	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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**A randomised, evaluator-blind comparative study to evaluate performance and safety of Restylane Lidocaine and no-treatment control for treatment of depressed facial acne scars**

Study product: Restylane<sup>®</sup> Lidocaine

Clinical trial number (CTN): 05DF1605

Coordinating Investigator:




Sponsor:

Q-Med AB



**Confidentiality Statement**

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

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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## Investigators and Study Administrative Structure

Coordinating Investigator:

[REDACTED]

Principal Investigator(s):

[REDACTED]

[REDACTED]

Sponsor:

Q-Med AB

[REDACTED]

Medical expert:

[REDACTED]

Study director:

[REDACTED]

Study statistician:

[REDACTED]

Contract research organisation (CRO):

[REDACTED]


Monitor(s):

To be decided

Provider of eCRF:

[REDACTED]

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

	<small>Title</small> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<small>Doc id</small> <b>MA-31665</b>
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## Sponsor Signatures

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

**Head of Medical Affairs, Q-Med AB**

[Redacted signature]

**Clinical Project Manager, Q-Med AB**

[Redacted signature]

**Study Director, Q-Med AB**

[Redacted signature]

**Statistician, Q-Med AB**

[Redacted signature]


**Medical Expert, Q-Med AB**

[Redacted signature]

Effective date: 2016-10-27 12:36

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Version: 3.0

	<small>Title</small> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<small>Doc id</small> <b>MA-31665</b>
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## Signed Agreement of the Clinical Study Protocol

CTN: 05DF1605

Title of the CSP: A randomised, evaluator-blind comparative study to evaluate performance and safety of Restylane Lidocaine and no-treatment control for treatment of depressed facial acne scars

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

Effective date: 2016-10-27 12:36

Effective

Version: 3.0

	<small>Title</small> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<small>Doc id</small> <b>MA-31665</b>
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## Synopsis

<b>Title of study:</b>	A randomised, evaluator-blind comparative study to evaluate performance and safety of Restylane Lidocaine and no-treatment control for treatment of depressed facial acne scars
<b>Clinical Trial Number:</b>	05DF1605
<b>Number of sites and subjects:</b>	Approximately 60 subjects will be recruited at 3-5 sites. Approximately 12-25 subjects will be included per site.
<b>Coordinating Investigator:</b>	[REDACTED]
<b>Principal Investigators:</b>	[REDACTED]
<b>Primary Objective:</b>	To show greater improvement in depressed facial acne scars treated with Restylane Lidocaine compared with untreated depressed facial acne scars in the same subject using a split-face design. The primary endpoint is proportion of subjects for whom the cheek treated by Restylane Lidocaine has a lower scar severity compared to the opposite untreated cheek [REDACTED]
<b>Secondary Objectives:</b>	<p>Assessment of:</p> <ul style="list-style-type: none"> <li>• Aesthetic improvement of depressed facial atrophic acne scars using the Global Aesthetic Improvement Scale (GAIS) [REDACTED]</li> </ul> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

Effective date: 2016-10-27 12:36

Effective

Version: 3.0

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------


Effective date: 2016-10-27 12:36

**Study Design:**

This is a 12-month prospective, randomised, evaluator-blinded, multi-centre study to evaluate performance and safety of facial acne scars treatment with Restylane Lidocaine by comparing with no-treatment control using a split-face design. Subjects will be randomised to receive treatment with Restylane Lidocaine on either the right or left cheek and no treatment on the opposite cheek.

**Inclusion criteria:**

1. Presence of 5-20 [REDACTED] scars with a diameter of up to approximately 4 mm within the treatment area [REDACTED]
2. Similar type, size and number of scars on both cheeks [REDACTED]
3. Intent to undergo treatment of depressed acne scars
4. Men or non-pregnant, non-breast feeding women [REDACTED]
5. Fitzpatrick skin type I-IV [REDACTED]
7. Signed and dated informed consent to participate in the study [REDACTED]


	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

<b>Exclusion criteria:</b>	<ol style="list-style-type: none"> <li>1. Presence of more than 3 scars per cheek (within the treatment area) of the following types: icepick scars or atrophic acne scars with a diameter of &gt; 4 mm.</li> <li>2. Active acne with inflammatory component</li> <li>3. Use of per oral or topical (facial) substances containing retinoids, bensoyl peroxide, alpha-hydroxy acid at concentrations above 10%, beta-hydroxy acid at a concentration above 2%, or antibiotic treatment for active acne within 4 months before treatment</li> <li>4. Use of isotretinoin within 6 months before treatment</li> <li>5. Post-surgical scars in the treatment area</li> </ol> <div data-bbox="619 741 1391 1512" style="background-color: black; height: 344px; width: 100%;"></div> <ol style="list-style-type: none"> <li>12. Previous tissue augmenting therapy or contouring with permanent filler or fat-injection in the treatment area</li> <li>13. Previous tissue augmenting therapy, contouring or revitalisation treatment with Calcium Hydroxyapatite (CaHa), or Poly L-Lactic Acid (PLLA), in the treatment area within 24 months before treatment</li> <li>14. Previous tissue augmenting therapy, contouring or revitalisation treatment with non-permanent filler such as HA or collagen in the treatment area within 12 months before treatment</li> <li>15. Previous tissue revitalisation treatment with neurotoxin, laser or light, mesotherapy, chemical peeling or dermabrasion in the treatment area within 6 months before treatment</li> <li>16. Previous surgery including aesthetic facial surgical</li> </ol>

