	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

A randomised, multi-center, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane® Perlane Lidocaine compared to Restylane® Perlane

Study products: Restylane® Perlane Lidocaine
Restylane® Perlane


Clinical Trial Number (CTN): 43TW1628

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 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Study Administrative Structure

Sponsor	Q-Med AB 
	   
Head of Global A&C Clinical Development	
Medical Expert	
Clinical Project Manager	
Study Statistician	

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> 43TW1628 Clinical Study Protocol	<small>Doc id</small> MA-34273
--	---	--

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 Global A&C Clinical Development,
Q-Med AB**

[REDACTED]

Electronically signed in the document management system within Q-Med quality management system

Sponsor's Medical Expert, Q-Med AB

[REDACTED]

Electronically signed in the document management system within Q-Med quality management system

Clinical Project Manager, Q-Med AB


[REDACTED]

Electronically signed in the document management system within Q-Med quality management system

Study Statistician, Q-Med AB

[REDACTED]

Electronically signed in the document management system within Q-Med quality management system

	<small>Title</small> 43TW1628 Clinical Study Protocol	<small>Doc id</small> MA-34273
--	---	--

Signed Agreement of the Clinical Study Protocol

CTN: 43TW1628

Title of the CSP: A randomised, multi-center, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane® Perlane lidocaine compared to Restylane® Perlane.

I, the undersigned, have read and understand the protocol specified above, and agree on the contents. The study protocol, the Clinical Trial Agreement and the additional information given in the Instruction For Use for Restylane® Perlane Lidocaine and Restylane® Perlane will serve as a basis for co-operation in this study.

Principal Investigator

Printed name

Signature


Date

Study site

Effective


Effective date: 2017-04-13 06:29

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Synopsis

Title of study:	A randomised, multi-center, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Restylane® Perlane lidocaine compared to Restylane® Perlane
Clinical Trial Number:	43TW1628
Countries involved, number of sites/country, number of subjects:	The study will be conducted at approximately 3 sites located in Taiwan. The aim is to include 70 subjects treated with Restylane® Perlane Lidocaine (Perlane-Lido) in one nasolabial fold (NLF) and Restylane® Perlane (Perlane) in the opposite NLF, as randomly assigned.
Objectives:	<p>Primary objective:</p> <ul style="list-style-type: none"> To evaluate the pain associated with injections of Perlane-Lido compared to Perlane for correction of moderate to severe NLFs. <p>Secondary objective:</p> <ul style="list-style-type: none"> To evaluate the dermal filler effectiveness of Perlane-Lido compared to Perlane for correction of moderate to severe NLFs. <p>Safety objective:</p> <ul style="list-style-type: none"> To evaluate the safety of Perlane-Lido and Perlane throughout the study.
Endpoints:	<p>Primary endpoint:</p> <p>Proportion of subjects that have a within-subject difference in VAS score (Perlane - Perlane-Lido) of at least 10 mm at injection.</p> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> Proportion of subjects that have a within-subject difference in VAS score (Perlane - Perlane-Lido) of at least 10 mm at 15, 30, 45 and 60 minutes after injection. [REDACTED] [REDACTED] [REDACTED] [REDACTED]

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

	<p>Safety endpoints:</p> <ul style="list-style-type: none">• Incidence, intensity, duration, and onset of adverse events (AEs) collected throughout the study.• Incidence, intensity, and duration of pre-defined expected post-treatment events collected using a subject diary for 14 days after each treatment.									
<p>Study Design:</p>	<p>This is a randomised, multi-center, subject-blinded and evaluator-blinded study in Taiwan to evaluate the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Perlane-Lido compared to Perlane.</p> <p>Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to study randomisation on Day 1. Subsequent to screening eligible subjects will be enrolled in the study.</p> <p>Each subject will receive treatment on Day 1 with Perlane-Lido in one NLF and Perlane in the opposite NLF, as randomly assigned. The first injection will always start in the right NLF. No topical or local anesthetic or other pain-relieving medication, including ice, should be used before all VAS assessments are finished. The second injection, that is the injection in the left NLF, will be performed 20±5 minutes after the first injection in order to reduce possible influence of immediate acute pain from the first injection on the pain perception of the second injection.</p> <p>The subject will assess pain experienced during treatment on a 100 mm VAS scale at the end of each injection (before massaging the treatment area). The time should be recorded in the eCRF and the pain will thereafter be assessed by the subject at 15±3, 30±3, 45±3, and 60±3 minutes on the VAS after the injection on the right and left NLF, respectively. Pain will also be assessed by a treatment preference question. At the end of the treatment of the left NLF, immediately after VAS assessment of the pain at injection, the Subject will be asked which treatment was least painful.</p> <p>Aesthetic improvement of the NLFs will be assessed by the subject and the Blinded Evaluator, independent of each other, [REDACTED]. Severity of the NLFs will be assessed by the Blinded Evaluator [REDACTED].</p> <p>The subjects will be provided with a diary in which to report symptoms for 14 days after treatment. [REDACTED]</p>									
<p>Scheduled visits:</p>	<table><tr><td>Visit 1</td><td>Screening</td><td>Day -14 to Day 1</td></tr><tr><td>Visit 2</td><td>Baseline (treatment)</td><td>Day 1</td></tr><tr><td>Visit 3</td><td>Follow-up/Final visit</td><td>Day 15 (after treatment)</td></tr></table>	Visit 1	Screening	Day -14 to Day 1	Visit 2	Baseline (treatment)	Day 1	Visit 3	Follow-up/Final visit	Day 15 (after treatment)
Visit 1	Screening	Day -14 to Day 1								
Visit 2	Baseline (treatment)	Day 1								
Visit 3	Follow-up/Final visit	Day 15 (after treatment)								
<p>Inclusion criteria:</p>	<p>The subject must meet the following criteria to be eligible for the study:</p> <ol style="list-style-type: none">1. Signed and dated informed consent to participate in the study.									

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

	<ol style="list-style-type: none"> 2. Men or women aged 20 years of age or older of Chinese origin. 3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim for the duration of the study of a maximum of 31 days (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency etc.). 4. Intent to undergo correction of both NLFs [REDACTED]
Exclusion criteria:	<p>The presence of any of the following exclusion criteria will exclude a subject from enrolment in the study:</p> <p>[REDACTED]</p> <ol style="list-style-type: none"> 1. [REDACTED] 2. [REDACTED] 3. [REDACTED] 4. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, ultrasound, cryotherapy, chemical peeling or dermabrasion in the midface within 6 months before treatment. 5. [REDACTED] 6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent filler, autologous fat, lifting threads or permanent implant below the level of the lower orbital rim. 7. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months before treatment. 8. [REDACTED] 9. [REDACTED] 10. Scars or deformities, active skin disease, inflammation or related conditions, such as infection, perioral dermatitis, seborrheic eczema, rosacea, acne psoriasis and herpes zoster near or in the area to be treated. <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>


	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

Effective

Version: 1.0

	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>20. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g. subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Investigational product:	<p>Restylane® Perlane lidocaine (Perlane-Lido)</p> <p>Perlane-Lido consists of stabilized hyaluronic acid of non-animal origin at a concentration of 20 mg/mL, in phosphate buffered saline with lidocaine hydrochloride 3 mg/mL. The study product is supplied in sterile 1 mL syringes with sterile contents, using a 29G thin walled (TW) × ½" needle.</p> <p>The Treating Investigator will check the randomisation via the eCRF system, for study product i.e. the NLF on one side of the face will be randomly assigned to treatment with Perlane Lido and the opposite NLF to treatment with Perlane.</p> <p>Perlane-Lido should be injected into the deep layer of the dermis and/or the surface layer of the subcutis of the facial skin in the NLF. The injection procedure should strictly follow the rules of aseptic surgical technique.</p> <p>For treatment, it is recommended not to use more than 2 mL for each NLF.</p> <p>The injection technique and the depth of injection should be the same for both sides of the face in any one subject to limit variability due to technique. Sufficient</p>

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

	<p>amounts of product should be injected to fully correct the defect. Defects should be fully corrected, but not overcorrected.</p> <p>No topical or local anaesthetic or other pain-relieving medication, including ice, should be used before all VAS assessment finished.</p>
Reference therapy:	<p>Restylane® Perlane (Perlane)</p> <p>Perlane consists of stabilized hyaluronic acid of non-animal origin at a concentration of 20 mg/mL, in phosphate buffered saline. The study product is supplied in sterile 1 mL syringes with sterile contents, using a 29G thin walled (TW) × ½” needle.</p> <p>The Treating Investigator will check the randomisation via the eCRF system, for study product i.e. the NLF on one side of the face will be randomly assigned to treatment with Perlane Lido and the opposite NLF to treatment with Perlane.</p> <p>Perlane should be injected into the deep layer of the dermis and/or the surface layer of the subcutis of the facial skin in the NLF. The injection procedure should strictly follow the rules of aseptic surgical technique.</p> <p>For treatment, it is recommended not to use more than 2 mL for each NLF.</p> <p>The injection technique and the depth of injection should be the same for both sides of the face in any one subject to limit variability due to technique. Sufficient amounts of product should be injected to fully correct the defect. Defects should be fully corrected, but not overcorrected.</p> <p>No topical or local anaesthetic or other pain-relieving medication, including ice, should be used before all VAS assessment finished.</p>
Duration of treatment and follow-up:	<p>A subject will be involved in the study for up to 31 days including an up to 14 days screening period, treatment on Day 1, and 14 (+3) days follow up.</p>
Assessments:	<p><u>Pain assessment by Visual Analogue Scale (VAS):</u></p> <p>The VAS is a subjective scale to measure pain intensity. The subject shall be instructed to put a vertical mark, approximating the pain experienced during the procedure, on a 100 mm horizontal line labelled “no pain” at the left end and “the worst pain you can imagine” at the right end. The distance in mm from the left end (no pain) to the subject’s VAS mark shall be measured with a standard ruler. Each NLF will be evaluated independently.</p> <p>Subjects will evaluate injection site pain for each side of the face at the time of injection (before massaging) and at 15, 30, 45, and 60 minutes post-treatment by completing a VAS.</p> <p>Visual Analogue Scale (VAS)</p> <p>Put a vertical mark () on the line below to show your pain experience.</p> <p>No pain _____ The worst pain you can imagine</p>

