DENOVA RESEARCH

# STUDY PROTOCOL

**PROTOCOL TITLE:** An Open-Label, Post-Market Study to Assess the Impact of Lip Rejuvenation with Restylane® Silk on Projected First Impressions and Mood Perceptions

**COSMECEUTICAL:** Restylane® Silk

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**CONFIDENTIALITY STATEMENT**

This study is confidential in nature. All information related to this study is considered proprietary and should not be made available to those not directly involved in this study. Authorized recipients of this information include investigators and co-investigators, other health care personnel necessary to conduct the study and institutional review boards. The above personnel

# INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will comply with Good Clinical Practice (GCP) regulations and guidelines during the conduct of this study. I certify that this study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that they are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 812, applicable laws, and the IRB requirements.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the treatment and the conduct of the study.

I will use only the informed consent form approved by the Institutional Review Board (IRB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information especially with respect to development of any serious adverse events to the Institutional Review Board or Ethics Committee responsible for this study.

Principal Investigator:

Steven H. Dayan _____ _____ _____

*PrintedName* *Signature* *Date*

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# 1 LIST OF ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| AE | Adverse Event |
| CFR | Code of Federal Regulation |
| CRF | Case Report Form |
| EC | Ethics Committee |
| FDA | Food and Drug Administration |
| FIQ | First Impression Questionnaire |
| GAIS | Global Aesthetic Improvement Scale |
| GCP | Good Clinical Practice |
| HIPAA | Health Information Portability and Accountability Act |
| HM | Happiness Measures |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IRB | Institutional Review Board |
| m | Meter |
| mg | Milligram |
| ml | Milliliter |
| OCR | Optimal Cosmetic Results |
| OCSS | Oral Commissure Severity Scale |
| PI | Principal Investigator |
| POLSS | Perioral Lines Severity Scale |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SHS | Subjective Happiness Scale |
| SOP | Standard Operating Protocol |

# 2 PROTOCOL SYNOPSIS

| | |
|---|---|
| **Title** | An Open-Label, Post-Market Study to Assess the Impact of Lip Rejuvenation with Restylane® Silk on Projected First Impressions and Mood Perceptions |
| **Indication** | Subjects with mild to severe oral commissures or none to severe perioral lines who request lip rejuvenation with Restylane® Silk |
| **Sample Size** | 20 |
| **Number of Centers** | One center in the United States |
| **Study Objectives** | The primary objective of this study is to determine if subjects who receive lip rejuvenation treatment with Restylane® Silk project a more positive first impression and report an improvement in mood perception. |
| **Subject Selection** | A total of 20 subjects who wish to receive lip rejuvenation treatment with Restylane® Silk and meet the specified criteria will be enrolled. |
| **Study Design** | 20 subjects with mild to severe oral commissures or none to severe perioral lines will be enrolled and injected with Restylane® Silk. Photographs will be taken prior to and 14 days after Optimal Cosmetic Results has been achieved, as judged by the investigator.<br><br>Changes in the projected first impression will be assessed by a total of 200 blinded evaluators rating the photographs of subjects from the baseline and from 14 days post achieving the Optimal Cosmetic Results. Changes in subjects' mood will be self-assessed through Subjective Happiness Scale and Happiness Measures questionnaires. Aesthetic alterations will be assessed by the investigator via the Global Aesthetic Improvement Scale, Oral Commissure Severity Scale, and the Perioral Lines Severity Scale as well as by the self-assessment of subjects using the Global Aesthetic Improvement Scale.<br><br>A schematic of the study design is presented in Appendix A. |

| | |
|---|---|
| **Study Duration** | Subjects will be followed for 14 days after a treatment that has produced Optimal Cosmetic Results. |
| **Clinical Hypothesis** | Subjects who are treated with Restylane® Silk for lip rejuvenation project a more positive first impression as compared to their pre-treatment baseline. Those who are treated with Restylane® Silk will also report a more positive mood perception after treatment as compared to pre-treatment. |

# 3 INVESTIGATOR

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# 4 BACKGROUND

A first impression can be defined as the initial judgment made of a person without a prior familiarity. It has been well recognized that these zero-acquaintance impressions, which are formed within seconds of seeing a person, are greatly influenced by physical appearances[1-3]. The perceived impression forms an image of personality, known as the *physical personality*, that induces a set of expectations and behaviors in others, which, in turn, impact the manner by which an individual is judged and treated in the society.

It has been suggested that '*attractive*' individuals receive better judgments and treatments[4] whereas those deemed '*unattractive*' generally seem to elicit negative responses[5]. Various clinical studies have also linked aesthetic enhancements, through surgical or non-surgical procedures, with improved projected first impressions[6-8]. Remarkably, the self-perception of physical appearances also seems to affect the development of inherent personality. It has been elucidated that self-dissatisfaction due to craniofacial abnormalities can elicit low self-esteem[5] while non-surgical aesthetic enhancements may improve self-esteem and lead to a better quality of life[9]. Thus, improvements of physical appearances can create a better projected first impression as well as a better self-satisfaction.

In the past decade, dermal fillers have become one of the most popular minimally invasive treatments for rejuvenation and body sculpturing. According to the American Society of Plastic Surgeons, over 1.6 million hyaluronic acid filler procedures were performed in 2013[10]. Restylane® Silk (Galderma Laboratories, L.P.) is a hyaluronic acid injectable filler, which is approved by the FDA for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids. The goal of this study is to determine if lip rejuvenation of patients with mild to severe oral commissures or none to severe perioral lines using Restylane® Silk would lead to an improved projected first impression and self-perception of mood.

