized using moist heat. The syringe is packaged individually in a blister, with two 27G x ½" Ultra thin wall needles. The needles have been sterilized using irradiation. The product is for single use only. To ensure traceability the package includes patient record labels that should be attached to patient records.

III. INTENDED USE

The product is intended to augment the volume of facial tissues. It is recommended to be used for correction of severe wrinkles, or to redefine the shape of the lips, cheeks or tear troughs. Depending on the area to be treated and the tissue support, the product should be injected in the mid to deep dermis, submucosal layer of the lips, subcutis or supraperiostic

zone. Lidocaine is added to the formulation to diminish the pain resulting from the injection during the treatment.

The product is only intended to be used by authorized personnel in accordance with local legislation, trained in the appropriate injection techniques. Before the first treatment session, it is recommended to contact your local Galderma representative or Restylane distributor for information about training opportunities.

IV. MODE OF ACTION

The product adds volume to the tissue thereby restoring the skin contours of the face to the desired level. The volume and lifting capacity originate from the ability of cross-linked hyaluronic acid to bind water.

V. CONTRAINDICATIONS

- Patients presenting with known allergy to hyaluronic acid filler or amide local anaesthetics
- Patients presenting with porphyria

VI. WARNINGS

- Do not use where there is active disease, such as inflammation, infection or tumours, in or near the intended treatment site.
- Do not inject intravascularly. As for other injectable medical devices, inadvertent injection into or next to blood vessels could potentially lead to vascular occlusion or compression, ischemia and necrosis.
- Do not use in patients with bleeding disorders or in patients who are taking thrombolytics or anticoagulants.
- Do not inject this product into an area where an implant other than hyaluronic acid has been placed.
- Do not resterilize.
- Do not mix with other products.

VII. PRECAUTIONS FOR USE

General considerations relevant to injectable medical devices

- Knowledge of the anatomy of treatment site and special caution are required in order to avoid perforation or compression of vessels, nerves and other vulnerable structures.
- Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections are to be observed.
- Special caution should be exercised when treating areas with limited collateral circulation, due to increased risk of ischemia.
- Special caution should be exercised in treating facial areas with limited soft tissue support or soft tissue cover, such as the periorbital area, to avoid formation of palpable lumps.
- Patients with pre-existing pigmented dark lower eye lid circles, thin skin and pre-existing tendency toward oedema formation are not suitable candidates for treatment of the lower periorbital region.
- Patients using immunosuppressants are not suitable candidates for treatment.
- Special caution should be exercised in treating patients with a tendency to form hypertrophic scars or any other healing disorders.
- Injection procedures can lead to reactivation of latent or subclinical herpes viral infections.
- Patients who are using substances that affect platelet function, such as aspirin and nonsteroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.
- Patients with unattainable expectations are not suitable candidates for treatment.
- Do not use the product if the package is damaged.
- Do not use the product if the contents of the syringe are cloudy.

Specific considerations relevant to the use of this product

- Considerations should be given to the total dose of lidocaine administered if dental block or topical administration of lidocaine is used concurrently. High doses of lidocaine (more than 400 mg) can cause acute toxic reactions manifesting as symptoms affecting the central nervous system and cardiac conduction.

- Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g., certain anti-arrhythmics, since the systemic toxic effects can be additive.
- Lidocaine should be used cautiously in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function or severe renal dysfunction.
- If the product is injected too superficially this may result in visible lumps and/or bluish discoloration.
- The patient must avoid exposing the treated area to heat (sun bathing, sauna, steam baths, etc.) or extreme cold until any signs of local inflammation have disappeared.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is performed after treatment with this product there is a theoretical risk of eliciting an inflammatory reaction at the implant site. This also applies if the product is administered before the skin has healed completely after such a procedure.
- At each treatment session a maximum dosage of 2 mL per treatment site is recommended.
- This product has not been tested in pregnant or breastfeeding women.
- Do not use in children.

VIII. ADVERSE EVENTS

Patients must be informed of the potential risks and adverse events related to the injection procedure and to the use of this product.

The following post market adverse events have been reported (non-exhaustive list): angioedema, atrophy/scaring, blisters, bruising, capillary disorders such as telangiectasia, dermatitis, discoloration, erythema, hypersensitivity, induration, infection, inflammation, ischemia/necrosis, mass, neurological symptoms such as paraesthesia, pain/tenderness, papules/nodules, pruritus, reactivation of herpes infection, short duration of effect, swelling and urticaria.