[illegible]

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

	<div style="background-color: black; height: 15px; width: 100%;"></div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20%; background-color: black;"></td><td style="width: 80%; background-color: black;"></td></tr> <tr> <td style="background-color: black;"></td><td style="background-color: black;"></td></tr> <tr> <td style="background-color: black;"></td><td style="background-color: black;"></td></tr> <tr> <td style="background-color: black;"></td><td style="background-color: black;"></td></tr> <tr> <td style="background-color: black;"></td><td style="background-color: black;"></td></tr> <tr> <td style="background-color: black;"></td><td style="background-color: black;"></td></tr> <tr> <td style="background-color: black;"></td><td style="background-color: black;"></td></tr> </table>														
	<p><u>Safety Assessments:</u></p> <p>AEs will begin to be collected after ICF has been signed. Each subject will be questioned about AEs at follow-up visit following the screening visit. The question asked will be “Since your last clinical visit have you had any health problems?”. Information on AEs can also be obtained from signs and symptoms detected during each examination, observations by the study personnel, subject diaries or spontaneous reports from the subjects.</p> <p>Pre-defined expected post-treatment events will be evaluated in a subject diary for 14 days after treatment, starting on the day of treatment. [REDACTED]</p> <div style="background-color: black; height: 30px; width: 100%;"></div>														
Statistical Methods:	<div style="background-color: black; height: 40px; width: 100%;"></div> <div style="background-color: black; height: 20px; width: 100%;"></div> <div style="background-color: black; height: 40px; width: 100%;"></div> <div style="background-color: black; height: 40px; width: 100%;"></div> <div style="background-color: black; height: 20px; width: 100%;"></div> <div style="background-color: black; height: 40px; width: 100%;"></div>														


	<div>Title</div> 43TW1628 Clinical Study Protocol	<div>Doc id</div> MA-34273
--	--	-----------------------------------

Effective date: 2017-04-13 06:29



Effective

Version: 1.0

	<div>[REDACTED]</div>
--	-----------------------

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

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.
Co-ordinating Investigator	An Investigator assigned the responsibility for the coordination of Investigators at different centers participating in a multicenter study
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
FAS	Full Analysis Set
G	Gauge
	
Generation 1	Includes parents, children and spouse.
Generation 2	Includes siblings, grandparents and grandchildren.
GCP	Good Clinical Practice
HA	Hyaluronic acid
ICF	Informed Consent Form
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 clinical studies are conducted.
Investigator	The Principal Investigator or other qualified person, i.e. sub-Investigator, designated and supervised by the Principal Investigator at a study site to perform critical study-related procedures and/or make important study-related decisions as specified on the delegation log.
Investigator File	Essential documents relating to a clinical study as defined in GCP guidance document and maintained by the Investigator.
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NLF	Nasolabial fold

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

NSAIDs	non-steroid anti-inflammatory drugs
Perlane lido	Restylane® Perlane lidocaine
Perlane	Restylane® Perlane
PI	Principal Investigator
PP	Per protocol
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
SDV	Source data verification
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
U-HCG	Urinary human chorionic gonadotropin
Unanticipated AE	Related Adverse Event not described in the Instructions For Use
VAS	Visual analogue scale
WHO	World Health Organization



	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

Table of Contents

STUDY ADMINISTRATIVE STRUCTURE	2
SPONSOR SIGNATURES	3
SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL	4
SYNOPSIS	5
ABBREVIATIONS AND DEFINITIONS OF TERMS	13
TABLE OF CONTENTS	15
1 ETHICAL CONSIDERATIONS	18
2 BACKGROUND INFORMATION	18
2.2 Investigational product description	18
2.3 Reference product description	19
2.4 Previous experience	19
2.4.1 Non-Clinical Documentation	19
2.4.2 Clinical Documentation	19
2.5 Study rationale and Justification for design	20
2.6 Risk and benefits	20
3 OBJECTIVES AND ENDPOINTS	21
3.1 Objectives	21
3.1.1 The primary objective	21
3.1.2 The secondary objective	22
3.1.3 The safety objective	22
3.2 Endpoints	22
3.2.1 Primary endpoint	22
3.2.2 Secondary endpoints	22
3.2.3 Safety endpoints	22
4 DESIGN OF THE STUDY	22
4.1 General Outline	22
4.2 Number of Subjects	24
4.3 Duration of Subject Participation	24
4.4 Randomisation and blinding	24
4.4.1 Randomisation	24
4.4.2 Blinding	25
4.4.3 Emergency un-blinding	25
4.5 Medical history	25
4.6 Concomitant Medication, Treatment, and Procedure	25
4.7 Schedule of events	26
4.8 Visits	27
4.8.1 Visit 1: Screening (Day -14 to Day 1)	27
4.8.2 Visit 2: Baseline (treatment) (Day 1)	27
4.8.3 Visit 3: Follow-up/Final visit (Day 15 (+3 days)) or early termination	27
5 SUBJECTS	28
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
6 STUDY PRODUCTS	31

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

6.1	Investigational Product	32
6.2	Reference Product	32
6.3	Additional Products and Material	32
6.4	Packaging, Labelling and Storage	32
6.5	Product accountability	32
6.6	Treatment	33
6.6.1	<i>Treatment Procedure</i>	33
6.6.2	<i>Treatment regimen (dose)</i>	34
6.6.3	<i>Post-treatment Care</i>	34
6.6.4	<i>Post-trial provisions</i>	34
6.6.5	<i>Electronic case report form recordings (eCRF)</i>	35
6.6.6	<i>Treatment compliance</i>	35
7	PAIN ASSESSMENTS	35
7.1	Pain assessment by Visual Analogue Scale (VAS)	35
7.2	Pain assessment by Treatment Preference Question	35
8	DERMAL FILLER EFFECTIVENESS ASSESSMENTS	36
8.1		36
8.2		36
8.3	Photography	37
9	SAFETY ASSESSMENTS	38
9.1	Pre-defined, expected, post-treatment events	38
9.2	Adverse Events	38
9.2.1	<i>Definition of Adverse Events</i>	38
9.2.2	<i>Definition of Serious Adverse Event</i>	38
9.2.3	<i>Recording Instructions</i>	39
9.2.4	<i>Reporting of Adverse Events</i>	40
9.2.5	<i>Reporting of Serious Adverse Events</i>	40
9.2.6	<i>Follow-up of Unresolved Events after study termination and Events with onset after study termination.</i>	42
9.2.7	<i>Pregnancy</i>	42
9.2.8	<i>Anticipated Adverse Events</i>	43
9.3	Device Deficiencies	43
9.3.1	<i>Definition of Device Deficiency</i>	43
9.3.2	<i>Recording Instructions</i>	43
9.3.3	<i>Reporting Device Deficiency</i>	44
10	DATA HANDLING AND MANAGEMENT	44
10.1	Data management	44
10.2	Electronic case report forms (eCRFs)	45
10.2.1	<i>Data entry</i>	45
10.2.2	<i>The query process</i>	45
10.2.3	<i>User identification</i>	46
10.2.4	<i>Audit trail</i>	46
10.3	Source documents	46
10.4	Record keeping and access to source data	46
10.5	Document and data retention	47
11	STATISTICAL METHODS	47
11.1	General	47
11.2	Analysis Populations	47
11.3	Demographics, baseline assessments, and subject characteristics	48
11.4	Analysis	48
11.4.1	<i>Primary analysis</i>	48
11.4.2	<i>Secondary analysis</i>	48
11.4.3	<i>Safety Analysis</i>	48
11.5	Handling of Missing Data	49
11.6	Interim Analysis	49
11.7	Data monitoring committee	49
11.8	Withdrawals and deviations	49

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

11.9	Sample Size	49
12	PROTECTION OF PERSONAL DATA	49
13	QUALITY CONTROL AND QUALITY ASSURANCE	50
13.1	Quality control	50
13.2	Quality assurance	50
13.3	Changes to the clinical study protocol	51
14	FINANCING, INDEMNIFICATION, AND INSURANCE	51
15	PUBLICATION POLICY	51
16	SUSPENSION OR PREMATURE TERMINATION	52
17	REFERENCES	53
18	APPENDICES	54

List of Tables

Table 1. Schedule of Events	26
-----------------------------------	----

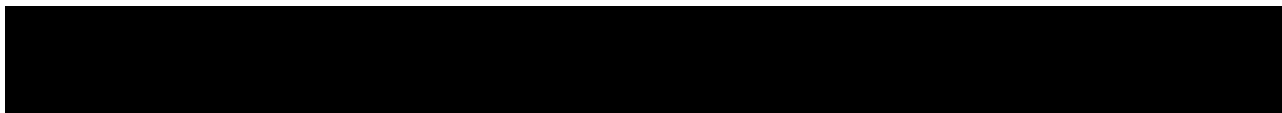




Table 5. Contact details for Sponsor and Sponsor's representative.....	42
--	----

List of Figures

Figure 1. Flow chart of the study.....	23
--	----

Figure 1. Flow chart of VAS Assessment.....	24
---	----

List of Appendices

Appendix 1	Declaration of Helsinki
	
Appendix 3	Restylane® Perlane lidocaine and Restylane® Perlane Taiwan IFU.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

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), applicable 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/Institutional Review Board and/or Regulatory Authorities

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CSP/CSP amendment(s) from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The study shall not begin until the required favourable opinion from the IEC/IRB has been obtained. The PI shall file all correspondence with the IEC/IRB in the Investigator file and copies of IEC/IRB approvals shall be forwarded to the Sponsor. In accordance to local requirements a regulatory authorities (RA) approval might be needed. Any additional requirements imposed by the IEC/IRB or RA shall be followed.