*Effective*


Version: 3.0

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

	<p>therapy, liposuction, or tattoo in the treatment area</p> <p>[REDACTED]</p> <p>23. Any medical condition that, in the opinion of the treating Investigator, would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease that may interfere with the outcome of the study)</p> <p>[REDACTED]</p>
<b>Investigational product, dose and mode of administration:</b>	<p>Commercially available Restylane Lidocaine (Q-Med AB, Sweden, Uppsala)</p> <p>[REDACTED]</p>
<b>Reference therapy, mode of administration:</b>	<p>Not applicable. The reference is a no-treatment control.</p>
<b>Duration of treatment and follow-up:</b>	<p>Subjects will be followed for 12 months after the first treatment with Restylane Lidocaine.</p> <p>[REDACTED]</p> <p>Each subject will be involved in the study for approximately 12-14 months.</p>




	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36



<b>Efficacy Assessments:</b>	<ul style="list-style-type: none"> <li>GAIS assessment [REDACTED]</li> <li>[REDACTED]</li> <li>Assessment of acne scar severity [REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>
<b>Safety Assessments:</b>	<ul style="list-style-type: none"> <li>Assessments of anticipated post-treatment events [REDACTED]</li> <li>Safety should also be assessed by recording AEs and device deficiencies throughout the study</li> </ul>
<b>Statistical Methods:</b>	[REDACTED]


*Effective*

Version: 3.0

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

## Abbreviations and Definitions of Terms

AE	Adverse event
Blinded evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject.
CE	French: <i>Conformité Européenne</i>
Coordinating Investigator	Investigator who is appointed by the Sponsor to coordinate work in a multicenter study
CRF	Case report form
CRO	Contract research organisation
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
First treatment	Initial injection of study product
First subject in	First subject screened, i.e. who signs the informed consent form
First subject out	First subject who completed his/her last study visit
G	Gauge
	
GCP	Good clinical practice
HA	Hyaluronic acid
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFU	Instructions for use
Investigational product	Medical device being assessed for safety or performance in a study. “Investigational product” is the same as “study device”, “investigational device”, or “investigational medical device”.
Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.
Investigator	The Principal Investigator (PI) or other qualified person, i.e. sub-investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log
Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
ISO	International Organization for Standardization
ITT	Intention-to-treat
MedDRA	Medical dictionary for regulatory activities


	<small>Title</small> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<small>Doc id</small> <b>MA-31665</b>
--	--	--

Effective date: 2016-10-27 12:36

NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
Reference product	Medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a study
SAE	Serious adverse event
█	█
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
Study files	The Investigator file and the Sponsor file
Study products	The investigational product and the reference product under study
Study site	Institution or site where the study is carried out
█	█
TW	Thin walled (needles)
U-HCG	Urinary human chorionic gonadotropin


*Effective*

Version: 3.0

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------


## Table of Contents

<b>INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE</b>	<b>2</b>
<b>SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL</b>	<b>4</b>
<b>SYNOPSIS</b>	<b>5</b>
<b>ABBREVIATIONS AND DEFINITIONS OF TERMS</b>	<b>10</b>
<b>LIST OF TABLES</b>	<b>15</b>
<b>LIST OF FIGURES</b>	<b>15</b>
<b>LIST OF APPENDICES</b>	<b>15</b>
<b>1. ETHICAL CONSIDERATIONS</b>	<b>16</b>
1.1 Statement of ethical compliance	16
1.2 Application to independent ethics committee	16
<b>2. BACKGROUND INFORMATION</b>	<b>16</b>
2.1 Indication and population description	16
2.2 Investigational product description	16
2.3 Reference product description	17
2.4 Previous experience	17
2.4.1 <i>Non-clinical documentation</i>	17
2.4.2 <i>Clinical documentation</i>	17
2.5 Study rationale	17
2.6 Justification for the design of the study	18
2.7 Risks and benefits	18
<b>3. OBJECTIVES AND ENDPOINTS</b>	<b>19</b>
3.1 Objectives and endpoints of the study	19
<b>4. DESIGN OF THE STUDY</b>	<b>19</b>
4.1 General outline	19
4.2 Number of subjects	20
4.3 Duration of subject participation	20
4.4 Randomisation and blinding	20
4.4.1 <i>Randomisation/treatment assignment</i>	20
4.4.2 <i>Blinding</i>	21
4.4.3 <i>Emergency unblinding</i>	21
4.5 Medical history	21
4.6 Previous and concomitant medications and procedures	21
4.6.1 <i>Definition</i>	21
4.6.2 <i>Categories</i>	21
4.6.3 <i>Recording</i>	22
4.6.4 <i>Authorised concomitant medications/procedures</i>	22
4.6.5 <i>Prohibited concomitant medications and procedures</i>	22