# 5 STUDY OBJECTIVES

The primary objective of this study is to determine if lip rejuvenation with Restylane® Silk results in an improved projected first impression as well as an improved self-perception of mood.

The secondary objective is to evaluate aesthetic improvements after lip rejuvenation treatment with Restylane® Silk and assess relations to any alternations in the projected first impression

and mood perception.

# 6 STUDY DESIGN

This is an open-label, post-market study to assess the impact of lip rejuvenation with Restylane® Silk on the projected first impression and the self-perception of mood.

20 subjects, at least 21 years of age, who display mild to severe oral commissures or none to severe perioral lines, as judged by the Principal Investigator (PI) utilizing the Oral Commissure Severity Scale (OCSS, Appendix G) or the Perioral Lines Severity Scale (POLSS, Appendix H), will be enrolled.

The study is composed of up to 4 patient visits and a post-visit evaluation of patients' photographs by blinded evaluators. A schematic of the study design is presented in Appendix A.

All subjects who meet the specified criteria, listed in Section 7, will complete the Subjective Happiness Scale[11,12] (SHS, Appendix B) and the Happiness Measures questionnaire[13] (HM, Appendix C) prior to receiving any treatments. The PI also records the severity of subjects' oral commissures and/or the perioral lines using the OCSS and/or the POLSS respectively. Furthermore, all subjects undergo photo- and videography, as described in Appendix I, prior to treatment.

Subjects will then be injected with Restylane® Silk with a volume sufficient to achieve Optimal Cosmetic Results (OCR), per treating investigator's discretion but not to exceed a total of 4 ml (4 syringes). Subjects will be assessed 14 ± 3 days after injection for achieving the OCR. If OCR has not been reached, as judged by the PI, a second, 'touch-up,' injection of Restylane® Silk will be performed.

The final evaluation of subjects will take place 14 ± 3 days after achieving OCR. Hence, this would be 14 ± 3 days after the first injection for those who achieved OCR with one treatment but 28 ± 3 days after the first injection for those who required a 'touch-up' injection. Subjects will complete the SHS and HM questionnaires as well as self-report any aesthetic alterations experienced using the Global Aesthetic Improvement Scale (GAIS, Appendix D). They will also undergo photo- and videography, as described in Appendix I. Furthermore, the PI will rate the subjects on the GAIS (Appendix E) as well as on the OCSS and the POLSS.

Photographs taken at pre-treatment and 14-Day Post-OCR will be randomly divided into 4 binders, for a total of 10 photographs per binder. Each binder will be evaluated at least by 50 blinded evaluators using the First Impressions Questionnaire (FIQ, Appendix F) to rate each photograph.

# 7 SUBJECT SELECTION

A total of 20 subjects who meet all of following inclusion criteria and none of the exclusion criteria will be enrolled in this study.

### 7.1 Inclusion Criteria

All subjects must meet the following inclusion criteria:

1. Subject is an adult of at least 21 years of age;
2. Subject has mild to severe oral commissures or none to severe perioral lines, as assessed by the treating investigator;
3. Subject is willing and able to provide written informed consent prior to the performance of any study related procedure;
4. Subject is willing and able to comply with the protocol requirements; and
5. Subject is willing and able to provide written photo consent and adhere to the photography and video procedures such as removal of jewelry and makeup.

### 7.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Subjects who have received lip filler treatments in the past 12 months or neurotoxin injections in the past 6 months;
2. Subjects who plan to undergo neurotoxin treatments, ablative skin treatments, facial cosmetic surgery, or other injectable filler treatments during the course of the study;
3. Subjects with a known allergy or sensitivity to any component of the study ingredients;
4. Subjects with a history of bleeding disorders;
5. Female subjects who are pregnant or nursing as well as those who are of childbearing potential but do not employ adequate birth control methods;
6. Subjects with severe allergies manifested by a history of anaphylaxis or presence of multiple severe allergies;
7. Subjects with previous history of sensitivity to amide type local anesthetics;
8. Current history of chronic drug or alcohol abuse;
9. Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study product;
10. Subjects who, in the investigator's opinion, have a history of poor cooperation, non- compliance with medical treatment, or unreliability; and
11. Enrollment in any active study involving the use of investigational devices or drugs.

## 8 TREATMENT AND STUDY SUPPLIES

### 8.1 Description of Study Supplies and Handling

Restylane® Silk (Galderma Laboratories, L.P.) is a gel of hyaluronic acid produced by the *Streptococcus* species of gram-positive bacteria that is chemically crosslinked with butanediol diglycidyl ether (BDDE) and suspended in phosphate buffered saline (pH 7) at a concentration of 20 mg/ml with 0.3% lidocaine. Restylane® Silk supplies are stored in a secure cabinet at room temperature at the investigation site.

## 8.2 Packaging and Labeling

Restylane® Silk is supplied in disposable glass syringes with a Luer-Lok® fitting and is co-packed with a sterilized 30 G x ½ needle. Each syringe contains 1 ml of the injectable gel (20 mg/ml of hyaluronic acid) with 0.3% lidocaine. Each package is for single patient use. A patient record label, which is included in the syringe label, will be attached to each patient's records for product traceability.

## 8.3 Method of Application

### *8.3.1 Pre-treatment Guidelines*

Prior to treatment, the patient is advised to avoid taking aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, and high doses of vitamin E supplements 14 days prior to the day of treatment, as these agents may increase bruising and bleeding at the injection site.