As the study products are approved for use in Taiwan, application for approval from RA is not required.

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

2 Background Information

2.1 Indication and population description

[REDACTED]

2.2 Investigational product description

[REDACTED]

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------


[REDACTED]

2.3 Reference product description

[REDACTED]

2.4 Previous experience

[REDACTED]

	<p>Title 43TW1628 Clinical Study Protocol</p>	<p>Doc id MA-34273</p>
--	--	-----------------------------------

[REDACTED]

[REDACTED]

[REDACTED]

2.5 Study rationale and Justification for design

[REDACTED]

[REDACTED]

2.6 Risk and benefits

[REDACTED]

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3 Objectives and Endpoints

3.1 Objectives

3.1.1 The primary objective

- To evaluate the pain associated with injections of Perlane-Lido compared to Perlane for correction of moderate to severe NLFs.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

3.1.2 The secondary objective

- To evaluate the dermal filler effectiveness (including wrinkle severity and aesthetic improvement in the NLFs after treatment) of Perlane-Lido compared to Perlane for correction of moderate to severe NLFs.

3.1.3 The safety objective

- To evaluate the safety of Perlane-Lido and Perlane throughout the study.

3.2 Endpoints

3.2.1 Primary endpoint

- Proportion of subjects that have a within-subject difference in VAS score (Perlane - Perlane-Lido) of at least 10 mm at injection.



4 Design of the Study

4.1 General Outline

This is a randomised, multi-center, subject-blinded and evaluator-blinded study in Taiwan to evaluate the pain and the safety profile associated with correction of moderate to severe nasolabial folds using Perlane-Lido compared to Perlane.

Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to study randomisation on day 1. Subsequent to screening eligible subjects will be enrolled in the study.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

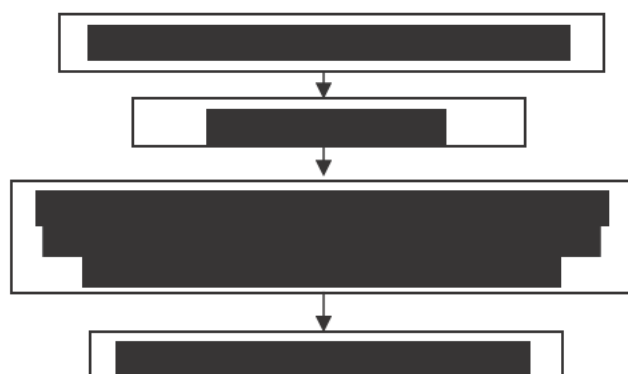
Each subject will receive treatment on Day 1 with Perlane-Lido in one NLF and Perlane in the opposite NLF, as randomly assigned. The first injection will always start in the right NLF. No topical or local anesthetic or other pain-relieving medication, including ice, should be used before all VAS assessments are finished. The second injection, that is the injection in the left NLF, will be performed 20±5 minutes after the first injection in order to reduce possible influence of immediate acute pain from the first injection on the pain perception of the second injection.


In order to be able to evaluate the pain of injection separated from the pain of the needle insertion alone, a pause of 3 to 5 seconds is required after insertion of the needle before starting injection. Aspiration for blood should be done in order to avoid accidental intravascular injection. The injection procedure for the two NLFs will be standardised as far as possible in terms of volume used, time needed for injection, and injection technique and will be recorded in the CRFs.

The subject will assess pain experienced during treatment on a 100 mm VAS scale at the end of each injection (before massaging the treatment area).

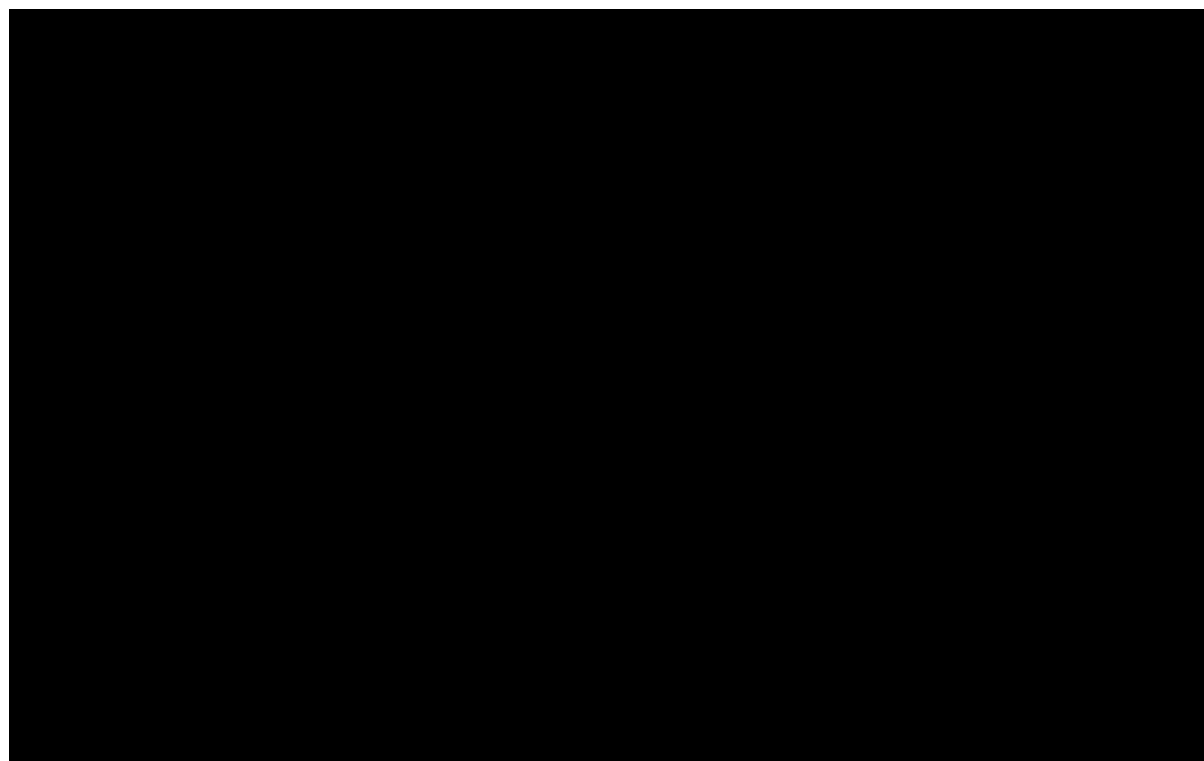
Pain will also be assessed by a treatment preference question. At the end of the treatment of the left NLF, immediately after VAS assessment of the pain at injection, the Subject will be asked which treatment was least painful (right NLF/left NLF/both NLFs alike).

Subjects will be provided with a diary in which to report symptoms for 14 days after treatment.



	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29



4.2 Number of Subjects

The study will be performed at approximately 3 hospitals in Taiwan and 70 subjects will be randomised and treated.

4.3 Duration of Subject Participation


A subject will be involved in the study for up to 31 days including an up to 14 days screening period, treatment on Day 1, and 14 (+3) days follow up.

4.4 Randomisation and blinding

4.4.1 Randomisation

Each subject will be randomised to one of two treatment sequences; either Perlane-Lido in the subject's right NLF followed by Perlane in the subject's left NLF, or Perlane in the subject's right NLF followed by Perlane-Lido in the subject's left NLF. Treatment will always start in the subject's right NLF. The randomisation list will be prepared under the supervision of a designated statistician. The randomisation list will be stratified by center.

Each subject will be assigned a subject number as they arrive for the treatment visit. Randomisation will be assigned via the eCRF system. At the time for randomisation, the subject's initials, date of randomisation, subject number, randomised treatment sequence, and the signature of the Investigator must be documented in a randomisation log. The treatment information will be kept by the Treating Investigator during the study not to be disclosed to the Blinded Evaluator.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

4.4.2 Blinding

Because the method of administration is similar, the treatment can be partially masked from the subjects by simply preventing them from viewing the syringes during administration of the study products. This will be done by placing an opaque drape or patch over the subject's eyes during the injection procedure. The Treating Investigator should also make sure that the subjects are kept blinded during the intervals between the two treatments.

The Blinded Evaluator shall not be allowed to retrieve study supplies or to be present during opening of the study supplies or injections. The Treating Investigator is not allowed to discuss treatments with the Blinded Evaluator or the subjects. All documents with information on study products shall be kept in a separate binder not available to the Blinded Evaluator.

4.4.3 Emergency un-blinding

Not applicable as the Treating Investigator is un-blinded.

4.5 Medical history

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

Any concomitant medications and any relevant medical history (including prior facial dermatological procedures performed, and fillers or implants used) or concurrent diseases will be asked for.

4.6 Concomitant Medication, Treatment, and Procedure

Except as noted below, concomitant medications or other treatments or procedures may be utilised when the PI or his/her authorised designee considers it medically necessary. Information regarding any use of concomitant medications, including over-the-counter medications administered during the study is to be recorded in the eCRF. The generic name or the trade name of all concomitant medication or a description of the procedure and the reason for its use shall be documented in the eCRF.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id
		MA-34273

Effective date: 2017-04-13 06:29

- [REDACTED]
- [REDACTED]
- [REDACTED]

If a subject has used any of the above prohibited medications or performed any of the above prohibited procedures, a protocol deviation will be documented. The subject should continue in the study for the scheduled follow-up visits.

4.7 Schedule of events

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

[REDACTED]

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

4.8 Visits

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]


- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

- [REDACTED]
- [REDACTED]
- [REDACTED]

5 Subjects

5.1 Subject information and informed consent

The PI or his/her authorised designee must always use the IEC/IRB-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/IRB.

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/IRB. The subject shall be informed that the participation is confidential and voluntary and that the subject has the right to withdraw from the study at any time, without any effect on his/her future medical care, treatment or benefits to which the subject is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the Subject Information and 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 his/her authorised designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and transferred to countries outside Taiwan. The data will not contain any information that can be used to identify any subject.