Other potential adverse events that have been reported following injection of hyaluronic acid gels in general and may occur when using the product include the following: abscess, acne, device dislocation, fistula, granuloma, rash and visual disturbance.

Injection related adverse events such as bruising, erythema, itching, swelling, pain and tenderness generally resolve spontaneously within one week after injection.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as ischemia or necrosis at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolisation. Following facial aesthetic treatments isolated rare cases have been reported regarding ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction. After injections of the nose ischemia/necrosis may occur, especially in patients who had prior rhinoplasty.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions infections should be excluded and treated if necessary since inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended. In case of persistent or recurrent inflammatory symptoms, consider removal of the product by aspiration/drainage, extrusion or enzymatic degradation (use of hyaluronidase has been described in scientific publications). Before any removal procedure is performed, the swelling may be reduced by using e.g. NSAID for 2-7 days or a short course of corticosteroids for less than 7 days, in order to more easily palpate any remaining product.

For patients who have experienced medically important adverse events, a decision for retreatment should take into consideration the cause and severity of previous reactions.

For reporting adverse events contact your local Galderma representative or distributor for this product.

IX. PERFORMANCE

In a randomized controlled multicenter study with Restylane Defyne for correction of moderate to severe nasolabial folds, 69.8% of subjects maintained a clinically significant improvement at 48 weeks after treatment.

X. TREATMENT PROCEDURE

Inform the patient about the precautions to be taken, the expected result and the possible adverse events.

It is important to use a sterile, appropriate needle or blunt cannula. Suitable needles (27G x ½" Ultra thin wall) are supplied with the syringe in the blister pack. As an alternative, a blunt thin walled cannula with a recommended size of 27G can be used.

Assembling the needle/cannula and syringe:

- use surgical gloves
- unscrew the protective cap from the stopper
- carefully remove the stopper from the syringe
- firmly screw the needle/cannula with its shield onto the tip of the syringe
- remove the shield just before injection

Cleanse the area to be treated with an antiseptic and allow it to dry before injection.

To avoid breakage of the needle/cannula, do not attempt to bend or otherwise manipulate it before or during treatment.

Before injecting the product, depress the plunger rod carefully until a small droplet is visible at the tip of the needle/cannula.

Align the bevel of the needle by turning the syringe on its axis. If a blunt cannula is used, an entry point is made in the skin, for example with a sharp needle of appropriate size.

Aspiration is recommended prior to injection in order to reduce the risk of inadvertent injection into a blood vessel. Inject slowly. During injection, keep the side hole of the cannula facing downwards, away from the skin surface.

Inject the gel by gently pressing down on the plunger rod with the thumb or palm of the hand.

Choose from a variety of injection techniques, i.e. serial puncture, linear threading or cross-hatching.

It is recommended to change needle/cannula for each new treatment site.

Defects should be fully corrected, but not overcorrected, at each treatment session.

If "blanching" of the skin is observed as a result of over-superficial injection, the whitened area should be massaged gently until it returns to a normal colour.

Gently massage the treated area after injection.

The syringes and needles/cannulas must be discarded immediately after use in accordance with accepted medical practice and applicable national, local or institutional guidelines. The product shall not be reused due to risk for contamination of unused material and the associated risk including infection.

Standard precautions apply when handling the needles. Needles should be disposed in a container dedicated for sharp devices.

XI. SHELF LIFE AND STORAGE

Do not use after the expiry date indicated on package. Store up to 25°C. Protect from freezing and sunlight.

XII. MANUFACTURER

Q-Med AB, Seminariegatan 21, SE-75228 Uppsala, Sweden

Phone +46(0)18 474 90 00, Fax +46(0)18 474 90 01

www.q-med.com, e-mail: info.q-med@galderma.com

Last pages

CCI

Manufacturer of the needles in the blister pack: (only in English)

GALDERMA (logotype)

6. Conclusion

The contents of the Instructions for Use are in accordance with Medical Device Directive, Council Directive 93/42/EEC, SS-EN 1041 and ISO 15223.

Summary of Product Characteristics for medicinal products containing lidocaine have been evaluated and relevant parts have been included.

Appendix 4 Global Aesthetic Improvement Scale (GAIS)

The 5-graded GAIS will be used to live assess the aesthetic improvement of the treatment area by the Treating Investigator and CCI, by comparing to a photograph taken at the baseline visit before the first treatment.

The Treating Investigator and CCI will, independently of each other, respond to the question: "How would you describe the subject's/CCI aesthetic appearance of the lower face, i.e. the treated area, compared to the photographs taken before treatment?" by using the respective categorical scale below.