### *8.3.2 Treatment Procedure*

- The patient's face is washed with soap and water and dried with a clean towel. The treatment area is cleansed with alcohol or Benzalkonium Chloride.
- Topical anesthetic (30% lodocaine) is applied to the injection area. Alternatively, at patient's request, an infraorbital/mental nerve block with 3% mepivacaine is used to anesthetize the treatment area.
- Restylane® Silk is administered using a thin gauge needle (30 G x ½) or a 22 gauge cannula. The needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle, fold, or lip. For rhytids, Restylane® Silk is injected into the mid-to-deep dermis.
- A maximum dose of 4.0 ml is used per treatment.

### *8.3.3 Injection Technique*

Restylane® Silk may be injected by a number of different techniques depending on the treating physician's experience and preference as well as the specific characteristics and needs of each patient (Restylane® Silk Package Insert[14]). The appropriate injection method will be employed per treating investigator's discretion.

# 9 STUDY PROCEDURES

## 9.1 Visit 1: Screening Assessments

The PI and/or designee is responsible for keeping a record of all subjects screened for entry into the study as well those who did not meet the criteria, as described in Section 7, and hence were excluded.

The following procedures will be performed:

1. The PI or designee evaluates and confirms that the subject fulfills all the inclusion/exclusion criteria, as described in Section 7.

2. A written informed consent, signed by the subject as well as by the investigator or designee, is obtained.
3. Demographic information and medical history are obtained.
4. List of concomitant medications is collected.
5. Vital signs (blood pressure and pulse rate) are measured.
6. If the subject is a female of child bearing potential, a urine collection for in-clinic pregnancy test will be conducted.
7. Subject completes the SHS questionnaire
8. Subject completes the HM questionnaire.
9. Subject undergoes standardized digital photography and video of full face in accordance with the site's SOP (described in Appendix I).

## 9.2 Visit 2: Treatment

Visit 2 will take place no later than 14 days after the screening assessments. If the period between the screening assessments and the treatment is greater than 14 days, the in-clinic urine pregnancy test will be repeated for females of childbearing potential. The following procedures will be performed:

1. Subject's medical history and concomitant medications are reviewed for changes since Visit 1, Screening Assessments.
2. PI rates the subject on the OCSS and POLSS at rest.
3. The injection area is wiped with a Benzalkonium Chloride towelette.
4. A topical anesthetic containing 30% lidocaine is applied to the injection areas. Alternatively, subject may choose to receive a nerve block, infraorbital/mental with 3% mepivacaine, to numb the treatment area.
5. Subject is injected with Restylane® Silk with a volume sufficient to deliver satisfactory cosmetic results per treating investigator's discretion but not to exceed a total of 4 ml (4 syringes).
6. The volume injected is recorded.
7. The subject is monitored for any Adverse Events (AEs)

## 9.3 Visit 3: OCR Evaluation

The following procedures will be performed 14 ± 3 days after Visit 2, Treatment:

1. PI assesses the subject for achieving the OCR.
2. At PI's discretion, subject may receive a touch-up treatment in order to achieve OCR (not to exceed a total dose of 4 ml of Restylane® Silk).
3. A report of any AEs and changes in concomitant medications is obtained from the subject.

Subjects who require a touch-up injection will be instructed to return for the forth and final visit in 14 ± 3 days. For those who have achieved OCR, and hence do not require a touch-up injection, the following procedures will be performed:

1. Subject completes the SHS questionnaire.

2. Subject completes the HM questionnaire.
3. Subject completes a self-reported GAIS (S-GAIS).
4. PI completes the GAIS form (PI-GAIS).
5. PI rates the subject on the OCSS and POLSS at rest.
6. Subject undergoes standardized digital photography and video of full face in accordance with the site's SOP (described in Appendix I);

## 9.4 Visit 4: 14-Day Post-OCR

Visit 4 will take place 14 ± 3 days after Visit 3, OCR Evaluation only for subjects who required a touch-up injection in Visit 3 in order to achieve OCR.

The following procedures will be performed:

1. Subject completes the SHS questionnaire.
2. Subject completes the HM questionnaire.
3. Subject completes a self-reported GAIS (S-GAIS).
4. PI completes the GAIS form (PI-GAIS).
5. PI rates the subject on the OCSS and POLSS at rest.
6. Subject undergoes standardized digital photography and video of full face in accordance with the site's SOP (described in Appendix I);
7. A report of occurrence of any AEs and changes in concomitant medications is obtained from the subject.

## 9.5 Post-Visit Evaluations

Photographs of subjects taken at Visit 1, Screening Assessments and at Visit 4, 14-Day Post- OCR will be used to assess alterations in the projected first impression (see Section 10.1.1 for further details).

# 10 RESPONSE CRITERIA

## 10.1 Primary Variable Assessments

The primary assessment of this study is to determine if subjects who receive lip rejuvenation treatment with Restylane® Silk would project a more positive first impression as well as experience a more positive mood perception as compared to their baseline. The primary efficacy will be established by comparing the projected first impression of subjects at 14-Day Post-OCR with that of the baseline. The change is mood perception will be determined by comparing the SHS and HM results from 14-Day Post-OCR with those from the baseline.