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 subject must meet the following criteria to be eligible for the study:

1. Signed and dated informed consent to participate in the study.
2. Men or women aged 20 years or older of Chinese origin.
3. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures below the level of the lower orbital rim for the duration of the study of a maximum of 31 days(e.g., laser or chemical resurfacing, needling, facelift, radiofrequency, etc.).

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

4. Intent to undergo correction of both NLFs [REDACTED]

5.3 Exclusion Criteria

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

4. Previous tissue revitalization treatment with laser or light, mesotherapy, radiofrequency, ultrasound, cryotherapy, chemical peeling or dermabrasion in the midface within 6 months before treatment.

6. Previous tissue augmentation therapy or contouring with any permanent (non-biodegradable) or semi-permanent filler, autologous fat, lifting threads or permanent implant below the level of the lower orbital rim.


7. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months before treatment.

10. Scars or deformities, active skin disease, inflammation or related conditions, such as infection, perioral dermatitis, seborrheic eczema, rosacea, acne psoriasis and herpes zoster near or in the area to be treated.

Effective date: 2017-04-13 06:29

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

20. Other condition preventing the subject from entering the study in the Investigator's opinion, e.g. subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.

[REDACTED]

[REDACTED]

[REDACTED]

5.4 Screening and Subject Numbers

Each screened subject will be assigned a screening number consisting of "S" and the site number followed by a consecutive number starting with 01 at each site, e.g. S101, S102. The screening number 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 eCRF screening visit shall be completed to an extent that makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria. The reason for excluding a subject from entering the study shall also be specified in the subject screening and inclusion log.

When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each enrolled subject will be assigned a subject number by the eCRF consisting of the site number followed by a consecutive number starting with 01 at each site, e.g. 101, 102.

The screening number, 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.

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

5.5 Withdrawal of Subjects

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

[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/pages 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 early termination visit should be completed. The subject will need to follow the same requirements for the visit at day 15.


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

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

If 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 months shall be provided to the Sponsor.

6 Study Products

The term "study products" refers to Perlane-Lido and Perlane.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

6.1 Investigational Product

Perlane-Lido is a sterilized injectable gel consisting of stabilized HA of non-animal origin with concentration 20 mg/mL in phosphate buffered saline with lidocaine hydrochloride 3 mg/mL. The gel is transparent and colorless. The product is supplied in single use sterile syringes with a luer-lock fitting. Each syringe contains 1 mL gel. The syringe is labeled and packaged in a blister, with two 29G thin walled (TW) × ½" needles. The Investigational Product is a commercial product intended for the Taiwan market. An Instruction for Use (IFU) is included in the carton.

6.2 Reference Product

Perlane is a sterilized injectable gel consisting of stabilized HA of non-animal origin with concentration 20 mg/mL in phosphate buffered saline. The gel is transparent and colorless. The product is supplied in single use sterile syringes with a luer-lock fitting. Each syringe contains 1 mL gel. The syringe is labeled and packaged in a blister with two 29G thin walled (TW) × ½" needles. The Reference Product is a commercial product intended for the Taiwan market. An Instruction for Use (IFU) is included in the carton.

6.3 Additional Products and Material

Perlane-Lido and Perlane will be supplied by the Sponsor. Any other materials will be supplied by the site.

6.4 Packaging, Labelling and Storage

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

6.5 Product accountability

The study product will be released to the PI or his/her authorised designee after study approvals have been received from the IEC/IRB and the CTA has been signed by all parties.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

The PI must ensure that the study product is kept in a secure location, with access limited to those authorised by the PI.

The study product must be traceable from the manufacturer to its use in subjects until return or disposal. It is therefore important that the PI maintains accurate product accountability records, i.e. documentation of the physical location of all study product, deliveries, and return of study product between the Sponsor or a third-party vendor and the PI, and documentation of administration of product to the subject. A shipping record shall be kept of all study products received from the Sponsor; including the product name, date received, batch number, expiration date, and amount received. In addition, dispensing logs shall be maintained including the product name, dispense date, the number of syringes used, the number of syringes left in stock, and the subject receiving study product. A log for accountability procedure is provided by the Sponsor.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor or a third-party vendor for destruction. Any malfunctioning study products shall be reported as described in Section 8.5.3.

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

6.6 Treatment

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.6.6 Treatment compliance

The treatment is an implant administered by the Treating Investigator and the details of the administration are recorded in the eCRF. No other measurements of treatment compliance will be made.

7 Pain Assessments

7.1 Pain assessment by Visual Analogue Scale (VAS)

The VAS is a subjective scale to measure pain intensity. The subject shall be instructed to put a vertical mark, approximating the pain experienced during the procedure, on a 100 mm horizontal line labelled “no pain” at the left end and “the worst pain you can imagine” at the right end. The distance in mm from the left end (no pain) to the subject’s VAS mark shall be measured with a standard ruler. Each NLF will be evaluated independently.

Subjects will evaluate injection site pain for each side of the face at the time of injection (before massaging) and at 15, 30, 45, and 60 minutes post-treatment by completing a VAS.

Visual Analogue Scale (VAS)

Put a vertical mark (|) on the line below to show your pain experience.

No pain _____ The worst pain you can imagine

[REDACTED]

[REDACTED]

Version: 1.0

Effective

[illegible]

[REDACTED]

[REDACTED]

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Effective date: 2017-04-13 06:29

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

8.3 Photography


Digital photographs will be taken of each subject at baseline and at follow-up visit. Photographs from straight frontal view will be taken both pre- and post-treatment at baseline when treatment is performed. If necessary, additional photo should be taken when AEs occurred.

The same photographic equipment and standardised setting must be used at each visit (e.g. distance, light, facial position and expression). No covering make-up should be used on the photographs.

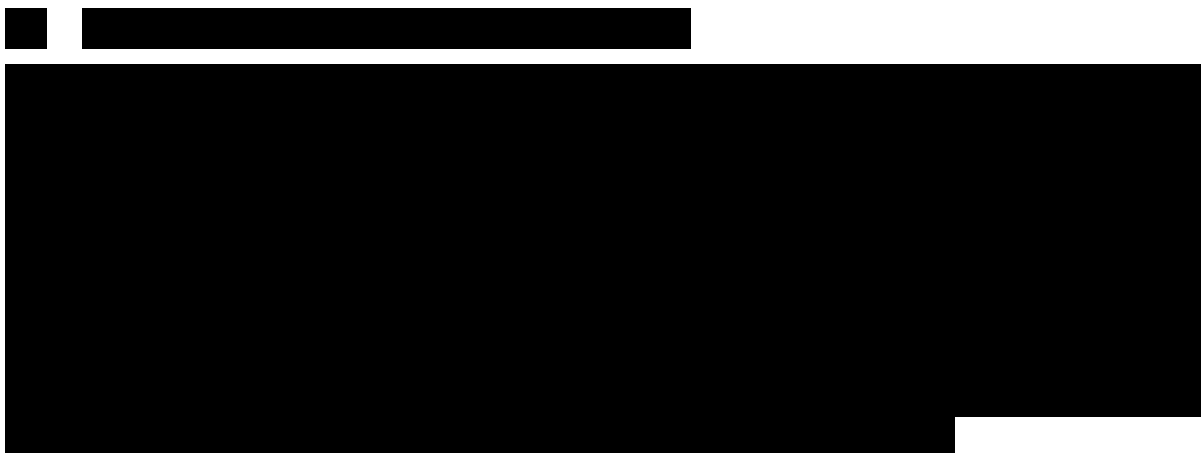
Photographs will be identified by subject initials, subject number, visit number and date/time of visit. The photographs will be used to document condition at baseline, [REDACTED] and to document AEs in the treated area.

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

9 Safety Assessments



[Redacted]	
[Redacted]	[Redacted]
[Redacted]	[Redacted]
[Redacted]	[Redacted]
[Redacted]	[Redacted]

9.2 Adverse Events

9.2.1 Definition of Adverse Events

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*, 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

*For users or other persons, this definition is restricted to events related to the investigational product

9.2.2 Definition of 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** illness or injury, or
 2. a permanent impairment of a body structure or body function, or
 3. in-patient or prolonged hospitalisation***, 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

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

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

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (see Section 9.2.5).

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

******* Planned 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).

9.2.3 Recording Instructions

AEs will begin to be collected after ICF has been signed. Each subject will be questioned about AEs at each clinical visit following the screening visit. The question asked will 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 by the study personnel, subject diaries or spontaneous reports from the subjects.

When an AE is related to a device deficiency (refer to Section 9.3), including technical device malfunction, the AE shall be recorded on the AE module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form.


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

- Event term (recorded in standard medical terminology and avoiding abbreviations),
- Description of event and affected area (if applicable),
- Start date (First day with symptoms)
- Stop date (Last day with symptoms)
- Intensity (mild, moderate or severe according to definition in Section 9.2.3.1)
- Seriousness (serious or not serious, according to definition in Section 9.2.2)
- Causal relationship to study product and study product injection procedure (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment or other procedures/ tests, subject withdrawn)
- Outcome of the AE (ongoing, recovered, recovered with sequele, death, chronic/ stable, not recovered at study end)

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

9.2.3.1 Intensity

For each reported AE, the intensity will be recorded. The following definitions of intensity are to be used:

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

- Mild:** A mild AE means awareness of symptoms or signs, but easily tolerated (acceptable).
- Moderate:** A moderate AE means enough discomfort to interfere with usual activity (disturbing).
- Severe:** A severe AE means incapacity to work or to do usual activity (unacceptable).

If the intensity changes over time the maximum intensity of the AE should be recorded.

9.2.3.2 Causal Relationship and Seriousness

Each AE, serious as well as non-serious, will 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) will be used for 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 with a ‘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.

9.2.4 Reporting of Adverse Events

AE reporting on each subject will start at the screening visit. The reporting will 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.

