PRO 2018-02

A Multicenter, Double-blind, Randomized, Controlled Study of the Safety and Effectiveness of PN40082 for Lip Augmentation

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Clinical Phase 3

Trial Sponsor:	Prollenium Medical Technologies Inc.
Key Sponsor Contact:	[redacted]
Date:	02 October 2018

SIGNATURE PAGE

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Signatures of the following individuals indicate that all agree this version is final.

[redacted]

Date

[redacted]

Prollenium Medical Technologies Inc.

[redacted]

Date

[redacted]

Prollenium Medical Technologies, Inc.

[redacted]

Date

[redacted]

1 SYNOPSIS

Title of Study: A Multicenter, Double-blind, Randomized, Controlled Study of the Safety and Effectiveness of PN40082 for Lip Augmentation

Name of Sponsor: Prollenium Medical Technologies Inc.

Name of Finished Product: PN40082

Device Composition: Hyaluronic acid gel with lidocaine (0.3% w/w)

Objectives: To compare the safety and efficacy profile of PN40082 versus Restylane Silk Injectable Gel with 0.3% lidocaine (Restylane Silk) for lip augmentation.

Study Design: This is a double-blind, randomized, controlled, multicenter clinical study of subjects seeking lip augmentation. Subjects meeting inclusion/exclusion criteria will be randomized 1:1 to treatment with either PN40082 or Restylane Silk. The Evaluating Investigator will be blinded to the treatment. Injections of the study device will be performed by an unblinded Treating Investigator.

At each visit, the blinded Evaluating Investigator evaluations and subject evaluations of the treated areas will be performed and recorded. Visits and telephone contacts will occur at:

Visit 1 / Week 0 (Day 1) – baseline and treatment

-Day 3 (±2 days) - Safety follow-up telephone call

-Day 14 (±2 days) – Safety follow-up telephone call

Visit 2 / Day 28 (±2 days) / Month 1 – interim visit (touch-up if necessary)

-Day 33 (±2 days) – Safety follow-up telephone call (for subjects with touch-up treatment

-Day 44 (±2 days) – Safety follow-up telephone call (for subjects with touch-up treatment)

Visit 3 / Day 56 (±4 days) / Month 2 – interim visit

Visit 4 / Day 84 (±4 days) / Month 3 – interim visit

-Day 112 (±4 days) / Month 4 – Safety follow-up telephone call

-Day 140 (±4 days) / Month 5 – Safety follow-up telephone call

Visit 5 / Day 168 (±7 days) / Month 6 – End of Study (EOS) Visit. All subjects will undergo the consent procedure for the open-label retreatment protocol.

Evaluations include:

Lip Fullness Grading Scale (LFGS) (Overall lip fullness considering both lips together, fullness of the upper lip and fullness of the lower lip)

Perioral lines at rest severity scale (POL) (Overall perioral lines at rest severity considering both lips together, perioral lines at rest severity of the upper lip and perioral lines at rest severity of the lower lip)

Patient Global Aesthetic Improvement (pGAI)

Investigator Global Aesthetic Improvement (iGAI)

Safety will be assessed by monitoring adverse events (AEs) at all study visits

Other Safety Evaluations include:

Lip Function

Lip Sensation

Lip Texture

Lip Firmness

Lip Symmetry

Lip Movement/Function

Other evaluations include:

Investigator Ease of Use Assessment

Swelling Assessment

Subject Satisfaction with Lips Assessment

Number of Study Centers: Approximately 7 sites in the United States

Duration of Participation: Subjects will participate in the study for approximately 6 months from the time they sign the informed consent form (ICF) through the EOS visit.

Duration of Study: The study will require approximately 20 months from the first subject signing the ICF to the Month 6 EOS visit for the last subject

Number of Subjects: Approximately 158 subjects will be randomized

Inclusion Criteria:

1. Men or non-pregnant or non-breastfeeding women over 21 years of age
2. If female and of childbearing potential, a negative urine pregnancy test at Baseline (Day 1) and the subject agrees to use adequate contraception during the study period
3. Has an overall score of very thin, or thin on the LFGS, as agreed upon by the Treating and Evaluating Investigators, and desires at least a 1-point improvement in overall LFGS score; OR

   Has a Fitzpatrick skin phototype IV, V or VI and has an LFGS score of thick or full, as agreed upon by the Treating and Evaluating Investigators, and desires treatment to the vermilion body of 1 or both lips
4. Willing to give written informed consent

Exclusion Criteria:

1. Women who are pregnant, lactating, or planning a pregnancy
2. History of allergy, anaphylaxis or hypersensitivity to injectable hyaluronic acid products, local anesthetics of the amide type such as lidocaine, or to latex, or is planning to undergo desensitization therapy during the study