### *10.1.1 Assessment of First Impressions*

Upon completion of the study, a minimum of 200 blinded evaluators will assess one of four binders, for a minimum of 50 blinded evaluators per binder, each comprised of 10 photographs selected randomly from Visit 1 (baseline) or Visit 4 (14-Day Post-OCR) for each subject. The

FIQ will be completed by each evaluator for each photo (see Appendix F). Each photograph will be graded based on a 10-point numerical rating scale for each of the 8 categories listed below:

- *Social skills*: Social desirability, temperament, positive mood, getting along with others, friendliness
- *Academic performance*: Intelligence, educational skills
- *Dating success*: Frequently invited, lack of dating anxiety, thought of positively after dating encounter
- *Occupational success*: Job performance, competence, motivation for success, suitability as potential employee
- *Attractiveness*: Pleasing appearance
- *Financial success*: Has achieved or is a member of an elevated socioeconomic status
- *Relationship success*: Willingness to compromise put the relationship health before their own desires or gain, Ability to maintain long term friendships
- *Athletic skills*: Ability to excel at athletic events, including individual and team sports

#### *10.1.2 Subjective Happiness Scale (SHS) Evaluation*

Changes in subjects' mood will be determined partially through the SHS questionnaire (Appendix B) completed by subjects at Visit 1, Screening Assessments (baseline) and at Visit 4, 14-Day Post-OCR.

#### *10.1.3 The Happiness Measures (HM) Evaluation*

Changes in subjects' mood will be determined partially through the HM questionnaire (Appendix C) completed by subjects at Visit 1, Screening Assessments (baseline) and at Visit 4, 14-Day Post-OCR.

## 10.2 Secondary Variable Assessments

The secondary variables evaluated in this study include changes in the overall aesthetic improvements, determined as described below.

#### *10.2.1 Subject Global Aesthetic Improvement Scale (S-GAIS) Evaluation*

Changes in global aesthetics will be determined through subjects' self-assessments utilizing the GAIS (Appendix D) at Visit 4, 14-Day Post-OCR.

#### *10.2.2 PI Global Aesthetic Improvement Scale (PI-GAIS) Evaluation*

Changes in global aesthetics will be determined partially by the PI's assessment of subjects at Visit 4, 14-Day Post-OCR utilizing the GAIS (Appendix E).

#### *10.2.3 Oral Commissure Severity Scale (OCSS) Evaluation*

Aesthetic improvement will be determined by the PI's assessment of subjects at Visit 1, Treatment (baseline) and at Visit 4, 14-Day Post-OCR partially through utilizing the OCSS (Appendix G)

#### *10.2.4 Perioral Lines Severity Scale (POLSS) at Rest Evaluation*

Aesthetic improvement will be determined by the PI's assessment of subjects at Visit 1, Treatment (baseline) and at Visit 4, 14-Day Post-OCR partially through utilizing the POLSS (Appendix H).

# 11 DATA MANAGEMENTS

## 11.1 Case Report Forms

For each subject enrolled who has given informed consent, completed the screening process, and began the study process, a Case Report From (CRF) will be created and signed by the PI or designee to certify completeness and correctness.

If a subject is withdrawn from the study due to a treatment-related AE, due diligence must be used to document the outcome. Source documentation verification will be performed by the study monitors. All CRFs will remain at the study site.

## 11.2 Data Handling

Data management based on GCP refers to the activities defined to achieve safe routines for efficiently entering clinical data information into a database while avoiding errors. The data management routines include procedures for handling CRFs, database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process.

The database, the data entry screens, and program will be designed in accordance with the study protocol and the CRF. Single data entry and proofreading will be used for data entry and verification. Data validation will be performed after data entry and verification by manual review. When the clinical study coordinator has made all efforts to ensure that the data recorded in the CRFs and entered in the database is as correct and complete as possible, "clean file" is declared, and the database is closed. The clinical study coordinator should document the database closure in a signed written document. Final statistical analysis should be generated using data from the closed database. Any additional subsequent changes or corrections to the closed database should be documented in an audit trail.

## 11.3 Publication

Following completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific or medical journal.

# 12 STATISTICAL METHODS

## 12.1 Sample Size

20 subjects will be enrolled as described in Section 7. Using the primary end point of FIQ scores, and assuming a standard deviation of 14 and a difference of 2.5[6] in the total FIQ score between the baseline and 14-Day Post-OCR, a sample size of 20 will provide a power of approximately 8% (with =0.05).

## 12.2 Study Population

The study population will include all subjects who are enrolled and have received treatment. The entire study population will be included in the statistical analyses.

## 12.3 Study Endpoints

### *12.3.1 Primary Endpoints*

1. FIQ completed by 200 blinded evaluators using the photos of subjects from the baseline and the 14-Day Post-OCR visits
2. Subjects' execution of the SHS at 14-Day Post-OCR
3. Subjects' completion of the HM questionnaire at 14-Day Post-OCR

### *12.3.2 Secondary Endpoints*

1. S-GAIS evaluation at 14-Day Post-OCR
2. PI-GAIS evaluation at 14-Day Post-OCR
3. OCSS evaluation at 14-Day Post-OCR
4. POLSS evaluation at 14-Day Post-OCR

## 12.4 Methods of Analysis

Descriptive statistics will be used to analyze the data. The number of subjects (n), minimum (min), maximum (max), mean, median, and standard deviation (SD) will be reported for the continuous data. Frequencies and percentages will be reported for the categorical data. Unless otherwise stated, statistical testing will be two-sided and executed using a significance level of
0.05. All statistical analyses, summary tables, and data listings will be performed using the SPSS (IBM) or the Excel (Microsoft Co.) software.