9.2.5 Reporting of Serious Adverse Events

The Investigator shall report any SAE (both related and unrelated) to Sponsor and Sponsor’s representative immediately but not later than 24 hours of awareness of the event. This initial report shall be made via the eCRF system by completing the SAE module. Via the eCRF-system, the SAE-report will be automatically sent to Sponsor and Sponsor’s representative via the pre-programmed e-mail address in the eCRF system. If there are difficulties accessing the eCRF, an SAE paper form should be completed and sent via fax or e-mail to Sponsor and Sponsor’s representative (see contact details in Table 5).

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:

- Clinical Trial Number (CTN)

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

- Subject identification (age, gender, subject number)
- AE description
- Classification of seriousness (according to definition in Section 9.2.2)
- Date when AE occurred
- Date when AE became serious
- Name of PI and original reporter (if other than Investigator)
- Name of study product
- Treatment specification

The Investigator will assure completeness of the SAE information and the supporting documentation.

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported via the eCRF system 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
- AE Form/list
- Medical History Form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

If fax or e-mail is used for SAE-reporting, separate lists including the above information shall be submitted together with the SAE form.

Effective date: 2017-04-13 06:29

Effective

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Table 5. Contact details for Sponsor and Sponsor's representative

	Sponsor's representative in Taiwan	Sponsor (Q-Med AB)
E-mail for SAE-reporting	[REDACTED]	[REDACTED]
Fax number for SAE-reporting	[REDACTED]	[REDACTED]
Surface mail for providing non-urgent complementary information:	[REDACTED]	[REDACTED]

The SAE module/form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE module/form the fully completed and signed SAE module/form shall be sent to the Sponsor and Sponsor's representative. 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/IRB without undue delay, if applicable according to national regulations. The PI is responsible for checking what reporting procedures are applicable for his/her IEC/IRB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor's representative in Taiwan (see Table 5) is responsible for completing the local SAE form used for reporting to the local RA, if applicable, and according to national regulations.

9.2.6 Follow-up of Unresolved Events after study termination and Events with onset after study termination.

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

All unanticipated AEs, serious as well as non-serious with onset after the study termination (last patient study visit) should be reported to Sponsor in accordance with the contact details described in Table 5, Section 9.2.5. This report should as minimum include the information described in Sections 9.2.3 and 9.2.5.

9.2.7 Pregnancy

Pregnancy itself is not regarded as an AE.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

If there is a pregnancy during the study period the subject must continue to be followed within the study and the outcome of pregnancy must be reported even if the expected date of delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator immediately upon acknowledge. The report can be prospective or retrospective. The report shall be made via the eCRF system by completing the Pregnancy report module. The pregnancy report will be automatically sent to the Sponsor and Sponsor's representative via pre-programmed e-mail address in the eCRF system. If there are difficulties accessing the eCRF, a paper pregnancy report form should be completed and sent via fax or e-mail to Sponsor and Sponsor's representative according to contact details specified in Table 5.

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 and Sponsor's representative immediately but no later than 24 hours after the Investigators awareness and sent via fax or e-mail according to contact details specified in Table 5. 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, in accordance to Section 9.2.5.

Elective abortions without complications will not be reported as AEs.

9.2.8 Anticipated Adverse Events

After the injection some common injection-related reactions might occur with both products. These reactions include bruising, erythema, swelling, pain, tenderness and itching at the injections site. Typically these reactions start on the day of treatment and resolve spontaneously within a few days after injection.

Refer to the Perlane-Lido and Perlane Taiwan IFU.

9.3 **Device Deficiencies**

9.3.1 Definition of Device Deficiency


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

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

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

9.3.2 Recording Instructions

When a device deficiency is discovered the Clinical Study Complaint Form in the eCRF will be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE module or a SAE Form should be completed following instructions in Section 9.2. 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:

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

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

The Sponsor will also make the same assessment in the Clinical Study Complaint Form.

9.3.3 Reporting Device Deficiency

The Investigator will complete the Clinical Study Complaint Form in the eCRF system and send to the Sponsor and Sponsor's representative via the pre-programmed e-mail address in the eCRF system. If there are difficulties accessing the eCRF, a paper Clinical Study Complaint Form should be completed and sent via e-mail or fax to Sponsor [REDACTED]

A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported within 24 hours after the Investigator's awareness in accordance to Section 9.2.5.

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

If an SAE has resulted from a device deficiency or if either the Investigator or the Sponsor assesses that the device deficiency could have led to an SAE the event will be reported in accordance with Regulatory requirements, as applicable.


10 Data Handling and Management

10.1 Data management

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

The database, the data entry screens and program will be designed in accordance with the 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) in the clinical database will be reconciled against the data in the safety database.

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

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

10.2 Electronic case report forms (eCRFs)

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 will be transcribed 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 study 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 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.

10.2.1 Data entry

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed within 5 working days after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

10.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency by 100%. 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 eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or 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.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

10.2.3 User identification

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

10.2.4 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.

10.3 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 photographs, 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 photographs, should be clearly identified with the subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

10.4 Record keeping and access to source data

The PI/institution shall permit study-related monitoring, audits and IEC/IRB review 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 should 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 should be informed in writing.

The Sponsor shall verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs shall 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 should be available in the medical record. The source data location log should also specify the data for which the eCRF serves

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

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.

10.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, Informed Consent Forms, study product accountability records, source documents, and other study documentation must be retained after study completion according to national legislation and the CTA. Sponsor will inform the sites as to when these documents no longer needs to be retained. Measures should 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 Q-Med AB in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else

11 Statistical Methods

11.1 General

[REDACTED]

[REDACTED]

11.2 Analysis Populations

The following populations will be defined:


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

[REDACTED]

[REDACTED]

[REDACTED]

The FAS population is the primary population for all effectiveness analyses. All safety analyses will be based on the Safety population.

	<p>Title</p> <p>43TW1628 Clinical Study Protocol</p>	<p>Doc id</p> <p>MA-34273</p>
---	---	--------------------------------------

11.3 Demographics, baseline assessments, and subject characteristics

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

11.4 Analysis

[illegible]

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

11.5 Handling of Missing Data

As the design is intra-individual, in which the outcome of both treatments to be compared is available on each subject, it is expected that when a data is missing, it will be missing for both NLFs in most of the cases. A majority of the deviations to the protocol can be expected to affect both NLFs and evaluations of the same subject the same way.

FAS analysis of VAS at the time of injection will impute a difference (Perlane minus Perlane-Lido) of 0 mm as the primary method of imputation. This corresponds to assuming no pain relief using Perlane-Lido compared to Perlane and is considered as a worst case approach. An alternative imputation method might also be used as a sensitivity analysis.

All other endpoints will be analysed on available data, i.e. no imputations will be done.

11.6 Interim Analysis

No interim analysis is planned.

11.7 Data monitoring committee

Not applicable for this study.

11.8 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 in protocol Deviation log.

[REDACTED]

12 Protection of personal data

For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

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

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

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 outside Taiwan, 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 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.

13 Quality Control and Quality Assurance

13.1 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 in the PD log, which shall be verified, discussed, and collected, by the monitor and appropriate corrective and preventive actions shall 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/IRB if required by national regulations. Deviations shall be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations shall be performed as described in the monitoring manual.

13.2 Quality assurance

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

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

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

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.

13.3 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/IRB, 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.

14 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.

15 Publication Policy

The PI's, institutions, 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 multicentre study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved*. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria should 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.

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

	<small>Title</small> 43TW1628 Clinical Study Protocol	<small>Doc id</small> MA-34273
--	---	--

16 Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IEC/IRB 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.

Effective


Effective date: 2017-04-13 06:29

Version: 1.0

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

17 References

1. Monheit GD, Coleman KM. Hyaluronic acid fillers. *Dermatol* 2006 May-Jun; 19(3):141-50.
2. Gold M. The science and art of hyaluronic acid dermal filler use in esthetic applications. *J Cosmet Dermatol* 2009 Dec; 8(4):301-7.
3. Fernandez-Cossio S and Castano-Oreja MT. Biocompatibility of two novel dermal fillers: histological evaluation of implants of a hyaluronic acid filler and a polyacrylamide filler. *Plast Reconstr Surg*. 2006 May; 117(6):1789-96.
4. Heden P, Fagrell D, Jernbeck J, Rylander R, Samuelson U, Sellman G, Stark B. Injection of stabilized hyaluronic acid-based gel of non-animal origin for the correction of nasolabial folds: comparison with and without lidocaine. *Dermatol Surg*. 2010;36:775-781.
5. Brandt F, Bank D, Cross SL, Weiss R. A lidocaine-containing formulation of large-gel particle hyaluronic acid alleviates pain. *Dermatol Surg*. 2010 Nov;36 Suppl 3:1876-85.
6. Hamilton RG, Strobos J, Adkinson NF, Jr. Immunogenicity studies of cosmetically administered nonanimal-stabilized hyaluronic acid particles. *Dermatol Surg*. 2007;33 Suppl 2:S176-85.
7. Taylor SC, Burgess CM, Callender VD. Safety of nonanimal stabilized hyaluronic acid dermal fillers in patients with skin of color: a randomised, evaluator-blinded comparative trial. *Dermatol Surg*. 2009;35 Suppl 2:1653-60.
8. Taylor SC, Burgess CM, Callender VD. Efficacy of Variable-Particle Hyaluronic Acid Dermal Fillers in Patients with Skin of Color: A Randomised, Evaluator-Blinded Comparative Trial. *Dermatol Surg*. 2010;36:741-9.
9. Glogau RG, Kane MA. Effect of injection techniques on the rate of local adverse events in patients implanted with nonanimal hyaluronic acid gel dermal fillers. *Dermatol Surg*. 2008;34 Suppl 1:S105-9.
10. Dover JS, Rubin MG, Bhatia AC. Review of the efficacy, durability, and safety data of two nonanimal stabilized hyaluronic acid fillers from a prospective, randomised, comparative, multicenter study. *Dermatol Surg*. 2009;35 Suppl 1:322-30.
11. Lindqvist C, Tveten S, Bondevik BE, Fagrell D. A randomised, evaluator-blind, multicenter comparison of the efficacy and tolerability of Perlane versus Zyplast in the correction of nasolabial folds. *Plast Reconstr Surg*. 2005;115(1):282-9.
12. Carruthers A, Carey W, De LC, Remington K, Schachter D, Sapra S. Randomised, double-blind comparison of the efficacy of two hyaluronic acid derivatives, Perlane Perlane and Hylaform, in the treatment of nasolabial folds. *Dermatol Surg*. 2005;31(11 Pt 2):1591-8.
13. Ascher B, Bayerl C, Brun P, Kestemont P, Rzany B, Poncet M, et al. Efficacy and safety of a new hyaluronic acid dermal filler in the treatment of severe nasolabial lines - 6-month interim results of a randomised, evaluator-blinded, intra-individual comparison study. *J Cosmet Dermatol*. 2011;10(2):94-8.
14. Brandt F, Bassichis B, Bassichis M, O'Connell C, Lin X. Safety and effectiveness of small and large gel-particle hyaluronic acid in the correction of perioral wrinkles. *J Drugs Dermatol*. 2011;10(9):982-7.
15. Weiss R, Bank D, Brandt F. Randomised, double-blind, split-face study of small-gel-particle hyaluronic acid with and without lidocaine during correction of nasolabial folds. *Dermatol Surg* 2010; 36:750–7.