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

4.7	Schedule of events	23
4.8	Visits	24
4.9	Demographics and baseline assessments	27
<b>5.</b>	<b>SUBJECTS</b>	<b>28</b>
5.1	Subject information and informed consent	28
5.2	Inclusion criteria	28
5.3	Exclusion criteria	29
5.4	Screening and subject numbers	30
5.5	Withdrawal of subjects	31
<b>6.</b>	<b>STUDY PRODUCTS</b>	<b>32</b>
6.1	Investigational product	32
6.2	Reference product	32
6.3	Additional products and material	32
6.4	Packaging, labelling, and storage	32
6.4.1	<i>Investigational product</i>	32
6.4.2	<i>Reference product</i>	32
6.5	Product accountability	33
6.6	Treatment	33
6.6.1	<i>Treatment procedure</i>	33
6.6.2	<i>Treatment regimen (volume and interval)</i>	35
6.6.3	<i>Post-treatment care</i>	35
6.6.4	<i>Post-trial provisions</i>	36
6.6.5	<i>Electronic case report form recordings</i>	36
6.6.6	<i>Treatment compliance</i>	36
<b>7.</b>	<b>PERFORMANCE ASSESSMENTS</b>	<b>36</b>
7.1	General information	36
7.2	Photography	37
7.3	Global aesthetic improvement scale	38
		39
7.5	Blinded Evaluator's live assessment of scar severity comparing both cheeks	39


	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

■	■	■
■	■	■
■	■	■
■	■	■
<b>8.</b>	<b>SAFETY ASSESSMENTS</b>	<b>41</b>
8.1	Anticipated, post-treatment events and local tolerability	41
8.2	Adverse events	41
8.2.1	<i>Definition of an adverse event</i>	41
8.2.2	<i>Definition of a serious adverse event</i>	42
8.2.3	<i>Definition of adverse events of special interest</i>	42
8.2.4	<i>Recording instructions</i>	42
8.2.5	<i>Reporting of adverse events</i>	43
8.2.6	<i>Reporting of serious adverse events</i>	44
8.2.7	<i>Follow-up of unresolved events after termination of the study</i>	45
8.2.8	<i>Pregnancy</i>	45
8.3	Device deficiencies	45
8.3.1	<i>Definition of a device deficiency</i>	45
8.3.2	<i>Recording instructions</i>	46
8.3.3	<i>Reporting of device deficiencies</i>	46
8.4	Data safety monitoring board	46
<b>9.</b>	<b>DATA HANDLING AND MANAGEMENT</b>	<b>47</b>
9.1	Data management	47
9.2	Electronic case report forms	47
9.2.1	<i>Data entry</i>	47
9.2.2	<i>The query process</i>	48
9.2.3	<i>User identification</i>	48
9.2.4	<i>Audit trail</i>	48
9.3	Source documents	48
9.4	Record keeping and access to source data	49
9.5	Document and data retention	49
<b>10.</b>	<b>STATISTICAL METHODS</b>	<b>49</b>
10.1	General	49
10.2	Analysis populations	50
10.3	Demographics, baseline assessments, and subject characteristics	50
10.4	Performance analysis	50
10.4.1	<i>Primary analysis</i>	50
10.4.2	<i>Secondary analysis</i>	50
10.5	Safety analysis	51
10.6	Handling of missing data	51

Effective

Version: 3.0

	<small>Title</small> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<small>Doc id</small> <b>MA-31665</b>
--	--	--

10.7	Analysis of data during the study	51
10.8	Withdrawals and deviations	51
10.9	Sample size	51
<b>11.</b>	<b>PROTECTION OF PERSONAL DATA</b>	<b>52</b>
<b>12.</b>	<b>QUALITY CONTROL AND QUALITY ASSURANCE</b>	<b>53</b>
12.1	Quality control	53
12.2	Quality assurance	53
12.3	Changes to the clinical study protocol	53
<b>13.</b>	<b>FINANCING, INDEMNIFICATION, AND INSURANCE</b>	<b>54</b>
<b>14.</b>	<b>PUBLICATION POLICY</b>	<b>54</b>
<b>15.</b>	<b>SUSPENSION OR PREMATURE TERMINATION</b>	<b>54</b>
<b>16.</b>	<b>REFERENCES</b>	<b>55</b>


## List of Tables


## List of Figures

--	--

## List of Appendices

Appendix 1	Declaration of Helsinki .....	57

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

## 1. Ethical Considerations

### 1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2011 shall be followed. The International Conference on Harmonisation (ICH) guideline for GCP (E6) shall be followed as applicable for medical device. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix 1).