# 13 ADVERSE EVENTS

## 13.1 Definition

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical or medical device product that does not necessarily have a causal relationship with this treatment. Adverse events include the following: all suspected adverse device or procedure reactions, occurrence of apparently unrelated illnesses

(i.e., symptoms or diseases that were not present at study entry), worsening of a pre-existing illness (i.e., concurrent symptoms or diseases), injuries or accidents, and abnormalities in physiological or laboratory testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test). Throughout the study, subjects will be monitored for signs and symptoms of adverse events.

All adverse events reported during the study period will be recorded in detail in the subject's medical file and CRF.

## 13.2 Recording of Adverse Events

Subjects will be instructed by the PI to immediately report the occurrence of any adverse event. Each subject should be questioned at all visits whether any side effects or adverse events have occurred. All spontaneously volunteered, inquired, and observed adverse experiences will be recorded in detail.

## 13.3 Serious Adverse Events and Unanticipated Adverse Device Effects

### *13.3.1 Definition*

Serious Adverse Events (SAEs) are defined as undesirable events experienced by a subject that suggest a significant hazard, contraindication, side effect, or precaution, whether or not considered to be device-related by the Investigator. An AE is defined as being serious if:

1. It is fatal or life threatening (life threatening means that in the opinion of the Investigator, the subject was at immediate risk of death from the adverse reaction)
2. It is permanently or temporarily disabling
3. It requires inpatient or prolonged hospitalization
4. Is a congenital anomaly/birth defect

An unanticipated adverse device effect is defined as any serious adverse effect on health or safety, any life threatening problem, or death that was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relate to the rights, safety, or welfare of subjects.

### *13.3.2 Serious Adverse Events Recording and Reporting*

Any serious and/or unexpected adverse event that occurred while on study or one month after completion of study must be reported to DeNova Research via telephone. The Serious Adverse Event Report Form must be completed and faxed to DeNova Research and IRB within 24 hours of notification.

In addition, the local IRB or EC must be notified of all adverse events that are serious and/or unexpected.

All adverse events, including serious and unexpected events, must be recorded by the Investigator on the standard Adverse Event Report form. This form will be included in the CRF. All Adverse Event Reports describing adverse events other than serious or unexpected adverse events will be inserted into the CRF. In addition, any serious and treatment-related unexpected adverse events must be reported to the local IRB within 5 business days of the event.

Subjects who have had a serious adverse event must be followed clinically until all parameters, including laboratory values, have either returned to normal or are otherwise explained. If death was the outcome of the event on the initial Adverse Event Report, a Follow-up/Final Report, including an autopsy report, when performed, must be completed.

# 14 QUALITY ASSURANCE

## 14.1 Institutional Review Board Approval

An IRB shall review and have authority to approve, require modifications, or disapprove the investigation. Accordingly, this protocol, the informed consent document, and any relevant supporting information must be submitted to the IRB for review and receive approval prior to study initiation. Except in an emergency, any amendments to the protocol require approval by both Sponsor and the IRB prior to their implementation.

Additionally, the PI is responsible for providing the IRB with progress reports of the investigation at regular intervals (at least once per year) as well as with any other accurate, complete, and current information that the IRB may request concerning the investigation.

## 14.2 Informed Consent

Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy of the final, IRB-approved document must be provided for record-keeping purposes. Originals of the IRB-approved consent form and sign individual consent documents must be retained in the site's study files. Each subject must be provided with a copy of his/her signed consent form.

## 14.3 Study Monitoring

The PI will allow designees from the study sponsor to periodically audit all CRFs and corresponding source documents for each subjects, as well as, any data related to the study file. The monitoring visits provide for an opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, and to assure that all protocol requirements, applicable regulations, and Investigator's obligations are being met. The PI must maintain source documents such as lab reports, photographs, history, and physical examination reports, etc., for possible review.

## 14.4 Modification of Protocol

If modification of the protocol is necessary, the modification must be confirmed with the IRB. No changes to the protocol that would significantly affect the safety, scope, or quality of the study may be implemented prior to written approval of the IRB. Changes to the protocol, however, may be made when necessary for the health of the subject. All modifications must be documented at the site. Moreover, if the study protocol is revised at any point during the study, IRB will be notified according to CRF 21 Part 812.

## 14.5 Departure from the Protocol

Minor deviations to the study protocol may be permitted if they will not increase the subject's risk or affect the validity of the study. All deviations must be documented at the study site.

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The PI in such an emergency will, if circumstances and time permit, contact the IRB prior to departing from the protocol. If this is not possible, such contact must be made as soon as possible in order to allow for an evaluation of the significance of such departure to the affected subject and to other subjects and to permit a decision as to whether or not the subject, for whom the departure from the protocol was affected, is to continue in the study. The CRFs will completely describe the departure from the protocol and state the reasons for such departure. In addition, IRB will be notified in writing of such departure from protocol.

## 14.6 Confidentiality of Subject Records

The information obtained during the conduct of this study is confidential, and will be disclosed only to the Investigator and regulatory authorities as deemed necessary and/or as required by law. The PI must provide full disclosure of all study data and make study files available for inspection upon request by the IRB and/or relevant authorities including the study sponsor. Upon notice, the local authorities may inspect and copy records that identify subjects through number and initial combinations. However, such copies have to be blinded (i.e., all personally identifiable data have to be blacked out) in order to prevent identification. The sponsor will be notified of any impending inspections relating to the study.