Global Aesthetic Improvement Scale

Rating (CCI)	**Description (for the Investigator and CCI)**
Very much improved	Optimal cosmetic result for the subject.
Much improved	Marked improvement in appearance from the original condition, but not completely optimal for this subject.
Improved	Obvious improvement in appearance from the original condition.
No change	The appearance is essentially the same as the original condition.
Worse	The appearance is worse than the original condition.

Appendix 5 Naturalness, CCI [redacted] (Investigator's questionnaire)

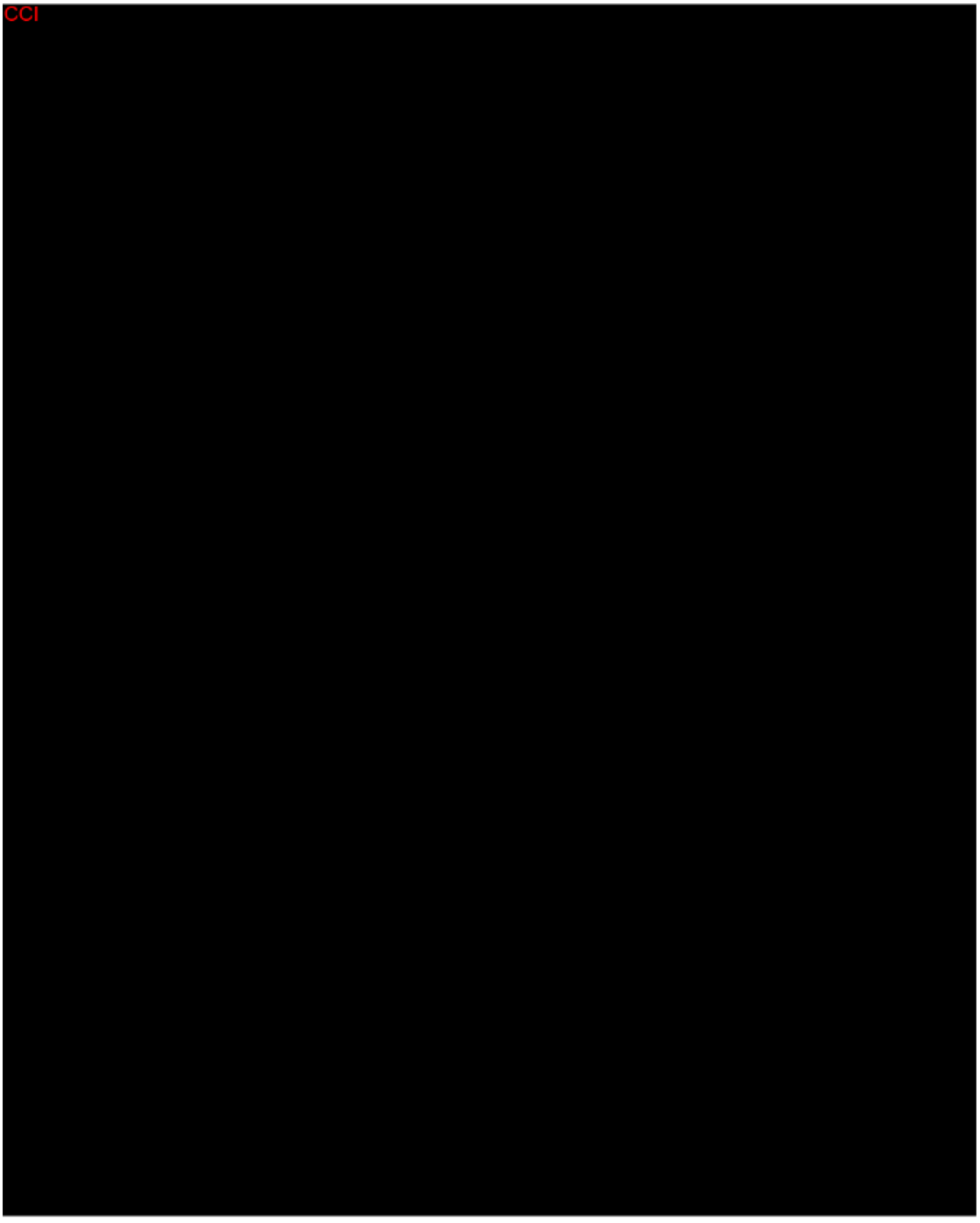
Naturalness

The Investigator will assess naturalness of the treatment result based on review of baseline photographs and live assessment by indication how much they agree or disagree to the statement: "The treatment results are natural looking"