### 1.2 Application to independent ethics committee

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

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

## 2. Background Information

[REDACTED]

[REDACTED]

[REDACTED]



Effective date: 2016-10-27 12:36

\_\_\_\_\_

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\_\_\_\_\_

[REDACTED] [REDACTED]

[REDACTED]

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\_\_\_\_\_, \_\_\_\_\_

Age Group	Gender	U.S. should take action (%)	U.S. should not take action (%)
18-29	Male	85	15
18-29	Female	85	15
30-49	Male	80	20
30-49	Female	80	20
50-69	Male	75	25
50-69	Female	75	25
70+	Male	65	35
70+	Female	65	35

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[REDACTED] [REDACTED]

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	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

[REDACTED]

### 3. Objectives and Endpoints

#### 3.1 Objectives and endpoints of the study

The **primary** objective of the study is to show greater improvement in depressed facial acne scars treated with Restylane Lidocaine compared with untreated depressed facial acne scars in the same subject using a split face design. The primary endpoint is proportion of subjects for whom the cheek treated by Restylane Lidocaine has a lower overall scar severity compared to the untreated opposite cheek [REDACTED]

The **secondary objectives** of the study are to evaluate acne scar treatment by assessing:

- Aesthetic improvement of depressed facial atrophic acne scars using the Global Aesthetic Improvement Scale (GAIS) [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Short- and long-term safety throughout the entire study by collecting AEs and device deficiencies


### 4. Design of the Study

#### 4.1 General outline

This is a 12-month prospective, randomised, evaluator-blinded, multi-centre study to evaluate performance and safety of facial acne scars treatment with Restylane Lidocaine by comparing with no-treatment control. A split-face design will be used, i.e. subjects will be randomised to treatment with Restylane Lidocaine on the right or left cheek and no treatment on the other cheek.

Blinding will be accomplished by using a treating Investigator to administer the treatment and a blinded evaluator, to whom randomisation and treatment assignment are concealed, to conduct the assessments. The subjects and Sponsor will not be blinded to treatment assignment.

The first treatment will be administered by the treating Investigator according to a standardised procedure. [REDACTED]

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

[REDACTED]

Subjects will be followed for 12 months [REDACTED]  
[REDACTED] Photographs will be taken before treatment and during each follow-up visit.

AEs device deficiencies will be recorded after treatment by the treating Investigator. Anticipated post-treatment events of expected severity do not have to be recorded as AEs in the eCRF (Section 8.1). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 4.2 Number of subjects

Approximately 60 subjects will be recruited at 3-5 sites. The duration of the enrolment period is expected to approximately 3 months.

Approximately 12-25 subjects will be included per site.


## 4.3 Duration of subject participation

A subject will be involved in the study for approximately 12-14 months.

## 4.4 Randomisation and blinding

### 4.4.1 Randomisation/treatment assignment

Before starting the study, a randomisation list will be generated by a statistician. Treatment assignment for each cheek (Restylane Lidocaine to right or left cheek and no treatment on the

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

other cheek) will be randomised for each subject when all inclusion criteria and exclusion criteria have been verified at the treatment visit. Right or left side/cheek is defined as the subject's right or left side in this study protocol.

All treatment information will be kept by the treating Investigator during the study not to be disclosed to the blinded evaluator.

#### 4.4.2 Blinding

The blinded evaluator shall not be allowed to retrieve study supplies or to be present during opening of the study supplies or injections. The treating Investigator or the subjects are not allowed to discuss treatments with the blinded evaluator. All documents with information about study product and treatment shall be kept separately and not available to the blinded evaluator.

The treating Investigator, the subjects, Sponsor and the Sponsor representative shall not be blinded to treatment assignment during the study.

#### 4.4.3 Emergency unblinding

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

### 4.5 **Medical history**

History of surgical events and medical conditions that are judged as relevant by the treating Investigator shall be documented in the eCRF using medical terminology in English.

### 4.6 **Previous and concomitant medications and procedures**

#### 4.6.1 Definition

Previous medications or procedures are defined as therapies that have been stopped within 1 day preceding the Screening visit.

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

#### 4.6.2 Categories

The following two categories are to be considered for previous and concomitant medications or procedures:

- Medications [REDACTED]
- Medical and surgical procedures [REDACTED]

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

#### 4.6.3 Recording

Previous and concomitant medications and procedures administered during the study are to be recorded on the dedicated forms in the eCRF. Concomitant medications and procedures are to be recorded, reviewed, and updated at each visit. The generic name or the trade name of all concomitant medications or a description of the procedure and the reason for its use shall be documented in the eCRF. Any new concomitant medication/procedure or modification of an existing therapy may be linked to an AE or medical history. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

#### 4.6.4 Authorised concomitant medications/procedures


Unless listed under the exclusion criteria (Section 5.3) or in prohibited concomitant medications/procedures (Section 4.6.5), all medications/procedures are authorised.

#### 4.6.5 Prohibited concomitant medications and procedures

[REDACTED]	
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]
■	[REDACTED]

Participation in any other clinical study is prohibited.


If a subject receives prohibited therapy during the study, a protocol deviation should be documented.

	<small>Title</small> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<small>Doc id</small> <b>MA-31665</b>
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	<div>Title</div> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<div>Doc id</div> <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

*Effective*

Version: 3.0

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	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

*Effective*

Version: 3.0

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	<div>Title</div> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<div>Doc id</div> <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

*Effective*

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	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

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[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		

## 5. Subjects

### 5.1 Subject information and informed consent

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

It is the responsibility of the PI or his/her authorised 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 affect on his/her future medical care, treatment or benefits to which the subject is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the informed consent form and to consider participation in the study. Before any study-related activities are performed, the informed consent form shall be personally signed and dated by the subject and the PI or delegated Investigator. The consent includes information that data will be collected, recorded, processed, and may be transferred to other EU or 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 by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study. The subjects will be recognisable on the photographs, but their names will not be disclosed.