3. Has lip tattoos, piercings, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments
4. Has abnormal lip function, with inability to effectively sip water through a straw
5. Has abnormal lip sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip
6. Has moderate or severe abnormal lip asymmetry
7. Has any mass formation on the lip
8. Has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities as judged by the Treating Investigator. Subjects planning to undergo extensive dental procedures such as dental implants, multiple tooth extractions, or oral surgery should not participate. Minor dental procedures such as teeth cleaning and repair of caries are not exclusionary
9. Has undergone facial plastic surgery or received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene, polyacrylamide, lifting threads) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
10. Has undergone semi-permanent dermal filler treatment (e.g., calcium hydroxylapatite, poly-L-lactic acid) in the lower face (below the orbital rim) within 12 months before enrollment or is planning to undergo such treatment during the study
11. Has undergone facial tissue augmentation with fat injections, botulinum toxin injections in the lower face (below the orbital rim), mesotherapy, or cosmetic procedures in the face or neck (e.g., face-lift, laser, photo-modulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, microneedling, or other ablative procedures) within 9 months before enrollment or is planning to undergo any of these procedures during the study
12. Has used ANY lip filling agents within 12 months of study enrollment (hyaluronic acid products, collagen-based products, etc.)
13. Has used any lip plumping products or devices within 10 days before enrollment or is planning to use such products during the study
14. Has begun using any over-the-counter (OTC) or prescription oral or topical anti-wrinkle products for the lips or around the mouth within 90 days before enrollment or is planning to begin using such products during the study (Subjects who have been on a stable regimen of such products for at least 90 days are eligible for the study and must continue their regimen throughout the study.)
15. Is on an ongoing regimen of anticoagulation therapy (e.g., warfarin), thrombolytics, or inhibitors of platelet aggregation or nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., aspirin, ibuprofen) or other substances known to increase coagulation time (e.g., herbal supplements with garlic or gingko) within 10 days of undergoing study device injections. Subjects who will withhold such therapy for 10 days before AND after any injection session may participate

16. Has a history or presence of bleeding disorders
17. Has used systemic corticosteroids or immunosuppressive medications within 30 days prior to treatment
18. Is on a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine)
19. Has an active inflammation (skin eruptions such as cysts, pimples, rashes, or hives), infection, cancerous or precancerous lesion, or unhealed wound on the face
20. Has a history of known susceptibility to keloid formation or hypertrophic scars
21. Has porphyria
22. Has active herpes labialis lesions at the time of injections. Subjects with a history of herpes labialis who have had four (4) or more outbreaks in the 12 months prior to enrollment are also excluded even in the absence of lesions at the baseline visit
23. Has impaired cardiac conduction, severely impaired hepatic function, or severe renal dysfunction that, in the opinion of the investigator, would place them at risk of associated complications from these illnesses during the course of the study
24. Has any uncontrolled disease, i.e., a condition that has not been appropriately diagnosed, evaluated, and received medically appropriate treatment or care
25. Has severe cardiovascular disease; examples include but are not limited to New York Heart Association heart failure classification III or IV, unstable angina, and internal pacemakers. Potential subjects with other significant cardiovascular diseases should be discussed with the Medical Monitor before enrolling

Study Devices

Test device: PN40082: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 mg/mL of stabilized hyaluronic acid and lidocaine 0.3% w/w

Comparator device: Restylane Silk: a clear, colorless gel in 1.0 mL pre-filled syringes formulated to a concentration of 20 mg/mL of stabilized hyaluronic acid and lidocaine 0.3% w/w

Statistical Methods

Sample Size Determination:

A total of 158 subjects will be randomized.

Analysis Populations:

Intent-to-treat (ITT/safety) population: All randomized subjects who received study device

Modified intent-to-treat (mITT): All randomized subjects who met the inclusion/exclusion criteria, were randomized, and received study device

Per-protocol (PP): All randomized subjects who met all inclusion/exclusion criteria; received study device, completed Visit 5 within the specified window; had LFGS score by the Blinded Evaluating Investigator at Visit 3/Month 2 within the specified visit window, and had no significant protocol violations that would affect the treatment evaluation

Efficacy analyses will be performed on the mITT and PP populations, with PP as the primary population and mITT supportive.

Safety analyses will be performed on the ITT population.

Efficacy Analysis:

The primary efficacy endpoint is change from baseline to Month 2 in overall lip fullness based on the Blinded Evaluating Investigator assessment using the LFGS. If the lower limit of the 95% confidence interval (CI) for (PN40082 minus Restylane Silk) with respect to the primary endpoint is above a pre-specified NI limit -0.50, PN40082 will be claimed non-inferior to the Restylane Silk.

Secondary analysis include

- percent of subjects with treatment success (responder: overall LFGS based on the Blinded Evaluating Investigator Assessment) at Visit 3/Month 2 where responder is defined as a subject with at least a 1-grade increase from baseline on the LFGS post augmentation,
- percent of responders overall on the POL severity scale at Visit 4/Month 3 (defined as a subject demonstrating ≥ 1-point improvement, i.e., decrease in severity, from baseline),
- change from baseline to Visit 4/Month 3 in overall LFGS based on the Blinded Evaluating Investigator Assessment,
- change from baseline to Visit 5/Month 6 in overall LFGS based on the Blinded Evaluating Investigator Assessment.

Other efficacy analysis include

- pGAI, iGAI, and Swelling Assessment at each scheduled visit,
- percent of subjects with treatment success (responder: upper lips, lower lips LFGS) at Visit 3/Month 2 where responder is defined as a subject with at least a 1-grade increase from baseline on the LFGS post augmentation,
- percent of responders (upper lips, lower lips) on the POL severity scale at Visit 4/Month 3 (defined as a subject demonstrating ≥ 1-point improvement, i.e., decrease in severity, from baseline),
- satisfaction with lips VAS at each scheduled visit,
- change from baseline to Visit 4/Month 3 and Visit 5/Month 6 in upper lips, lower lips LFGS.