	<p>Title 43TW1628 Clinical Study Protocol</p>	<p>Doc id MA-34273</p>
--	--	-----------------------------------

18 Appendices

Appendix 1 Declaration of Helsinki



Appendix 3 Restylane® Perlane Lidocaine and Restylane® Perlane Taiwan IFU

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

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.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Appendix 1

Declaration of Helsinki

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.


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

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

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

Vulnerable Groups and Individuals

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

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Appendix 1

Declaration of Helsinki

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

Research Ethics Committees

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


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

Privacy and Confidentiality

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

Informed Consent

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

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Appendix 1


Declaration of Helsinki

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

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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

Appendix 1

Declaration of Helsinki

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

Unproven Interventions in Clinical Practice

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



Title
43TW1628 Clinical Study Protocol

Doc id
MA-34273

Effective date: 2017-04-13 06:29

Effective

Version: 1.0

[Redacted]

[Redacted]

[Redacted]

	<div>Title</div> 43TW1628 Clinical Study Protocol	<div>Doc id</div> MA-34273
--	--	-----------------------------------

Effective date: 2017-04-13 06:29

Effective

Version: 1.0

[REDACTED]

[REDACTED]

[REDACTED]

	<div>Title</div> 43TW1628 Clinical Study Protocol	<div>Doc id</div> MA-34273
--	--	-----------------------------------

Effective date: 2017-04-13 06:29

Effective

Version: 1.0

Appendix 3

Restylane® Perlane Lidocaine and Restylane® Perlane Taiwan IFU

“奇美德”玻麗舒(含利多卡因)

“Q-Med” Restylane Perlane Lidocaine

衛署醫器輸字第 022991 號

注意:使用前請務必詳閱原廠之使用說明書並遵照指示使用

處方

玻尿酸 (Hyaluronic acid, Stabilized)	20 mg/ml
鹽酸利多卡因 (Lidocaine hydrochloride)	3 mg/ml
磷酸緩衝液	足量

產品描述

Restylane Perlane Lidocaine 是無菌透明的非動物性穩定型玻尿酸膠體含有 0.3% Lidocaine hydrochloride。Restylane Perlane Lidocaine 充填於具有螺旋接頭的玻璃注射器內。注射器內容物經過熱滅菌。本產品只供單次使用。注射器附有可拋棄式無菌針頭。滅菌方式與針頭尺寸標示於針頭的包裝上。產品外包裝上註明每一包裝內含的物件數量和每一注射器內含的玻尿酸容量。注射器上貼有使用記錄貼紙。這個記錄貼紙可以貼在病人的病歷上，以確保本產品在使用後仍能進行有效的追蹤。

產品型號 / 規格

0.5 ml 包裝

Syringe volume: 0.5 ml

Enclosed needle: 29G x 1/2" x 1 needle

1.0 ml 包裝

Syringe volume: 1.0 ml

Enclosed needle: 29G x 1/2" x 2 needles

用途

Restylane Perlane Lidocaine 用於豐盈面部組織。它被推薦用來塑造面部輪廓、矯正皺褶以及豐唇。Restylane Perlane Lidocaine 必須被注射於真皮層深層和/或皮下組織表層。Lidocaine hydrochloride 可在治療過程中提供止痛效果。當面部軟組織支撐與包覆量有限時，例如：眼睛四周，建議注射於皮下脂肪組織或骨膜上。

作用機制

Restylane Perlane Lidocaine 是一種增加組織容積的填充物，因此可以重塑皮膚輪廓，或增加嘴唇的豐盈程度，並且可以根據需要，

矯正至滿意的程度。體積的維持與拉提能力來自玻尿酸的高吸力，透過穩定化製程可進一步提升吸力。Restylane Perlane Lidocaine 會隨時間以等容(isovolemic)的方式進行分解，也就是說產品在分解過程中仍可維持固定的體積。

警告

- 已知對 lidocaine 或酰胺類麻醉劑(amide-type local anaesthetics)過敏的病人請勿使用本產品。
- 切勿注射進入血管內。其他注射型的醫療器材若不慎注射入血管內可能會導致血管阻塞、暫時性缺血或皮膚壞死。建議注射前先抽吸以確認沒有插入血管。
- 如果觀察到變白反應時，即皮膚表面發白，必須立刻停止注射，並按摩此部位直到皮膚恢復為正常顏色。
- 凝血功能失調的病人或正在接受血栓溶解劑或抗凝血劑的病人請勿使用本產品。
- 請勿將 Restylane Perlane Lidocaine 重複滅菌。
- 請勿將本產品和其他產品混合後注射。

注意事項注射型醫療器材的一般注意事項

- 注射程序正確與否與感染的風險有關。請遵守無菌技術與標準操作程序以避免交叉感染。
- 當治療部位極接近永久性植入物時，操作上應特別小心。
- 對於治療部位應具備充分解剖學知識，且操作時應特別小心，以免觸及血管與其他脆弱組織。
- 當治療部位的側枝循環不良時，由於會增加局部缺血的風險，操作時應特別小心。
- 對於軟組織支持和包覆量有限的面部組織，例如：眼眶周圍，進行注射時應特別小心，以避免形成明顯的腫塊。
- 已有下眼周黑眼圈、眼皮薄和體質容易水腫的病人，不適合注射於下眼周周圍。
- 預定治療部位及其附近不可有活動性疾病，如發炎、感染或腫瘤。
- 注射程序可能會導致潛伏性或無臨床症狀的疱疹病毒再度活化感染。
- 病人正在服用會影響血小板功能的藥物，如阿斯匹靈(Aspirin)和非類固醇抗炎藥(NSAID)時，與接受其他任何注射一樣，注射部位發生瘀血或出血的情形會增加。
- 對治療結果存有過度期待的病人不適合使用本產品。
- 如果發現包裝損壞，請勿使用。

使用 Restylane Perlane Lidocaine 的特別注意事項

- 除了其他 Restylane 產品之外，Restylane Perlane Lidocaine 不能注射於該處已有其他注射性植入劑的部位。Restylane Perlane Lidocaine 不能注射於該處已有非注射性植入劑的部位。
- 至少在最初的紅腫情況消退之前，病人應儘量避免將治療部位暴露於高溫或處於極度寒冷的環境之下。
- 在植入 Restylane Perlane Lidocaine 之後，執行任何會使皮膚產生反應的雷射治療、化學換膚或其他治療，理論上植入部位會有產生發炎反應的危險。如果經上述治療後但皮膚尚未痊癒前植入 Restylane Perlane Lidocaine 也會發生相同的反應。
- Restylane Perlane Lidocaine 不曾進行孕婦、哺乳婦或小孩之測試。
- 如果同時使用牙科麻醉劑或局部給予 Lidocaine，則必須考量 Lidocaine 的總使用劑量。高劑量的 Lidocaine(超過 400mg)會導致急性毒性反應，影響中樞神經系統與心臟傳導。
- 病人如使用其他局部麻醉劑或與酰胺類局部麻醉劑(amide-type local anaesthetics)結構有關的藥物，例如某些抗心律不整藥物，在使用 Lidocaine 時應更加注意，因為可能會加重全身性毒性。
- 癲癇、心臟傳導受損、肝功能嚴重受損或嚴重腎功能不全的病人在使用 Lidocaine 時應更加小心謹慎。
- 眼周周圍注射局部麻醉劑對於持續性眼部肌肉功能失調(persistent ocular muscle dysfunction)者的風險較低。

預期的注射相關反應

在注射 Restylane Perlane Lidocaine 之後，可能會發生一些常見的注射相關反應。這些反應包括在注射部位有紅斑、腫脹、疼痛、發癢、瘀血或壓痛等症狀。一般來說，在注射於皮膚的數天內，注射於唇部的 1 週內會自然消退。

不良反應

Restylane 系列產品上市後最常被回報的不良反應為腫脹、瘀血、紅斑、團塊、疼痛與壓痛。他們被回報的頻率為每 10,000-20,000 次治療，大約會發生 1 次。

其次的不良反應為感染、發炎反應、變色、結節與丘疹，回報率為每 50,000 次治療發生 1 次。

以下為罕見但曾被回報過的不良反應，包括感染引起膿瘍、搔癢、過敏反應、面部無臨床症狀的疱疹病毒再度活化感染、瘙癢般的皮膚病、肉芽腫、水泡、泡囊、硬化、面部水腫、蕁麻疹、皮膚炎、疤痕或皮膚萎縮、短暫的注射後反應、暫時性缺血、注射部位壞死以及微血管擴張。

Appendix 3

Restylane® Perlane Lidocaine and Restylane® Perlane Taiwan IFU

104.