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

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

### 5.2 Inclusion criteria

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

1. Presence of 5-20 [REDACTED] scars with a diameter of up to approximately 4 mm within the treatment area [REDACTED]

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

2. Similar type, size and number of scars on both cheeks [REDACTED]

3. Intent to undergo treatment of depressed acne scars

4. Men or non-pregnant, non-breast feeding women [REDACTED]

5. Fitzpatrick skin type I-IV

7. Signed and dated informed consent to participate in the study

### 5.3 Exclusion criteria

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

1. Presence of more than 3 scars per cheek (within the treatment area) of the following types: icepick scars or atrophic acne scars with a diameter of > 4 mm.
2. Active acne with inflammatory component
3. Use of per oral or topical (facial) substances containing retinoids, bensoyl peroxide, alpha-hydroxy acid at concentrations above 10%, beta-hydroxy acid at a concentration above 2%, or antibiotic treatment for active acne within 4 months before treatment
4. Use of isotretinoin within 6 months before treatment
5. Post-surgical scars in the treatment area


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

12. Previous tissue augmenting therapy or contouring with permanent filler or fat-injection in the treatment area

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

13. Previous tissue augmenting therapy, contouring or revitalisation treatment with Calcium Hydroxyapatite (CaHa), or Poly L-Lactic Acid (PLLA), in the treatment area within 24 months before treatment
14. Previous tissue augmenting therapy, contouring or revitalisation treatment with non-permanent filler such as HA or collagen in the treatment area within 12 months before treatment
15. Previous tissue revitalisation treatment with neurotoxin, laser or light, mesotherapy, chemical peeling or dermabrasion in the treatment area within 6 months before treatment
16. Previous surgery including aesthetic facial surgical therapy, liposuction, or tattoo in the treatment area

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

23. Any medical condition that, in the opinion of the treating Investigator, would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease that may interfere with the outcome of the study)

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

#### 5.4 Screening and subject numbers

Each subject who has signed the informed consent form will be assigned a screening number and shall be listed on a subject screening and inclusion log.

A “screening failure” is defined as a subject who does not fulfil the eligibility criteria. For screening failures, the screening visit shall be completed to an extent that makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria. The reason for excluding a subject from entering the study shall also be specified in the subject screening and inclusion log.

When the treating Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each subject will be assigned a subject number.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

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

### 5.5 Withdrawal of subjects

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The reason and date for withdrawal shall be documented in the eCRF. When possible, an explanatory comment shall be added in the study termination module to further explain the reason for withdrawal.


If withdrawal of a subject occurs during a regular study visit, the eCRF for that specific visit shall be completed as far as possible together with the study termination eCRF module.

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

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

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

If 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 or is assessed by the Investigator to be "chronic" or "stable". Follow-up information for at least three (3) months shall be provided to the Sponsor.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

## 6. Study Product

The term “study product” refers to Restylane Lidocaine.

### 6.1 Investigational product

Commercially available Restylane (Q-Med AB, Sweden, Uppsala) with lidocaine will be provided by the Sponsor. [REDACTED]

### 6.2 Reference product

Not applicable. The reference in this study is a no-treatment control [REDACTED]

### 6.3 Additional products and material

The study site will provide urine pregnancy tests (U-HCG).

Topical or local anaesthesia 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 study site shall provide adequate equipment in case of emergency.

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]





	<div>Title</div> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<div>Doc id</div> <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

*Effective*

Version: 3.0

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	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

*Effective*

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[REDACTED]

#### 6.6.6 Treatment compliance

The study product shall be injected by the treating Investigator. No other measurements of treatment compliance shall be made.


## 7. Performance Assessments

### 7.1 General information

The methods for collecting performance data include photography (section 7.2), global aesthetic improvement scale<sup>31</sup> (GAIS) (section 7.3), [REDACTED] assessment of scar severity [REDACTED]

Right or left side/cheek is defined as the subject's right or left side in this study protocol.

Version: 3.0

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

To avoid inter-observer variability, every effort should be made by each study site to ensure that the same individual who made the initial baseline assessments completes all corresponding follow-up assessments.

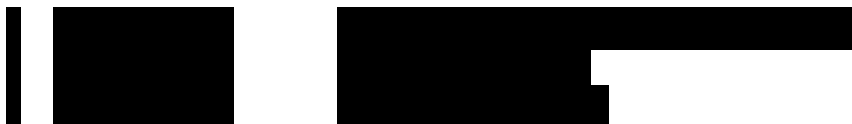
## 7.2 Photography

Standardised photographs shall be taken [REDACTED] prior to the first injection of the study product and at every follow-up visit in order to document treatment effect. Note that no covering make-up should be used on the photographs. Each Investigator and other study site personnel designated to take photographs shall be thoroughly trained in the photographic equipment and techniques before study start, if applicable.