## 14.7 Record Retention

The PI shall maintain accurate, complete, and current records relating to the participation in this study, including the following:

1. All correspondence including required reports
2. Records of device shipment and disposition
3. Signed Investigator Agreements
4. The protocol and any protocol amendments
5. Records concerning adverse events whether anticipated or not
6. Documentation of each subject's case history and exposure to the device, including any CRFs, signed and dated consent forms, and any relevant medical records

7. Any other records that the applicable authorities require to be maintained by regulation or by specific requirement for a particular device or category of devices

The PI shall maintain all detailed essential documents for the duration of the investigation and for a period of at least 2 years since the formal discontinuation of clinical development of the investigational product, or 2 years after the last approval of any marketing application, or as required by the applicable regulatory requirements, whichever is a longer period.

## 14.8 Additional Principal Investigator Responsibilities

The PI is responsible for protecting the rights, safety, and welfare of subjects under his/her care. The PI is responsible for ensuring that the study is conducted according to the signed agreement with the investigational protocol, applicable regulations, and any condition of approval imposed by the IRB.

# 15 APPENDICES

## Appendix A Schedule of Events

| Study Visit | Visit 1: Screening | Visit 2: Treatment | Visit 3: OCR Evaluation | Visit 4: 14-Day Post-OCR | Post-Visit Evaluation |
|---|---|---|---|---|---|
| **Scheduled Assessment Day** | *≤ -14* | *1* | *14 (±3)* | *28 (±3)* | |
| Informed Consent | X | | | | |
| Confirm Enrollment Criteria | X | | | | |
| Demographics | X | | | | |
| Photo- and Videography | X | | X[c] | X[d] | |
| **Safety Evaluations** | | | | | |
| Medical History | X | | | | |
| Vital Signs | X | | | | |
| Urine Pregnancy Test[a] | X | X[b] | | | |
| Adverse Events | | X | X | X | |
| Concomitant Medications | X | X | X | X | |
| **Patient-Reported Outcomes** | | | | | |
| SHS | X | | X[c] | X[d] | |
| MH | X | | X[c] | X[d] | |
| S-GAIS | | | X[c] | X[d] | |
| **PI-Reported Outcomes** | | | | | |
| OCSS | | X | X[c] | X[d] | |
| POLSS | | X | X[c] | X[d] | |
| OCR Evaluation | | | X | | |
| PI-GAIS | | | X[c] | X[d] | |
| **Blinded Evaluator-Reported Outcomes** | | | | | |
| FIQ | | | | | X |

[a] *For females of child-bearing age*
[b] *If the period between Visit 1, Screening Assessments and Visit 2, Treatment is greater than 14 days*
[c] *Subjects who have achieved OCR*
[d] *Subjects who required a touch-up injection in Visit 3*

## Appendix B Subjective Happiness Scale (SHS)

For each of the following statements and/or questions, please circle the point on the scale that **you feel** is the most appropriate in describing you.

**1.** In general, I consider myself:

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| *not a very happy person* | | | | | | *a very happy person* |

**2.** Compared with most of my peers, I consider myself:

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| *not a very happy person* | | | | | | *a very happy person* |

**3.** Some people are generally very happy. They enjoy life regardless of what is going on, getting the most out of everything. To what extent does this characterization describe you?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| *not a very happy person* | | | | | | *a very happy person* |

**4.** Some people are generally not very happy. Although they are not depressed, they never seem as happy as they might be. To what extent does this characterization describe you?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| *not at all* | | | | | | *a great deal* |

## Appendix C The Happiness Measures (HM)

DATE_____

NAME_____

AGE_____SEX _____

EMOTIONS QUESTIONNAIRE

**PART I :** Use the list below to answer the following question: IN GENERAL, HOW HAPPY OR UNHAPPY DO YOU USUALLY FEEL? Check the one statement below that best describes your *average happiness*.

Check just one of these

☐10. Extremely happy (feeling ecstatic, joyous, fantastic!

☐9. Very happy (feeling really good, elated!)

☐8. Pretty happy (spirits high, feeling good.)

☐7. Mildly happy (feeling fairly good and somewhat cheerful.)

☐6. Slightly happy (just a bit above neutral.)

☐5. Neutral (not particularly happy or unhappy.)

☐4. Slightly unhappy (just a bit below neutral.)

☐3. Mildly unhappy (just a little low.)

☐2. Pretty unhappy (somewhat "blue", spirits down.)

☐1. Very unhappy (depressed, spirits very low.)

☐0. Extremely unhappy (utterly depressed, completely down.)

**PART II :** Consider your emotions a moment further. *On the average*, what percent of the time do you feel happy? What percent of the time do you feel unhappy? What percent of the time do you feel neutral (neither happy nor unhappy)? Write down your best estimates, as well as you can, in the spaces below. Make sure the three figures add-up to 100%.