Safety Analysis:

Adverse events will be coded to system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20 or higher).

Frequency and percentage of subjects reporting treatment-emergent adverse events (TEAEs) will be tabulated for each treatment by preferred terms and further by severity and relationship to study device. In summaries of severity and relationship, subjects reporting more than one event in a treatment arm that are mapped to the same preferred term will be counted only once in that treatment arm under the strongest severity and relationship, respectively. In addition, visual

related TEAEs will be summarized separately for each treatment by preferred term.

Safety analyses will be conducted using the ITT population.

2 SCHEDULE OF ACTIVITIES

Visit Number (Month)	**Visit 1 (Week 0)**	**Phone Contacts**	**Visit 2 (Mo 1)**	**Phone Contacts [a]**	**Visit 3 (Mo 2)**	**Visit 4 (Mo 3)**	**Phone Contacts**	**Visit 5 (Mo 6) End of Study/Early Termination**	**Unsched Visit**
Scheduled Day(s)	**Day 1**	**Day 3 & Day 14**	**Day 28**	**Day 33 & Day 44**	**Day 56**	**Day 84**	**Day 112 & Day 140**	**Day 168 [b]**	
Scheduling Window	**none**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 7 days**	
Informed consent	X								
Medical history/ demographics	X								
Abbreviated Physical examination (including vital signs)	X								
Vision evaluations (Snellen visual acuity, confrontational visual fields, ocular motility)[d]	X		X		X	X	X	X	X[c]
Prior/Concomitant Medication/ Treatment	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria review	X								
Urine pregnancy test[e]	X								
Fitzpatrick Skin Type	X								
Lip Fullness Grading Scale (LFGS) (Overall, upper lip and lower lip)	X		X		X	X		X	X[c]
Perioral lines at rest severity scale (POL) (Overall, upper lip and lower lip)	X		X		X	X		X	X[c]
Randomization	X								
Treatment with study device	X		X [a]						
Investigator Ease of Use Assessment	X		X [a]						
Evaluation for touch-up			X						
Patient GAI (pGAI)			X		X	X		X	X[c]
Swelling Assessment			X		X	X		X	X[c]
Investigator GAI (iGAI)			X		X	X		X	X[c]
Subject Satisfaction with Lips			X		X	X		X	X[c]
Lip Function (prior to injections)	X		X		X	X		X	X[c]
Lip Sensation (prior to injections)	X		X		X	X		X	X[c]
Lip Texture (prior to injections)	X		X		X	X		X	X[c]
Lip Firmness (prior to injections)	X		X		X	X		X	X[c]

Lip Symmetry (prior to injections)	X		X		X	X		X	X[c]
Lip Movement/Function	X		X		X	X		X	X[c]
Adverse event assessment	X	X	X	X	X	X	X	X	X
Treatment question								X	
Subject Diary	Dispense		Collect/ dispense[f]		Collect[f]				

Note: The timing of each visit is relative to Day 1, which is defined as the day the subject is randomized and first treated.

a. For subjects who have touch-up treatment at Visit 2
b. All subjects will receive a follow-up phone call at 12 months after first treatment.
c. If/as needed
d. performed prior to any treatment and repeated 30 minutes following any treatment and all follow-up visits.
e. For women of childbearing potential, to be completed prior to enrollment.
f. Dispense/collect diary only if touch up is performed

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	adverse event
CFR	Code of Federal Regulations
CI	confidence interval
CRA	Clinical Research Associate
CRF	case report form, paper or electronic
DCF	data correction form
EOS	end of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
iGAI	Investigator Global Aesthetic Improvement
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
LFGS	Lip Fullness Grading Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
pGAI	Patient Global Aesthetic Improvement
PI	principal investigator
POL	perioral lines at rest
PP	per-protocol
SAE	serious adverse event
SAR	suspected adverse reaction
TEAE	treatment-emergent adverse event
VAS	visual analog scale

5 INTRODUCTION

5.1 Background

PN40082 is a stabilized hyaluronic acid dermal filler with lidocaine. Restylane Silk Injectable Gel with 0.3% lidocaine (hereafter referred to as Restylane Silk) is a stabilized hyaluronic acid dermal filler with lidocaine that is commercially available for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in adults over the age of 21 years. The purpose of this study is to compare the efficacy and safety of PN40082 and Restylane Silk for lip augmentation.

5.2 Rationale for the Study and Study Design

To be enrolled in the study subjects who have a Lip Fullness Grading Scale (LFGS) score of very thin, thin, or moderately thick must be seeking at least a 1-point improvement in their overall LFGS score and subjects who have an LFGS score of thick or full must be seeking treatment to the vermilion body of 1 for both lips. Subjects will be randomized 1:1 to treatment with either PN40082 or Restylane Silk. All subjects will be followed for efficacy and safety for 6 months. All subjects will be evaluated for retreatment and undergo consent procedure for the subsequent open-label retreatment protocol.

6 STUDY OBJECTIVES

To compare the safety and efficacy profile of PN40082 versus Restylane Silk for lip augmentation.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design

This is a double-blind, randomized, controlled, multicenter clinical study of subjects seeking lip augmentation. Subjects meeting inclusion/exclusion criteria will be randomized 1:1 to treatment with either PN40082 or Restylane Silk. The Evaluating Investigator will be blinded to the treatment. Injections of the study device will be performed by an unblinded Treating Investigator.