Photographs shall be taken at the baseline visit before treatment. If the photographs are considered as of good quality, the Investigator may proceed with treatment of the subject at the Day 1 visit, which can be scheduled separately from the screening visit or at the same day. If the photographs are considered not good enough, the photography shall be repeated.

[REDACTED] The quality of the photographs should be assessed by the Investigator or other designated person and repeat photography if needed.

All photographs shall be taken against a neutral background and artificial light only. Several lightning modalities, as specified in the separate instruction, including the parallel-polarized modality shall be used. The subject should keep the eyes closed during photography. The subject shall have a neutral facial expression. The photographs shall be taken in a standardised way according to the following scheme:



For further details, please see the instruction of images procedures in [REDACTED] user guide and study specific instructions regarding photography.

Each photograph shall be traceable and labelled with the subject number, the visit number and with which lighting modality 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.



Effective date: 2016-10-27 12:36

*Effective*

Version: 3.0

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Effective date: 2016-10-27 12:36

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Effective

Version: 3.0





	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

## 8. Safety Assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

### 8.2 Adverse events


#### 8.2.1 Definition of an adverse event

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

This definition includes:

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

<sup>a</sup> For users or other persons, this definition is restricted to events related to the investigational product.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

### 8.2.2 Definition of a serious adverse event

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

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
  1. a life-threatening<sup>a</sup> illness or injury, or
  2. a permanent impairment of a body structure or body function, or
  3. in-patient or prolonged hospitalisation<sup>b</sup>, or
  4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to foetal distress, foetal death, or a congenital abnormality or birth defect

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

### 8.2.3 Definition of adverse events of special interest

Not applicable.

### 8.2.4 Recording instructions

Each subject should be questioned about AEs at each study visit following the first treatment. 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 8.3), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported on the clinical study complaint form provided separately.

All AEs in the eCRF shall be recorded, including:

<sup>a</sup> 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).

<sup>b</sup> Planned hospitalisation for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

- a) Event term (recorded in standard medical terminology and avoiding abbreviations)
- b) Description of event and affected area
- c) Start date (first day with symptoms)
- d) Stop date (last day with symptoms)
- e) Intensity (mild, moderate, or severe according to definition in section 8.2.4.1)
- f) Seriousness (serious or not serious, according to definition in section 8.2.2)
- g) Causal relationship to study product or study product injection procedure (yes or no) should be assessed by treating Investigator
- h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
- i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/stable, not recovered at the end of the study)

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

#### 8.2.4.1 Intensity

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

- Mild:** Awareness of symptoms or signs, but easily tolerated (acceptable)
- Moderate:** Enough discomfort to interfere with usual activity (disturbing)
- Severe:** Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.

#### 8.2.4.2 Causal relationship and seriousness

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

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

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


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

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

#### 8.2.5 Reporting of adverse events

Adverse event reporting on each subject shall start after treatment. 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.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

### 8.2.6 Reporting of serious adverse events

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

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

- Subject identification (age, gender, subject number)
- AE description
- Date when AE occurred
- Name of PI and original reporter (if other than the 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 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 medication form/list
- Concomitant procedure/treatment form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

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**E-mail** for SAE reporting:

**Fax** number for SAE reporting:

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


**Surface mail** for providing complementary information:

Galderma Uppsala

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The SAE form must be signed and dated by the treating 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, if applicable according to national regulations. The PI is responsible for checking what reporting

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

procedures are applicable for his/her IEC regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

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

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

#### 8.2.7 Follow-up of unresolved events after 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. Follow-up information for at least three (3) months shall be provided to Sponsor. Final outcome after the end of the study shall be reported on the AE follow-up form.

#### 8.2.8 Pregnancy

Pregnancy itself is not regarded as an AE.

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

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge be submitted to the Sponsor according to contact details specified in section 8.2.6. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to foetal distress, foetal 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 hospitalisation, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

### 8.3 Device deficiencies


#### 8.3.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety<sup>a</sup>, or performance.

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

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<sup>a</sup> Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

Effective date: 2016-10-27 12:36

### 8.3.2 Recording instructions

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

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

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

### 8.3.3 Reporting of device deficiencies

The Investigator shall send the completed clinical study complaint form to the Sponsor using the contact details:

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**E-mail** for device deficiency reporting:



**Fax** number for device deficiency reporting:



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

Galderma Uppsala



A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the Sponsor within 24 hours after the Investigator's awareness (for contact information, see section 8.2.6).


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

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

The deficient study product shall be kept by the study site until the Quality Assurance (QA) complaints group has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study site.

## 8.4 **Data safety monitoring board**

Not applicable.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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## 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. Data validation will be performed by computerised logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

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

### 9.2 Electronic case report forms

A 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and shall be completed electronically for each screened subject (screening visit) and included subjects (subsequent visits).

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

Authorised study site personnel designated by the PI shall complete data collection. Appropriate training and security measures shall be completed with all authorised 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 authorised representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study site as part of the Investigator file.

Any delegation of collection of data shall be specified in a signature and delegation log.