曾有臉部上半部注射，而不慎注射入動脈，造成暫時性視障障礙。這樣特殊罕見的案例被回報。

曾有於注射治療後發生缺血/壞死而影響鼻子的特殊個案被回報，此病人先前曾進行過鼻整形手術。

發炎症狀為注射部位合併有發紅、腫脹、壓痛與硬化這些症狀。這些反應可能在植入後立刻產生，或是延遲至 2 到 4 週後才發生。假使發生不明原因的發炎反應時，必須予以排除或治療，因為若未能完全治療感染，可能會引起併發症，例如膿瘍生成。不建議只給予口服類固醇，而未同時給予抗生素治療。曾發生此類發炎反應的病人，在決定治療前應先考量前次發炎反應的發生原因與嚴重性。

臨床研究中，曾於深膚色的人種 (Fitzpatrick Type IV-VI) 觀察到發炎後色素沉澱，這是由於黑色素沉澱造成的。

有任何不良反應發生時，請務必通知您當地 Q-Med 的業務代表或 Restylane 代理商。

效能

在一對照、多中心的研究結果顯示，Restylane Perlane 用於矯正法令紋(nasolabial folds)時，75%的受試者於注射後可維持臨床上顯著的改善效果達 6 個月。

在一隨機、對照、追蹤 12 個月的研究結果顯示，Restylane Perlane Lidocaine 的矯正功效相當於 Restylane Perlane。

針頭

為了確保安全地使用 Restylane Perlane Lidocaine，選擇無菌、合適的針頭或鈍頭套針非常重要，其接頭應合於注射器的螺旋接頭。本產品附有無菌拋棄式 29G TW 針頭(薄壁針頭)。若需替換針頭，應使用 27G 標準針頭。

另一建議替換針頭是鈍頭套針(blunt cannula)。建議的尺寸是 23-25G。套針的尺寸與長度會影響擠出膠體時所需的力。若使用較細的套針，注射時的力阻可能太高，而導致增加滲漏的風險，或是套針與注射器脫離。一般針頭亦有相同考量。

針頭安裝至注射器

針頭正確地安裝至注射器非常重要。不正確的安裝可能會導致注射時針頭與注射器脫離。



以姆指與食指緊握玻璃注射筒與螺旋接頭。另一手拿取注射針套(若使用套針，則為拿取針座)。請推進並旋轉針套與注射筒，以將它們鎖緊。如圖示。請遵守嚴謹的無菌操作原則。

治療程序

正確的注射技術對最終治療結果是很重要的。建議於初次治療前先諮詢您當地的 Q-Med 業務代表或 Restylane 代理商以取得有關的注射技術與訓練資料。Restylane Perlane Lidocaine 必須在符合當地的法律之下，由合格的人員來進行操作。在治療前，必須先告知病人產品的用途、預期的結果、注意事項和潛在的不良反應。在使用之前，必須先評估病人是否需要使用止痛藥。做雙唇手術時，可以使用阻斷神經的局部麻醉法。

- 注射過程具有感染風險。必須遵守無菌技術與標準操作程序，以避免交叉感染。以適當的消毒液徹底清潔治療部位。
- 為了避免針頭的斷裂，切勿嘗試折彎針頭。
- 注射前先排除注射器內的空氣，小心推壓注射器，直到針頭有少量液體溢出。
- 當使用銳針注射時，建議注射前先抽吸以確認沒有插入血管。在抽出針頭的同時，慢慢將產品注入皮膚內。
- 為了防止植入材料的外漏，在針頭抽出皮膚表面前必須停止注射。
- 可使用鈍頭套針做為替換針頭。依照上述方式準備就緒，先以適當尺寸的銳針刺入皮膚，做為套針的下針處，慢慢地注射。建議於注射過程中，使套針側孔保持朝下，背離皮膚表面，以確保流出的膠體維持於皮下正確的深度。
- 任何時候都不可在注射器施加過大的壓力。若有疤痕組織時，可能會阻礙套針/針頭的推進。如果遇到阻力，可以先稍微撤回套針/針頭並重新放置，或是全部抽出，確認其功能是否正常。
- 建議於每個新的治療部位替換新的套針/針頭。
- 每次療程每一處治療部位的最大建議用量為 2 ml。
- 在每次療程，必須將所欲改善的缺陷完全矯正，但不能矯正過度。
- 注射後的矯正部位必須按摩使其和周圍組織有一致的輪廓。
- 如果皮膚明顯鬆弛，則建議在不同時間接受 2 次或更多次的 Restylane Perlane Lidocaine 注射。
- 為了要達到所希望的矯正程度，在第一次注射之後，後續可能需要額外再植入 Restylane Perlane Lidocaine，以達到所希望的矯正程度。定期性的注射可以使此項矯正始終維持在滿意的程度。
- 依據所希望達成的效果、矯正程度與個別病人的需求，視情況合併使用其他 Restylane 系列產品可能有益。

在療程後，必須立即將注射器、拋棄式針頭/鈍頭套針和任何未使用的材料丟棄，不可重複使用，因為未使用的材料可能被污染，而具有感染風險。請依照國家、當地或院內的準則來處理醫療廢棄物。

2

保存期限和保存方式

保存期限: 36 個月，有效期限標示於外包裝。將本產品保存於 25°C 以下。避免冷凍和陽光照射。

製造廠名稱: Q-Med AB

104. 7. 29(0): Seminariegatan 21, SE-752 28 Uppsala, Sweden

製造廠地址(P): Seminariegatan 31, SE-752 28 Uppsala, Sweden

電話: +46(0)18 474 90 00 傳真: +46(0)18 474 90 01

網址: www.q-med.com 電子信箱: info@q-med.com

藥商名稱: 香港商高德美有限公司台灣分公司

藥商地址: 台北市大同區承德路一段 17 號 9 樓之 4-6

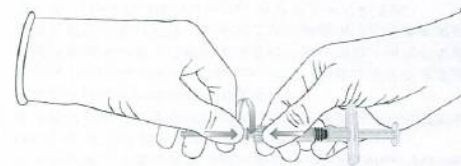
電話: 0800-200-212

包裝符號說明

	若發現包裝損壞，請勿使用。
	符合 MDD 93/42/EEC 之 CE 標誌。 0344 是 Restylane Perlane Lidocaine 認證機構的代碼。
	符合 MDD 93/42/EEC 之 CE 標誌。 0197 是注射針頭認證機構的代碼。

Restylane Perlane 與其他 Restylane 系列產品之品名以及 NASHA 是 Q-Med AB 公司的註冊商標。

以姆指與食指緊握玻璃注射筒與螺旋接頭。另一手拿取注射針套(若使用套針，則為拿取針座)。請推進並旋轉針套與注射筒，以將它們鎖緊。





Appendix 3

Restylane® Perlane Lidocaine and Restylane® Perlane Taiwan IFU

“奇美德”玻麗朗

“Q-Med” Restylane Perlane

衛署醫器輸字第 021891 號

第二版，2012 年 5 月 24 日修訂

注意：使用前請務必詳閱原廠之使用說明書並遵照指示使用

處方

玻尿酸 (Hyaluronic acid, Stabilized) 20 mg/ml
磷酸緩衝液 足量

產品描述

Restylane Perlane 是無菌透明的非動物性穩定型玻尿酸膠體。Restylane Perlane 充填於具有螺旋接頭的玻璃注射器內。注射器內容物經過濕熱滅菌。本產品只供單次使用。注射器附有可拋棄式無菌針頭。滅菌方式與針頭尺寸標示於針頭的包裝上。產品外包裝上註明每一包裝內含的物件數量和每一注射器內含的玻尿酸容量。注射器上貼有使用記錄貼紙。這個記錄貼紙可以貼在病人的病歷上，以確保本產品在使用後仍能進行有效的追蹤。

產品規格

0.5 ml 包裝

Syringe volume: 0.5 ml
Enclosed needle: 29G x 1/2" x 1 needle

1.0 ml 包裝

Syringe volume: 1.0 ml
Enclosed needle: 29G x 1/2" x 2 needles

用途

Restylane Perlane 用於豐盈臉部組織。它被推薦用來塑造面部輪廓、矯正皺褶以及豐唇。Restylane Perlane 必須被注射於真皮層深層和/或皮下組織表層。對於軟組織支持和覆蓋有限的臉部組織，例如：眼眶周圍，建議注射於皮下脂肪組織或骨膜上。

作用機制

Restylane Perlane 是一種增加組織容積的填充物，因此可以重塑皮膚輪廓，或增加嘴唇的豐盈程度，並且可以根據需要，矯正至滿意的程度。體積的維持與拉提能力來自玻尿酸的高吸水力，透過穩定化製程可進一步提升吸水力。Restylane Perlane 會隨時間以等容(isovolemic)的方式進行分解，也就是說產品在分解過程中仍可維持固定的體積。

警告

- 切勿注射進入血管內。其他注射型的醫療器材若不慎注入血管內可能會導致血管阻塞、暫時性缺血或皮膚壞死。建議注射前先抽吸以確認沒有插入血管。
- 如果觀察到變白反應時，即皮膚表面發白，必須立刻停止注射，並按摩此部位直到皮膚恢復為正常顏色。
- 凝血功能失調的病人或正在接受血栓溶解劑或抗凝血劑的病人請勿使用本產品。
- 請勿將 Restylane Perlane 重覆滅菌。
- 請勿將本產品和其他產品混合後注射。