At each visit, the blinded Evaluating Investigator evaluations and subject evaluations of the treated areas will be performed and recorded. Visits and telephone contacts will occur at:

Visit 1 / Week 0 (Day 1) – baseline and treatment

-Day 3 (±2 days) - Safety follow-up telephone call

-Day 14 (±2 days) – Safety follow-up telephone call

Visit 2 / Day 28 (±2 days) / Month 1 – interim visit (touch-up if necessary)

-Day 33 (±2 days) – Safety follow-up telephone call (for subjects with touch-up treatment)

-Day 44 (±2 days) – Safety follow-up telephone call (for subjects with touch-up treatment)

Visit 3 / Day 56 (±4 days) / Month 2 – interim visit

Visit 4 / Day 84 (±4 days) / Month 3 – interim visit

-Day 112 (±4 days) / Month 4 – Safety follow-up telephone call

-Day 140 (±4 days) / Month 5 – Safety follow-up telephone call

Visit 5 / Day 168 (±7 days) / Month 6 – End of Study (EOS) Visit. All subjects will be evaluated for retreatment and undergo the consent procedure for the subsequent open-label retreatment protocol.

Efficacy valuations include:

Lip Fullness Grading Scale (LFGS) (Overall lip fullness considering both lips together, fullness of the upper lip and fullness of the lower lip)

Perioral lines at rest severity scale (POL) (Overall perioral lines at rest severity considering both lips together, perioral lines at rest severity of the upper lip and perioral lines at rest severity of the lower lip)

Patient Global Aesthetic Improvement (pGAI)

Investigator Global Aesthetic Improvement (iGAI)

Safety will be assessed by monitoring adverse events (AEs) at all study visits. Adverse Events of Special Interest, any changes in vision and any events attributable to an embolic or ischemic cause (i.e., skin infarction) will be monitored. Other Safety evaluations include lip function, lip sensation, lip texture, lip firmness, lip symmetry, and lip movement/function. Other evaluations include Investigator Ease of Use Assessment, Swelling Assessment, and Subject Satisfaction with Lips Assessment.

7.2 Beginning and End of Study

A subject is considered to be enrolled in the study when he/she has provided written informed consent and has been randomized to treatment.

A subject is considered to have completed the study after he/she has completed Visit 5/ Month 6.

A subject is considered to have withdrawn after he/she has withdrawn consent or has been withdrawn under the conditions specified in Section 7.3.3.

A subject is considered to have been lost to follow-up if he/she cannot be contacted by the investigator. The investigator will document efforts to attempt to reach the subject at least twice by telephone and will send a certified letter before considering the subject lost to follow-up. The end of participation for a subject lost to follow-up is documented as the date of the certified letter.

Each subject will be monitored for the occurrence of AEs, including serious adverse events (SAEs), immediately after treatment initiation. Each subject will be followed for safety monitoring until he/she is discharged from the study.

Follow-up procedures related to pregnancy, AEs, or SAEs may continue beyond the end of the study.

Each subject will participate in the study for approximately 6 months. After determination of eligibility at Visit 1/Day 1, each subject will be treated with PN40082 or Restylane Silk.

It is anticipated that the duration of this study will be 20 months from the first subject signing the ICF to the Month 6 EOS visit last subject.

At the end of study visit the subjects who have completed Visit 5/Month 6 within window will be invited to participate in an open-label retreatment study, PRO 2018-03.

7.3 Study Population

Approximately 158 healthy males and females over 21 years of age seeking lip augmentation will be selected to participate in the study.

7.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Men or non-pregnant or non-breastfeeding women over 21 years of age
2. If female and of childbearing potential, a negative urine pregnancy test at Baseline (Day 1) and the subject agrees to use adequate contraception during the study period

3. Has an overall score of very thin or thin on the LFGS, as agreed upon by the Treating and Evaluating Investigators, and desires at least a 1-point improvement in overall LFGS score; OR

   Has a Fitzpatrick skin phototype IV, V or VI and has an LFGS score of thick or full, as agreed upon by the Treating and Evaluating Investigators, and desires treatment to the vermilion body of 1 or both lips
4. Willing to give written informed consent

7.3.2 Exclusion Criteria

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

1. Women who are pregnant, lactating, or planning a pregnancy
2. History of allergy, anaphylaxis or hypersensitivity to injectable hyaluronic acid products, local anesthetics of the amide type such as lidocaine, or to latex, or is planning to undergo desensitization therapy during the study
3. Has lip tattoos, piercings, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments
4. Has abnormal lip function, with inability to effectively sip water through a straw
5. Has abnormal lip sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip
6. Has moderate or severe abnormal lip asymmetry
7. Has any mass formation on the lip
8. Has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities as judged by the Treating Investigator. Subjects planning to undergo extensive dental procedures such as dental implants, multiple tooth extractions, or oral surgery should not participate. Minor dental procedures such as teeth cleaning and repair of caries are not exclusionary
9. Has undergone facial plastic surgery or received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene, polyacrylamide, lifting threads) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
10. Has undergone semi-permanent dermal filler treatment (e.g., calcium hydroxylapatite, poly-L-lactic acid) in the lower face (below the orbital rim) within 12 months before enrollment or is planning to undergo such treatment during the study
11. Has undergone facial tissue augmentation with fat injections, botulinum toxin injections in the lower face (below the orbital rim), mesotherapy, or cosmetic procedures in the face or neck (e.g., face-lift, laser, photo-modulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, microneedling, or other ablative procedures) within 9 months before enrollment or is planning to undergo any of these procedures during the study
12. Has used ANY lip filling agents within 12 months of study enrollment (hyaluronic acid products, collagen-based products, etc.)
13. Has used any lip plumping products or devices within 10 days before enrollment or is planning to use such products during the study
14. Has begun using any over-the-counter (OTC) or prescription oral or topical anti-wrinkle products for the lips or around the mouth within 90 days before enrollment or is planning to begin using

such products during the study (Subjects who have been on a stable regimen of such products for at least 90 days are eligible for the study and must continue their regimen throughout the study.)