#### 9.2.1 Data entry

All data shall be entered in English. The eCRF should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRF 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 eCRF or in the database. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments are not done, or if certain information is not available, not



	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

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 eCRF 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 authorised designee. The monitor cannot enter data in the eCRF. 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 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 authorised 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 source documents. These shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, shall be clearly identified with the CTN and subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.



	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

#### 9.4 Record keeping and access to source data

The PI/Institution shall permit study-related monitoring, audits, IEC review, and RA inspections and shall provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed informed consent forms and detailed records of study product accountability). The records shall be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records shall be documented and the Sponsor shall be informed in writing.

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

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

#### 9.5 Document and data retention

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

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

[REDACTED]

[REDACTED]

[REDACTED]

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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## 10.2 Analysis populations

The following populations will be defined:


- Safety/Intention-to-treat (ITT)
- Per protocol (PP)

Intention-to-treat is the primary population for all performance analyses. The primary performance outcome will also be analysed with the PP 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.

## 10.3 Demographics, baseline assessments, and subject characteristics

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

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 10.6 Handling of missing data

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

#### 10.7 Analysis of data during the study

Data will be analysed when all subjects have performed their 3-month visit (visit 4). Any withdrawn subjects prior to the 3-month visit will be included in the analyses.

#### 10.8 Withdrawals and deviations

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

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


Deviations from the statistical plan will be documented.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
--	---	---------------------------

## 11. Protection of personal data

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


All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the PI are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and the PI are located. The Sponsor will ensure that all requirements are complied with for data processing, which is carried out in Sweden by the Sponsor.

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

Effective date: 2016-10-27 12:36

Effective

Version: 3.0

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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## 12. Quality Control and Quality Assurance

### 12.1 Quality control

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

Any CSP deviation shall be reported 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 which 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. Handling of CSP deviations will be performed as described in the monitoring manual.

### 12.2 Quality assurance

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

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

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


### 12.3 Changes to the clinical study protocol

The PI and other site personnel involved in the study must not implement any deviation from or changes to the CSP without agreement with the Sponsor and prior review and documented approval from the IEC, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a written protocol amendment. However, administrative changes are to be documented in the Sponsor file without requiring a protocol amendment.

Effective date: 2016-10-27 12:36

Effective

Version: 3.0

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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### 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.<sup>34</sup> 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 RA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons.

The Sponsor may also decide to close a single study site due to unsatisfactory subject 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.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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	<p>Title</p> <p><b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b></p>	<p>Doc id</p> <p><b>MA-31665</b></p>
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	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

## 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.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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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

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

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

### **Privacy and Confidentiality**

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


### **Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

	Title <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	Doc id <b>MA-31665</b>
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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 performance 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 performance. In all cases, new information must be recorded and, where appropriate, made publicly available.

Effective date: 2016-10-27 12:36

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Version: 3.0



	<div>Title</div> <b>Clinical Study Protocol CTN 05DF1605 - Acne scars Restylane vs no-treatment control</b>	<div>Doc id</div> <b>MA-31665</b>
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Effective date: 2016-10-27 12:36

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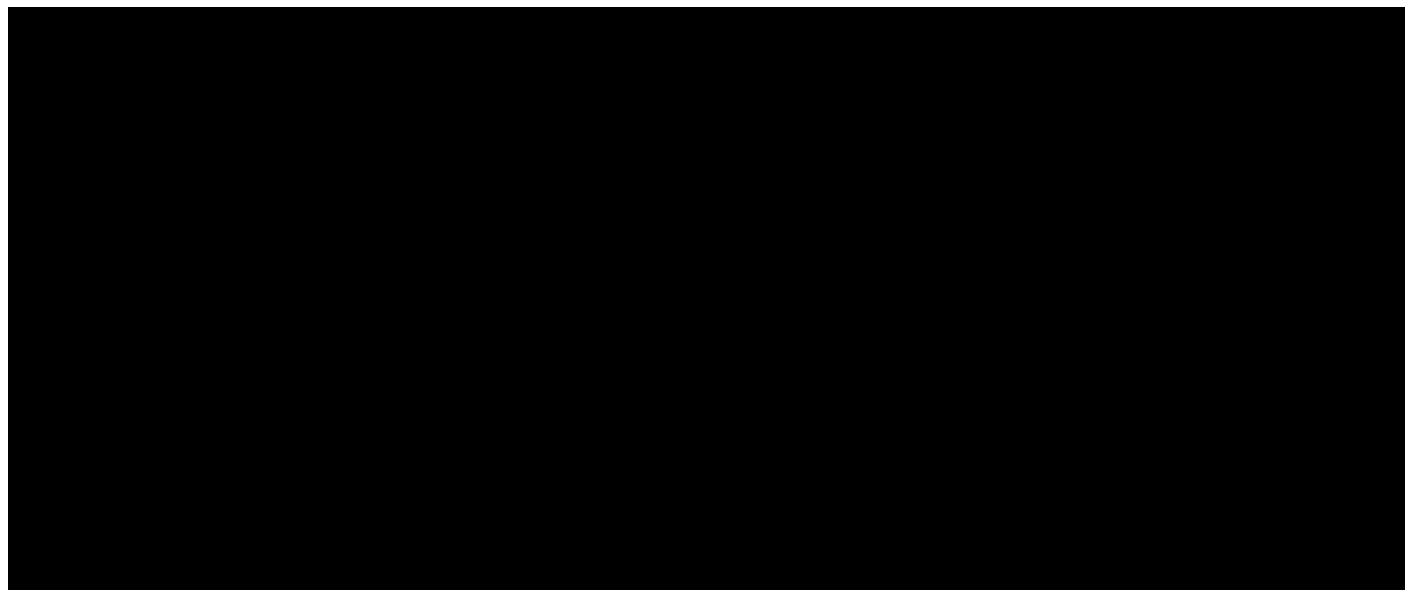
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Effective date: 2016-10-27 12:36