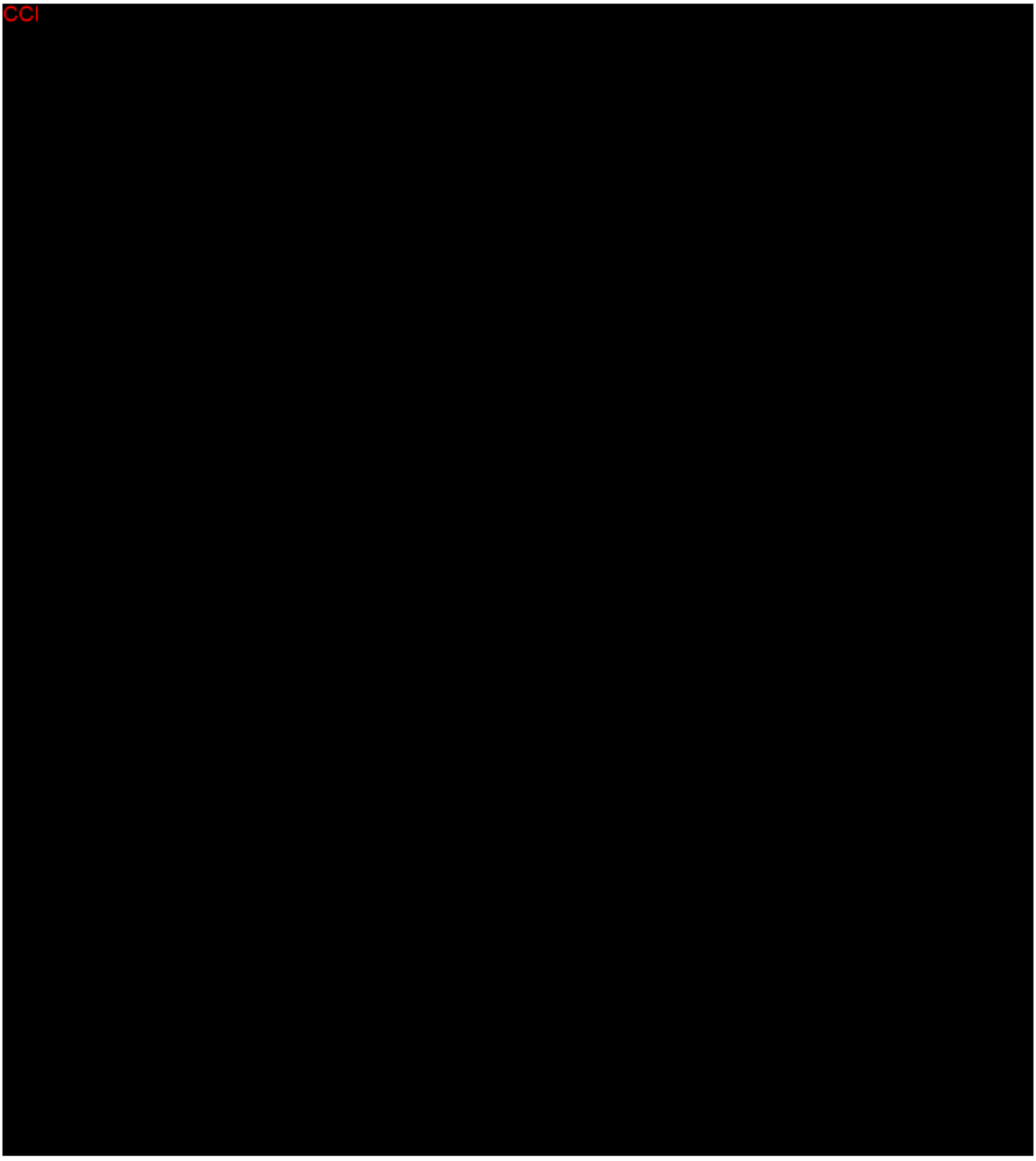
CCI [redacted]