ON THE AVERAGE:

The percent of time I feel happy

_____

% The percent of time I feel unhappy_____%

The percent of time I feel neutral_____

_____%

TOTAL ~~100~~ %

# Appendix D Subject Global Aesthetic Improvement Scale (S-GAIS)

Please rate the change in your appearance now as compared to before you received the Restylane® Silk lip rejuvenation treatment. Please circle the appropriate number that **you believe** corresponds to the change in your appearance.

| Rating | Description | |
|---|---|---|
| 1 | *Very Much Improved* | Optimal cosmetic result in subject |
| 2 | *Much Improved* | Marked improvement in appearance from the initial condition but not completely optimal for this subject |
| 3 | *Improved* | Obvious improvement in appearance from initial condition but a re-treatment is indicated |
| 4 | *No Change* | The appearance is essentially the same as the original condition |
| 5 | *Worse* | The appearance is worse than the original condition |

# Appendix E PI Global Aesthetic Improvement Scale (PI-GAIS)

Please rate the change in the patient's appearance now as compared to before the Restylane® Silk lip rejuvenation treatment. Please circle the appropriate number that you believe corresponds to the change in the subject's appearance.

| Rating | Description | |
|---|---|---|
| 1 | *Very Much Improved* | Optimal cosmetic result in subject |
| 2 | *Much Improved* | Marked improvement in appearance from the initial condition but not completely optimal for this subject |
| 3 | *Improved* | Obvious improvement in appearance from initial condition but a re-treatment is indicated |
| 4 | *No Change* | The appearance is essentially the same as the original condition |
| 5 | *Worse* | The appearance is worse than the original condition |

# Appendix F First Impressions Questionnaire (FIQ)

Date_____

Initials_____

Age _____

Sex: ☐Male ☐Female

**Introduction:**

Thank you for agreeing to participate in our study. All photographs are patients of this practice and have given their consent to be in the study.

- Please do not share your interpretations with others.
- Please attempt to be as honest and unbiased as possible and do not think too much before answering each question.
- We really would like your first impression.
- If you have any questions, please ask BEFORE starting.

**Instructions:**

| Step | Description |
|---|---|
| 1 | Please evaluate the following photographs in the books provided. |
| 2 | Complete the questionnaire for EACH photograph based on your FIRST impression. |
| 3 | EACH sheet is double-sided, so flip page to backside to complete next patient. |
| 4 | Hand the completed questionnaires and books back to study specialist. |

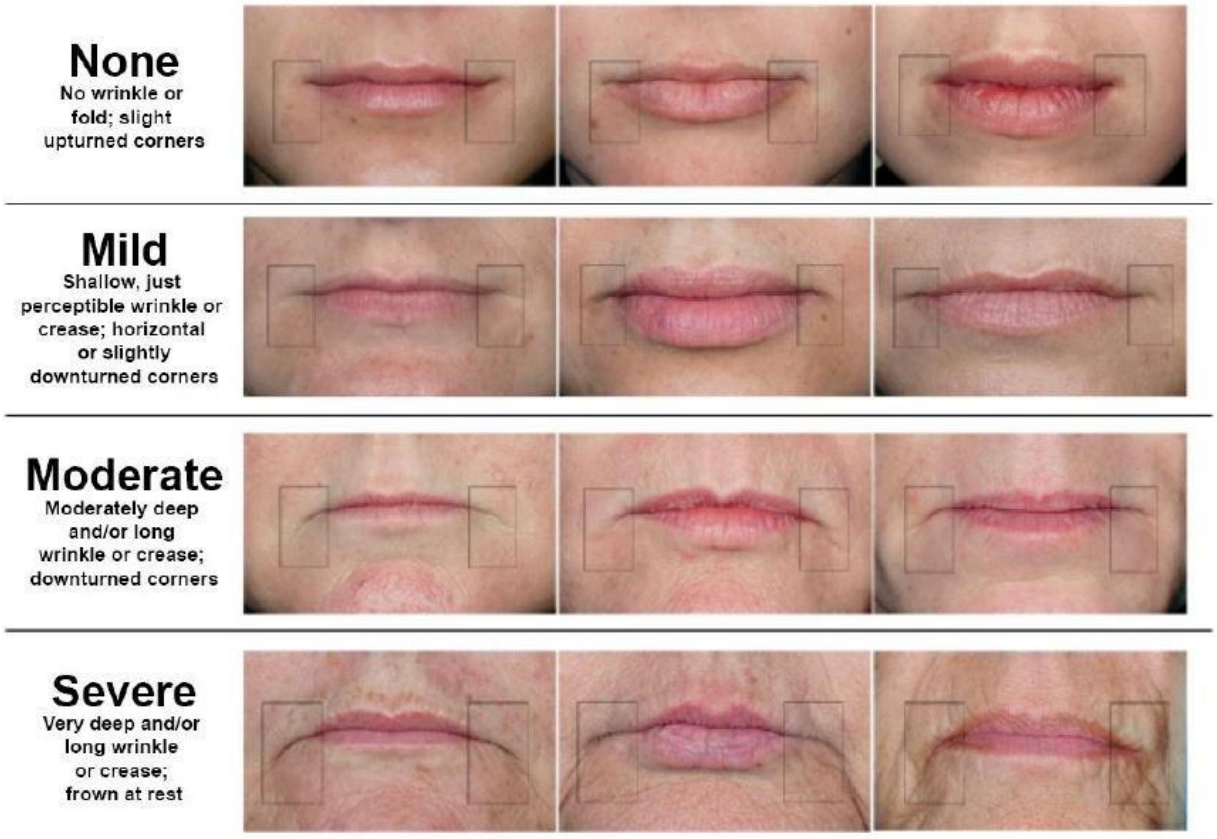
**Photo ID:** 2 **Your Initials:** _____