15. Is on an ongoing regimen of anticoagulation therapy (e.g., warfarin), thrombolytics, or inhibitors of platelet aggregation or nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., aspirin, ibuprofen) or other substances known to increase coagulation time (e.g., herbal supplements with garlic or gingko) within 10 days of undergoing study device injections. Subjects who will withhold such therapy for 10 days before AND after any injection session may participate
16. Has a history or presence of bleeding disorders
17. Has used systemic corticosteroids or immunosuppressive medications within 30 days prior to treatment
18. Is on a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine)
19. Has an active inflammation (skin eruptions such as cysts, pimples, rashes, or hives), infection, cancerous or precancerous lesion, or unhealed wound on the face
20. Has a history of known susceptibility to keloid formation or hypertrophic scars
21. Has porphyria
22. Has active herpes labialis lesions at the time of injections. Subjects with a history of herpes labialis who have had four (4) or more outbreaks in the 12 months prior to enrollment are also excluded even in the absence of lesions at the baseline visit
23. Has impaired cardiac conduction, severely impaired hepatic function, or severe renal dysfunction that, in the opinion of the investigator, would place them at risk of associated complications from these illnesses during the course of the study
24. Has any uncontrolled disease, i.e., a condition that has not been appropriately diagnosed, evaluated, and received medically appropriate treatment or care
25. Has severe cardiovascular disease; examples include but are not limited to New York Heart Association heart failure classification III or IV, unstable angina, and internal pacemakers. Potential subjects with other significant cardiovascular diseases should be discussed with the Medical Monitor before enrolling

7.3.3 Subject Withdrawal Criteria

A subject may withdraw from the study at any time for any reason.

A subject will be withdrawn from the study if his/her safety or well-being is determined to be at risk. Withdrawal will be made at the discretion of the investigator or at the subject's request.

A subject must withdraw from the study for any of the following reasons:

- The subject or legal representative withdraws consent
- The subject's study device assignment is unblinded
- There is a significant protocol violation as determined by the Sponsor or medical monitor.

A subject may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Investigator discretion

Withdrawal is permanent; after a subject has been withdrawn, he/she will not be allowed to enroll again.

If a subject is withdrawn from the study for any reason, the EOS or Early Termination procedures (Visit 5/Month 6) should be completed and any outstanding data and subject diaries should be collected. Data, including the date and primary reason for withdrawal, must be documented on the EOS case report form (CRF) and source document.

If a subject withdraws from the study at any time due to an AE, the reason for withdrawal, the nature of the AE, and its clinical course must be fully documented. The investigator must strive to follow the subject until the AE has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up. For any SAE, follow the procedures provided in Section 7.9.7.

7.3.4 Replacement of Subjects

A subject who withdraws from the study will not be replaced.

7.4 Treatments

The investigator will take responsibility for and will take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and use of study materials in accordance with the protocol and any applicable laws and regulations.

7.4.1 Dosage and Formulations

The following study devices will be used in the study and provided by the Sponsor:

Test device: PN40082 (manufactured by Prollenium Medical Technologies) is a clear, colorless gel in 1.0 mL pre-filled syringes with 25 mg/mL of stabilized hyaluronic acid and lidocaine 0.3% w/w.

Comparator device: Restylane Silk (manufactured by Q-Med AB for Medicis – A Division of Valeant Pharmaceuticals Corporation North America, LLC) is a clear, colorless gel in 1.0 mL pre-filled syringes formulated to a concentration of 20 mg/mL of stabilized hyaluronic acid and lidocaine 0.3% w/w.

7.4.2 Randomization

Subjects who satisfy all of the eligibility criteria will be randomized in a 1:1 ratio to treatment with PN40082 or Restylane Silk. Randomization will be performed according to a computer-generated randomization scheme that will be generated and maintained by an independent third party. A sealed copy of the randomization scheme should be retained at each site and should be available to regulatory authorities at the time of site inspection to allow for verification of the treatment identity for each subject.

A unique subject number will be assigned to each subject. Each site will receive the randomization scheme. Each eligible subject will be assigned a unique randomization code number in ascending order.

7.4.3 Study Device Administration

Subjects are physically masked (blindfolded) just prior to and during all injection procedures to prevent observation of the syringes containing study device. Any unblinded investigators and staff should be reminded NOT to discuss the treatment in the presence of the subject.

The subject should be positioned in a seated position and may be reclined to as much as 45°.

Any makeup should be removed with a gentle cleanser or a specific makeup remover product (such as Neutrogena Cleansing Makeup Remover Facial Wipes).