注意事項

注射型醫療器材的一般注意事項

- 注射程序正確與否與感染的風險有關。請遵守無菌技術與標準操作程序以避免交叉感染。
- 當治療部位極接近永久性植入物或脆弱組織，如神經、血管與其他重要組織時，操作時應特別小心。
- 醫師對於治療部位應具有充分的解剖學知識，若使用銳針需特別小心，以避免刺穿或壓迫血管以及其他脆弱組織。
- 當治療部位的側枝循環不良時，由於會增加局部缺血的風險，操作時應特別小心。
- 對於軟組織支持和覆蓋有限的臉部組織，例如：眼眶周圍，進行注射時應特別小心，以避免形成明顯的腫塊。
- 已有下眼周黑眼圈、皮膚薄和有形成水腫傾向的病人不適合注射於下眼周周圍。
- 預定治療部位及其附近不可有活動性疾病，如發炎、感染或腫瘤。
- 注射程序可能會導致潛伏性或無臨床症狀的皰疹病毒再度活化感染。
- 病人正在服用會影響血小板功能的藥物，如阿斯匹靈 (Aspirin) 和非類固醇抗發炎藥物 (NSAID) 時，與接受其他任何注射一樣，注射部位發生瘀血或出血的情形會增加。
- 對治療結果存有過度期待的病人不適合使用本產品。
- 如果發現包裝損壞，請勿使用。
- 注射鼻頭附近可能造成組織缺血性壞死及血管壓迫之風險。

使用 Restylane Perlane 的特別注意事項

- 除了其他 Restylane 系列產品之外，Restylane Perlane 不能注射於該處已有其他注射性植入劑的部位。Restylane Perlane 不能注射於該處已有非注射性植入劑的部位。
- 至少在最初的紅腫情況消退之前，病人應儘量避免將治療部位曝露於高溫或處於極度寒冷的環境之下。
- 在植入 Restylane Perlane 之後，執行任何會使皮膚產生反應的雷射治療、化學換膚或其他治療，理論上植入部位會有產生發炎反應的危險。如果經上述治療後但皮膚尚未痊癒前植入 Restylane Perlane 也會發生相同的反應。
- Restylane Perlane 不曾進行孕婦、哺乳婦或小孩之測試。

預期的注射相關反應

在注射 Restylane Perlane 之後，可能會發生一些常見的注射相關反應。這些反應包括在注射部位有紅斑、腫脹、疼痛、發癢、瘀血或壓痛等症狀。一般來說，在注射於皮膚的數天內，注射於唇部的 1 週內會自然消退。

不良反應

Restylane 系列產品上市後最常被回報的不良反應為腫脹、瘀血、紅斑、圓塊、疼痛與壓痛。他們被回報的頻率為每 10,000-20,000 次治療，大約會發生 1 次。

其次的不良反應為感染、發炎反應、變色、結節與丘疹，回報頻率為每 50,000 次治療發生 1 次。

以下為罕見但曾被回報過的不良反應，包括感染惡化為膿瘍生成、搔癢、過敏反應、臉部無臨床症狀的皰疹病毒再度活化感染、瘡癤般的皮膚病、肉芽腫、水泡、泡囊、硬化、臉部水腫、蕁麻疹、皮膚炎、疤痕或皮膚萎縮、短暫的注射後反應、暫時性缺血、注射部位壞死以及微血管擴張。

於注射臉上半部時，不慎注射入動脈而造成暫時性視覺障礙這個獨特罕見的案例也曾被回報。

曾有於注射治療後發生缺血/壞死而影響鼻子的特殊個案被回報。

有視覺障礙甚至失明及全層皮膚壞死之風險。

發炎症狀為注射部位合併有發紅、腫脹、壓痛與硬化這些症狀。這些反應可能在植入後立刻產生，或是延遲至 2 到 4 週後才發生。假使發生不明原因的發炎反應，必要時，必須排除和治療感染。因為若未能完全治療感染，可能會引起併發症，如膿瘍生成。不

Appendix 3

Restylane® Perlane Lidocaine and Restylane® Perlane Taiwan IFU

建議只給予口服類固醇，而未同時投與抗生素治療。曾發生此類發炎反應的病人，在決定治療前應先考量前次發炎反應的發生原因與嚴重性。

臨床研究中，曾於深膚色的人種（Fitzpatrick Type IV-VI）觀察到發炎後色素沉澱，這是由於黑色素沉澱造成的。

有任何不良反應發生時，請務必通知您當地 Q-Med 的業務代表或 Restylane Perlane 代理商。

效能

在一對照、多中心的研究結果顯示，Restylane Perlane 用於矯正法令紋(nasolabial folds)時，75%的受試者於注射後可維持臨床上顯著的改善效果達 6 個月。

注射針

為了確保使用 Restylane Perlane 的安全，使用無菌且適當的套針或注射針是相當重要的，套針/注射針的接頭必須與注射器的螺旋接頭(luer-lock)相符。本品附有合用且拋棄式的無菌 29G TW(薄壁)注射針。若需更換注射針應使用 27G 之注射針。

可使用鈍頭套針代替，建議的尺寸為 23-25G。套針的尺寸和長度會影響抽取膠體所需的力量。若使用較細的套針，在注射過程中，可能會因為阻力太高而增加滲漏或是套針與注射器分離的風險。使用一般銳針亦有相同的考量。

針頭安裝至注射器

針頭安裝適當與否是一項非常重要的工作。不正確的安裝可能會導致注射時針頭與注射器脫離。

以姆指與食指緊握玻璃注射筒與螺旋轉接頭。另一手拿取注射針套(若使用套針則拿取鈍頭套針)。請**推進並旋轉**針套與注射筒，以將它們鎖緊。如圖示。必須遵守嚴格的無菌操作技術。

治療程序

正確的注射技術對最終治療結果是很重要的。建議於初次治療前先洽詢您當地的 Q-Med 業務代表或 Restylane Perlane 代理商以取得有關的注射技術與訓練資料。Restylane Perlane 必須在符合當地的法律之下，由合格的人員來進行操作。在治療前，必須先告知病人產品的用途、預期的結果、注意事項和潛在的不良反應。在使用之前，必須評估病人是否需要使用止痛藥。為了降低病人的不適感，在進行皺紋矯正時，建議進行表面麻醉或局部麻醉。做豐唇手術時，可以使用阻斷神經的局部麻醉法。

- 注射程序與感染風險有關。須遵守無菌操作技術與標準程序以預防交叉感染。以適當的消毒液徹底清潔治療部位。
- 為了避免針頭的斷裂，切勿嘗試折彎針頭。
- 注射前先排除注射器內的空氣，小心推壓注射器，直到針頭有少量液體溢出。
- 若是使用銳針，建議注射前先抽吸。在抽出針頭的同時，慢慢將產品注入皮膚內。
- 請使用內含的針頭，在抽出針頭的同時，慢慢將產品注入真皮層深層和/或皮下組織表層。為了防止植入材料的外漏，在針頭抽出皮膚表面前必須停止注射。
- 可以使用鈍頭套針代替銳針。準備工作同上所述，先使用適當尺寸的銳針在皮膚上建立一個注射點，慢慢的注入。在注射過程中，建議保持套針的側孔朝下，背向皮膚表面，以確保流出的膠體維持在真皮層的正確深度。
- 任何時候都不可在注射器施加過大的壓力。疤痕組織的存在會阻礙套針/注射針推進。如果遇到阻力，可先稍微抽回套針/注射針並重新放置，或是全部抽出並確認其功能是否正常。
- 建議於每個新的注射部位使用新的注射針/鈍頭套針。
- 每次療程每一處治療部位的最大建議用量為 2 ml。
- 在每次療程，必須將所欲改善的缺陷完全矯正，但不能矯正過度。
- 注射後的矯正部位必須按摩使其和周圍組織有一致的輪廓。
- 如果有明顯的皮膚鬆弛，則建議在不同時間接受 2 次或更多次的 Restylane Perlane 注射。
- 為了要達到所希望的矯正程度，在第一次注射之後，後續可能需要額外再植入 Restylane Perlane，以達到所希望的矯正程度。定期性的注射可以使此項矯正始終維持在滿意的程度。
- 依據所希望達成的效果、矯正程度與個別病人的需求，視情況合併使用其他 Restylane 系列產品可能有益。

在療程後，必須立即將注射器、拋棄式針頭/套針和任何未使用的材料丟棄，且不可重複使用，因為未使用的材料可能被污染，且重複使用會有相關的感染風險。請依照國家、當地或院內的準則來處理醫療廢棄物。




保存期限和保存方式

保存期限標示於外包裝。將本產品保存於 25°C 以下。避免冷凍和陽光照射。

製造廠名稱：Q-Med AB

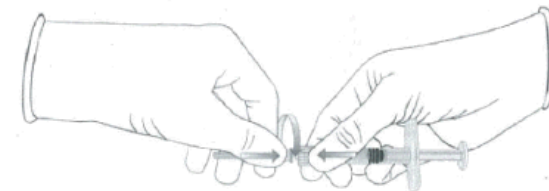
公司地址(O)：Seminariégatan 21, SE-752 28 Uppsala, Sweden
製造廠地址(P)：Seminariégatan 31, SE-752 28 Uppsala, Sweden
電話：+46(0)18 474 90 00 傳真：+46(0)18 474 90 01
網址：www.q-med.com 電子信箱：info@q-med.com
藥商名稱：友華生技醫藥股份有限公司
藥商地址：臺北市大安區復興南路一段 368 號 7 樓
電話：(02)27554881


包裝符號說明

	若發現包裝損壞，請勿使用。
	符合 MDD 93/42/EEC 之 CE 標誌。 0344 是 Restylane Perlane 認證機構的代碼。
	符合 MDD 93/42/EEC 之 CE 標誌。 0197 是所附注射針頭認證機構的代碼。


Restylane Perlane 與其他 Restylane 系列產品之品名以及 NASHA 是 Q-Med AB 公司的註冊商標。


以姆指與食指緊握玻璃注射筒與螺旋轉接頭。另一手拿取注射針套(若使用套針則拿取鈍頭套針)。請**推進並旋轉**針套與注射筒，以將它們鎖緊。





	Title 43TW1628 Clinical Study Protocol	Doc id MA-34273
--	--	---------------------------

SIGNATURES PAGE

Date	Signed by
2017-04-11 12:27	
Justification	Approved by Technical Expert

2017-04-11 12:35	
Justification	Approved by Owner

2017-04-11 13:12	
Justification	Approved by Technical Expert

2017-04-13 06:29	
Justification	Approved by Technical Expert

Effective date: 2017-04-13 06:29

Effective

Version: 1.0