**Instructions:**

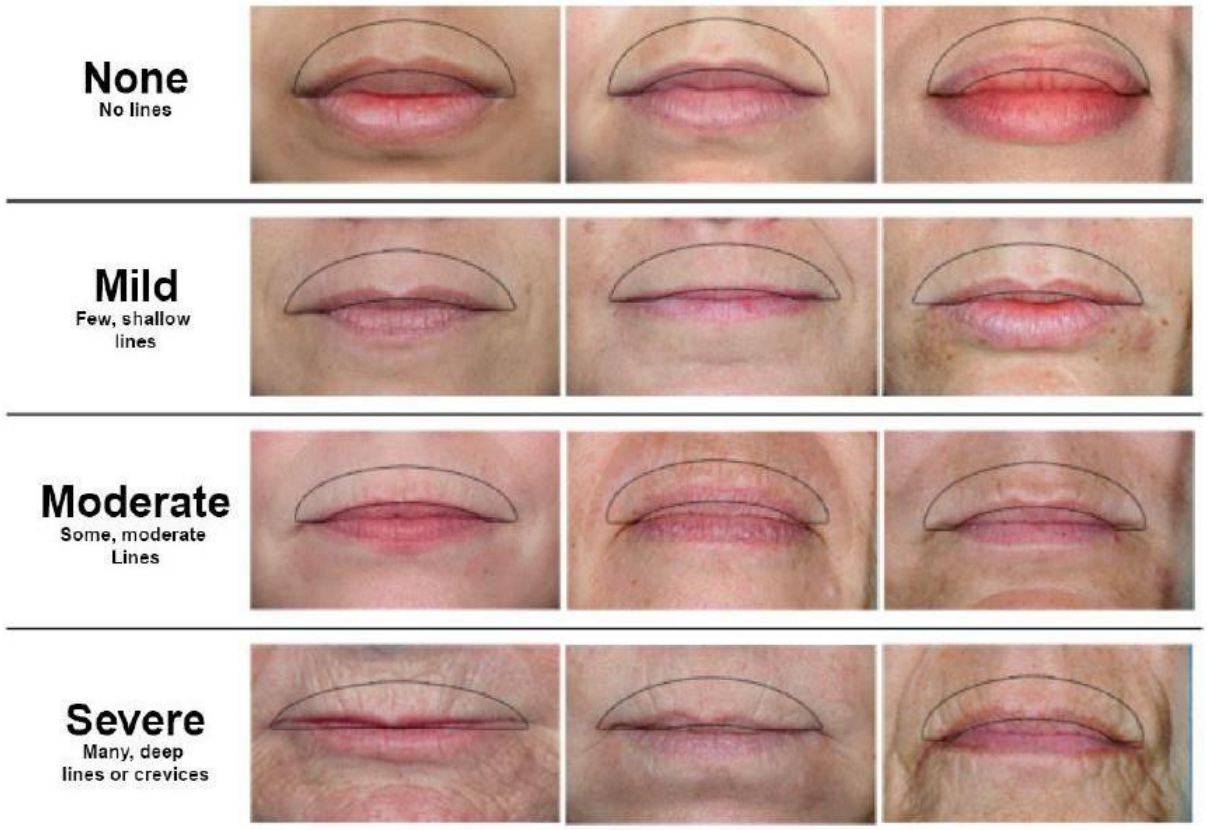
1. Please look at the picture and ensure the version and number match the Photo ID above.
2. Select the number rating that matches EACH question.
3. Scale is as follows for EACH questions: 1 is DISAGREE and 10 is the AGREE ranking

| | Subject: | Description: |
|---|---|---|
| 1 | Social Skills | Positive mood, gets along with others well, friendly<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |
| 2 | Academic Performance | Intelligent, highly educated, received good grades in school<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |
| 3 | Dating Success | Dates frequently, lacks dating anxiety<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |
| 4 | Occupational Success | Good worker, competent, motivated for success, suitable as potential employee<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |
| 5 | Attractiveness | Pleasing appearance<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |
| 6 | Financial Success | Has achieved financial success, member of a high social class<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |
| 7 | Relationship Success | Willingness to compromise, ability to maintain long term friendships<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |
| 8 | Athletic Success | Excels at athletic skills, plays individual and/or team sports<br>**1 2 3 4 5 6 7 8 9 10**<br>DISAGREE AGREE |

## Appendix G Oral Commissure Severity Scale (OCSS)



## Appendix H Perioral Line Severity Scale (POLSS) at Rest



# Appendix I Standard Operating Protocol for Photo- and Videography

Photography and Poses

- Use the grid feature on any of these viewers to ensure the Frankfort Plane (imaginary line from tragus to infraorbital rim) is parallel to the floor.
- Stand approximately 1.5 m from patient with the camera in a portrait position.
- Ensure the patient has a relaxed expression and that lips are closed and eyes are open for each photo.
- Give instructions like, "Slowly move your chin down" or "Slowly turn your nose to the left" to achieve the desired poses listed below

- Standard Poses (all at 1.5 m)

1. Frontal
   Make sure the patient doesn't have their chin high or low by checking the Frankfort Plane. For this view, the line on the viewfinder should extend from the right tragus, across both infraorbital rims and across the left tragus. This should be parallel to the floor.

2. 45° Left
   For this view, the tip of the nose should line up with the edge of the cheek.

3. Left Profile
   For this view, ensure the patient is not rotated to the left or right (hint: look at the eyebrows to see how much of the glabella you see).

4. 45° Right
   For this view, the tip of the nose should line up with the edge of the cheek.

5. Right Profile
   For this view, ensure the patient is not rotated to the left or right (hint: look at the eyebrows to see how much of the glabella you see).

Video

- 

- Stand approximately 1.75 m from the patient with the camera in a landscape position. Standard facial expressions (holding each expression for 2-3 seconds):

1. Maximum smile (showing teeth)
2. Maximum frown (furrowing brow)
3. Pucker lips
4. Read two rhymes of approximately 30 seconds

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