The non-vermillion areas of the upper and lower lips should be prepared by gentle washing with a surgical scrub product (Chlorhexidine, Technicare, etc.).

To prepare the syringes for use, the investigator should attach one of the needles included in the subject study device kit in a firm manner. The plunger should be gently depressed to express any unwanted air

until a small droplet of implant material appears at the tip of the needle.

Study device is administered using only a needle provided in the subject study device kit. The needle is inserted at an approximate angle of 30° parallel to the surface of the skin or lip. For rhytids, study device should be injected into the mid-to-deep dermis. Study device should be injected into the submucosal layer for lip augmentation; care should be taken to avoid intramuscular injection. If study device is injected too superficially this may result in visible lumps and/or bluish discoloration.

Inject study device applying light to moderate, even pressure on the plunger. Avoid injecting quickly as rapid injection can result in increased pain. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or being too superficially implanted into the skin.

Only correct or augment to 100% of the desired volume effect. Do not overcorrect or overfill.

The needle may be replaced as needed to ensure subject comfort. Only needles provided in the subject study device kit may be used. Before needle replacement, the plunger should be withdrawn slightly and once the needle has been replaced, the plunger re-advanced to ensure that the new needle is prefilled with implant material prior to restarting injections.

Typical usage for each treatment session is specific to the site as well as the amount of augmentation or rhytids correction desired. Based on U.S. clinical studies, the maximum volume allowed per treatment is 1.5 mL per lip (1.5 for upper, 1.5 for lower) and 1.0 mL for perioral rhytid correction. Thus, the maximum amount that can be used at one treatment session is 4.0 ml.

Amounts of material injected should be recorded separately for the upper lip, lower lip and perioral areas.

INJECTION TECHNIQUES

1. Study device can be injected by a number of different techniques that depend on the treating investigator's experience and preference and subject characteristics.
2. **Serial puncture** involves multiple, closely spaced injections along wrinkles, folds, or the vermillion border. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some subjects.
3. **Linear threading (includes retrograde and antegrade)** is accomplished by fully inserting the needle into the center of the area to be corrected or augmented and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle has been fully inserted and is being withdrawn, it can also be performed while advancing the needle - antegrade technique). To augment the lip, the retrograde linear threading technique is the most advisable.
4. Serial threading is a technique that utilizes elements of both approaches.

   Note! The correct injection technique is crucial for the final result of the treatment.
5. The following techniques should be avoided as they may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site:
   - Dissection of the sub-epidermal plane with lateral movement of the needle – "fanning"
   - Rapid flow rate (> 0.3 mL/min) of implant material injection
   - High injection volumes
   - The use of needles other than ones provided in the subject study device kit
6. The use of cannulas is prohibited.

7. When the injection is completed, the treated site should be **gently** massaged so that it conforms to the contour of the surrounding tissues. Massaging that substantially deforms the lips or causes blanching of compressed tissues is excessive and should be avoided except as described below.
8. If excessive material is implanted or irregularly implanted, massage the area somewhat more firmly than for the usual implantation procedure to obtain optimal results.
9. If blanching of the tissues is observed during or directly after injection and becomes a concern, the area may be gently massaged. If blanching persists, contact the Medical Monitor.
10. The lips should be augmented to achieve the maximum desirable appearance for both the treating investigator and the subject. Subjects should be provided a small hand mirror to observe the results and further injections conducted until maximum benefit has been obtained. Care should be taken to ensure that the lips are symmetric from right to left and that the upper and lower lips have relative proportionality.
11. The perioral area should be corrected AFTER the upper and lower lips have been corrected. Some correction of perioral rhytids may occur with lip augmentation, thus it is best to address any remaining perioral correction needs after the lip injections have been completed.
12. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period if the investigator deems it appropriate. Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
13. Subjects should be encouraged to avoid a recumbent position for several hours after injections to reduce swelling. The use of ice, cold packs or other therapies to reduce swelling should only be performed at instruction of the investigator. The subject should be instructed to contact the site if substantial swelling occurs.

7.4.4 Blinding of Study Device

Injections of the study device are performed by the unblinded Treating Investigator. The blinded Evaluating Investigator is not allowed to retrieve study supplies or to be present during opening of the study supplies or during the injections. The Treating Investigator is not to have any discussion with the Evaluating Investigator or subjects regarding the treatments.

Subjects are blinded to treatment assignment. Subjects are physically masked (blindfolded) just prior to and during all injection procedures to prevent observation of the syringes containing study device.

Subjects, investigators, the Sponsor's staff conducting the study, and members of the administrative team will not have access to individual subjects' treatment assignments. In the event of an emergency that requires breaking of the study blind, the randomization code will be maintained by each investigator that can be opened to reveal the study device.

See Section 7.9.10.2 for a description of the method of unblinding a subject during the study if such action is warranted.

At Visit 5, subjects and blinded evaluating investigators will be asked which treatment they thought was administered as a way of evaluating the blinding.

7.4.5 Method of Packaging, Labeling, Storage, and Dispensing

For PN40082, one 1.0 mL syringe is packaged along with two fine-gauge needles (30G) in an easy-open tray. Each syringe is equipped with a Luer-Lok as well as a custom finger grip and plunger rod. The syringes contain a peelable label to be placed on the subject record for tracking purposes. Two trays are packaged in a carton. A label that includes the protocol number and Sponsor name will be attached to each carton.