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Version: 3.0





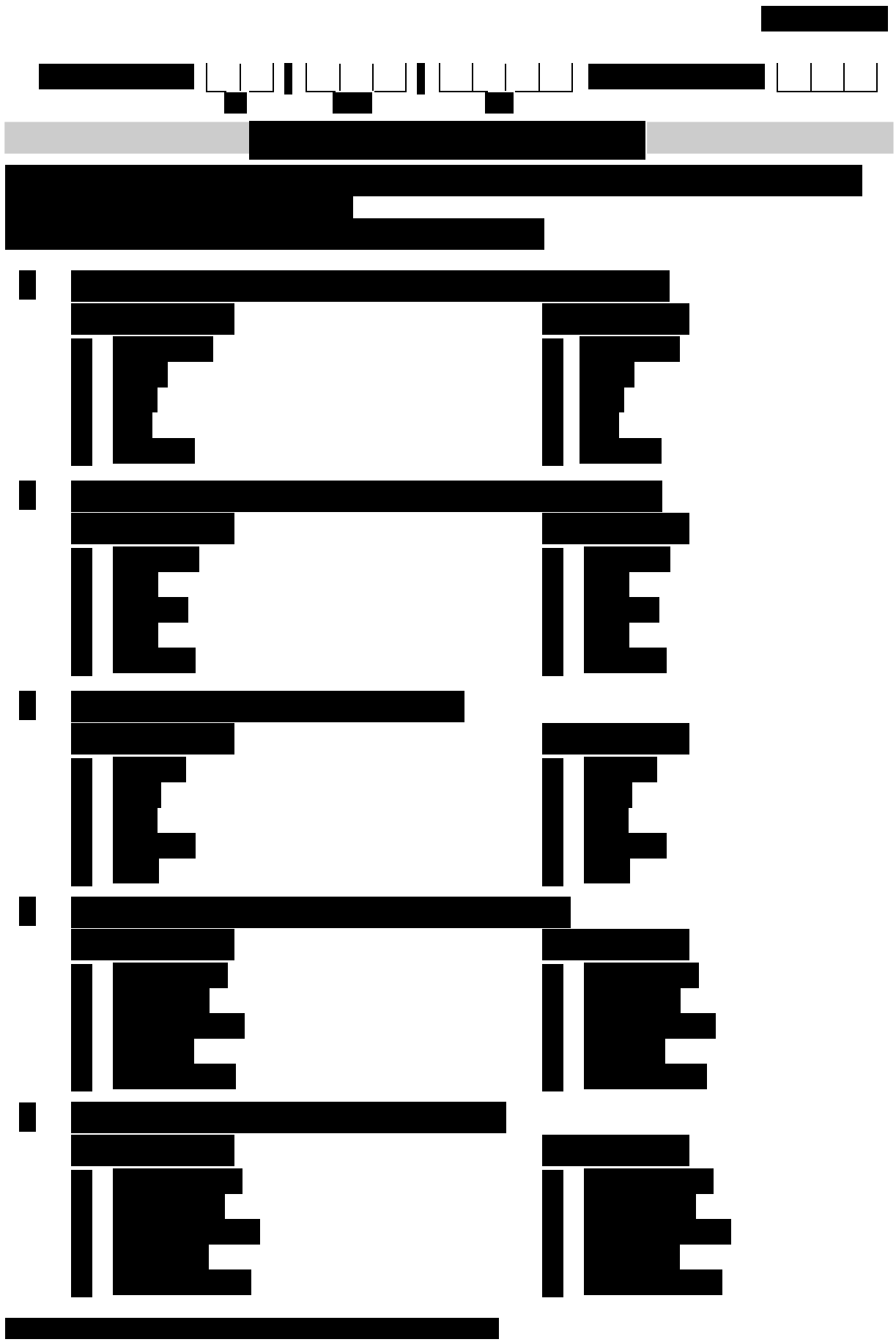





Effective date: 2016-10-27 12:36


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Version: 3.0





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## SIGNATURES PAGE

Date	Signed by
2016-10-27 09:08	
Justification	Approved by Technical Expert

2016-10-27 11:17	
Justification	Approved by Technical Expert

2016-10-27 11:57	
Justification	Approved by Medical Affairs

2016-10-27 12:36	
Justification	Approved by Owner

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