GALDERMA	Title **05DF1910 Clinical Study Protocol**	Doc id **MA-42248**

GALDERMA	Title **05DF1910 Clinical Study Protocol**	Doc id **MA-42248**



GALDERMA	Title **05DF1910 Clinical Study Protocol**	Doc id **MA-42248**



Appendix 9 Subject satisfaction questionnaire

1 My first treatment improved my appearance

2 Compared to my first treatment, treating both areas in combination improved my appearance

3 I am satisfied with the contour of my lower face after treatment

4 I am satisfied with the shape of my chin

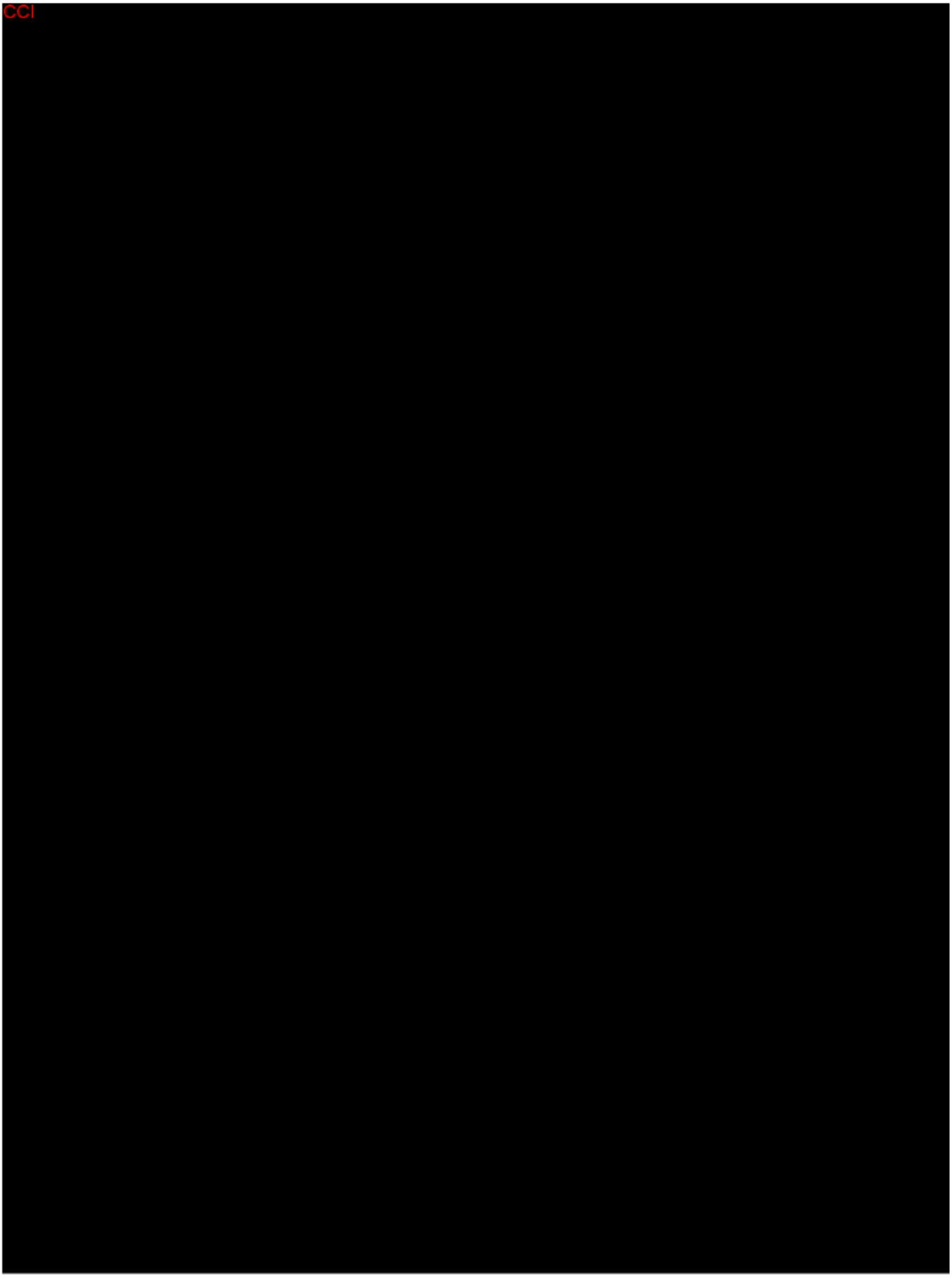
5 I am satisfied with how well defined my chin looks

6 I feel more attractive after treatment

7 I feel comfortable being photographed

GALDERMA	Title **05DF1910 Clinical Study Protocol**	Doc id **MA-42248**

CCI



SIGNATURES PAGE

Date	Signed by
2020-09-24 06:18	PPD
Justification	Approved by Technical Expert
2020-09-24 06:38	PPD
Justification	Approved by Technical Expert
2020-09-24 06:52	PPD
Justification	Approved by Project Manager
2020-09-24 09:16	PPD
Justification	Approved by Technical Expert
2020-10-02 11:10	PPD
Justification	Approved by PPD