Restylane Silk study device will be supplied by Prollenium in the commercial packaging. Investigators will be instructed to follow instructions regarding storage in accordance with the study device's Directions for Use.

All study device will be stored in a climate-controlled, limited access area.

The investigator agrees to store and administer the study device only at the site(s) listed on Form FDA 1572 (or investigator agreement/statement). The investigator, sub-investigator(s), or qualified designees also agree that the study device will be administered only to subjects who have provided written informed consent and have met all entry criteria. Study device may not be used for any purpose other than as stated in the protocol.

7.4.6 Study Device Accountability

Study device will be available on site for each subject. Receipt of study device will be documented and confirmed via the Investigational Product Receipt Form. All study device must be kept in a locked area with access restricted to designated study personnel in a climate-controlled, limited access area. The administration of study device will be recorded on the Study Device Dispensing Log. The site monitor will periodically check the supply of study device held by the investigator or pharmacist to ensure accountability. At study conclusion, all unused PN40082 study device will be returned to the Sponsor and documented using the Investigational Product Return Form.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to inspection by regulatory authorities at any time.

7.4.7 Prior and Concomitant Medications

All medications and other treatments taken by the subject within 6 months before Visit 1/Day 1 and during the study are to be recorded on the CRF using their generic name, if known, with the corresponding indication. The medications to be recorded include prescription and OTC medications and dietary supplements. All medications taken on a regular basis, including vitamins, aspirin, and acetaminophen, should be recorded prior to first use of the study device.

The use of any concomitant medication must relate to the subject's documented medical history, prophylaxis, or an AE.

7.4.7.1 Precautions

Subjects should be given the following additional instructions:

- Subject should minimize or avoid excessive natural or artificial sunlight exposure and extreme cold weather
- Subjects should avoid epilation, laser, mechanical or chemical peeling procedures during the study

7.4.7.2 Medications and Treatments Prohibited Before Study Entry and During the Study

The medications prohibited prior to Visit 1/Day 1 are listed in the exclusion criteria (Section 7.3.2).

Subjects will be advised to avoid the following for the duration of the study:

- Facial plastic surgery or permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene, polyacrylamide, lifting threads) anywhere in the face or neck
- Semi-permanent dermal filler treatment (e.g., calcium hydroxylapatite, poly-L-lactic acid) in the lower face (below the orbital rim)
- Other hyaluronic acid filler materials or collagen-based filler materials below the orbital rim

- Facial tissue augmentation with fat injections, botulinum toxin injections in the lower face (below the orbital rim), mesotherapy, or cosmetic procedures in the face or neck (e.g., face-lift, laser, photo-modulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, microneedling, or other ablative procedures)
- Use of any lip plumping products or devices
- Use of any OTC or prescription, oral or topical, anti-wrinkle products for the lips or around the mouth (Subjects who have been on a regimen of such products for at least 90 days are eligible for the study and must continue their regimen throughout the study.)

7.4.7.3 Concomitant Medications and Treatments Allowed During the Study

Permitted medications/treatments include any concomitant medication/treatment not listed in the exclusion criteria (Section 7.3.2).

7.4.8 Assessment of Compliance

Administration of the study device by the investigator is documented on the CRF.

7.5 Study Schedule

The visit-by-visit schedule of study activities is provided in Section 2. The timing of each visit is relative to Day 1, which is defined as the day the subject is randomized and first treated.

All visits should be performed within the windows specified on the schedule of study activities. Every attempt should be made to have each subject attend each visit as scheduled. If a subject is unable to attend a visit within the specified window the visit should be scheduled as closely as possible to the applicable window.

7.6 Study Procedures

The schedule of study activities summarizes the study procedures to be performed at each visit. Individual study procedures are described below.

All clinical assessments (LFGS, POL, iGAI, lip function, lip sensation, lip texture, lip firmness, lip symmetry, and lip movement/function evaluations) must be conducted by qualified investigators listed on the Form FDA 1572 who have been delegated these tasks by the principal investigator (PI). The PI may delegate this task only to physicians, physician assistants, or nurse practitioners who have documented training for this protocol and past experience conducting the assessment.

The LFGS, POL, iGAI, lip function, lip sensation, lip texture, lip firmness, lip symmetry, and lip movement/function evaluations are to be performed by a research team member who does not participate in treatment and who is blinded to the treatment assignment (blinded Evaluating Investigator).

To minimize variability of evaluations, the same investigator/sub-investigator should perform these assessments for any given subject and anticipate evaluating the subject at each visit, to the extent possible.

7.6.1 Study Roles

Each site will designate at least one Treating Investigator and at least one blinded Evaluating Investigator. In addition, one or more members of the study site staff may be designated as unblinded for the purposes of assisting in the management of study device use. Any study staff designated as unblinded should have no direct contact with subjects and may not perform any subject evaluations, assessments or measurements (including vital signs, questionnaires, etc.). Designation of unblinded study staff will be recorded in the Delegation of Authorities Log form.

The Treating Investigator will be responsible for conducting the injections, ensuring that the correct randomized study device is administered in accordance with the protocol and other study instructions. The Treating Investigator will assess subjects and determine the need for touch-up injections. Any AEs brought to the attention of the Treating Investigator will be forwarded to the blinded Evaluating Investigator for final adjudication and documentation.

The blinded Evaluating Investigator will be responsible for assigning grades for the various parameters (LFGS, POL, iGAI, lip function, lip sensation etc.). The blinded Evaluating Investigator will be responsible for recording AEs and determining their severity and relationship to the study device or the injection procedure.

7.6.2 Study Initiation

The investigational staff may not enroll any subjects prior to completion of a site initiation visit. This visit will include, but is not limited to, an inventory of study supplies (if present) and a detailed review of the protocol, CRFs, and the investigator's responsibilities as outlined on Form FDA 1572.

7.6.3 Written Informed Consent

The study personnel will review the ICF with each subject and give the subject an opportunity to have all questions answered before proceeding with any study procedures. A copy of the signed ICF will be given to every subject and the original will be maintained with the subject's records.

7.6.4 Significant Medical History/Demographic Information

Medical history and demographic information will be obtained at Visit 1/Day 1. The medical history will include a complete review of all current diseases and their respective durations and treatments. Demographic information will include date of birth, sex at birth, race, ethnicity, and Fitzpatrick skin type (Table 1).

Table 1. Fitzpatrick Classification Scale

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

7.6.5 Physical Examination (Including Vital Signs)

An abbreviated physical examination including height, weight, and vital signs will be recorded. Vital signs will include sitting blood pressure, temperature, heart rate, and respiratory rate. This physical examination will be performed at Visit 1/Day 1 to determine that the subject is healthy enough to participate in the study.

7.6.6 Vision Evaluations

Subjects will be assessed with Snellen visual acuity, confrontational visual fields, and ocular motility by a trained evaluator. These assessments will be performed prior to any treatment. These assessments will also be repeated 30 minutes following any treatment and at all follow-up visits.

7.6.7 Prior and Concomitant Medication/Treatment Review

Prior medications/treatments, including the necessary washout times, and concomitant medications (including prescription, OTC, and dietary supplements taken and other treatments and cosmetic products used by the subject) will be reviewed with the subject. A record of prior medications/treatments taken or used by the subject within 6 months before signing the ICF and concomitant medications/treatments will be obtained at Visit 1/Day 1. Concomitant medications or treatments will be reviewed with the subject at each study visit and telephone contact.

7.6.8 Urine Pregnancy Test and Acceptable Contraceptive Methods

Women of childbearing potential, in addition to having a negative urine pregnancy test at Visit 1/ Day 1, must be willing to use an acceptable form of birth control during the study. The following are considered acceptable methods of birth control for the purpose of this study: oral contraceptives, contraceptive patches, contraceptive implant, vaginal contraceptive, double barrier methods (e.g., condom and spermicide), contraceptive injection (Depo-Provera®), IUD, hormonal IUD (Mirena®), and abstinence with a documented second acceptable method of birth control if the subject becomes sexually active. Subjects entering the study who are on hormonal contraceptives must have been on the method for at least 90 days prior to the study and continue the method for the duration of the study. Subjects who had used hormonal contraception and stopped must have stopped no less than 90 days prior to Visit 1/Day 1.

7.6.9 Lip Fullness Grading Scale

The LFGS is a 5-point photonumeric rating scale that was developed to objectively quantify the 3-dimensional fullness of the lip. The scale ratings are 0 for very thin, 1 for thin, 2 for moderately thick, 3 for thick, and 4 for full (Carruthers et al, 2008). Photographs illustrating the ratings will be provided to each site. The assessments of overall lip fullness considering both lips together, fullness of the upper lip and fullness of the lower lip will be performed by the Treating Investigator at Visit 1 and by the blinded Evaluating Investigator at each study visit.

7.6.10 Perioral Lines at Rest Severity Scale

The POL is a 4-point rating scale which corresponds to the most severe perioral line attribute when the subject's mouth is at rest with the following ratings (Cohen et al, 2014):

0. None = a mouth with no perioral lines
1. Mild = a mouth with a few shallow perioral lines
2. Moderate = a mouth with some moderate lines
3. Severe = a mouth with many deep lines or crevices

The assessments of overall perioral lines at rest severity considering both lips together, perioral lines at rest severity of the upper lip and perioral lines at rest severity of the lower lip will be performed by the Treating Investigator at Visit 1 and by the blinded Evaluating Investigator at each study visit.

7.6.11 Review Inclusion/Exclusion Criteria

The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

7.6.12 Evaluation for Touch-up

The Treating Investigator will evaluate the subject at Visit 2 and determine in consultation with the subject the need for a touch-up treatment.

7.6.13 Patient Global Aesthetic Improvement (pGAI) Score

The pGAI score is a 5-point scale with the following categories:

1. Worse – the appearance is worse than the original condition.
2. No change – the appearance is the same as the original condition.
3. Improved – obvious improvement in appearance from the initial condition. A touch-up might further improve the result.
4. Much improved – marked improvement in appearance from the initial condition, but not completely optimal. A touch-up might slightly improve the result
5. Very much improved – optimal cosmetic result.

The pGAI score will be recorded by the blinded Evaluating Investigator at Visits 2, 3, 4, and 5. Subjects will be asked the question "How would you rate improvement in your appearance compared to your initial condition using the scale below?"

7.6.14 Investigator Global Aesthetic Improvement (iGAI) Score

The iGAI score is a 5-point scale with the following categories:

1. Worse – the appearance is worse than the original condition.
2. No change – the appearance is the same as the original condition.
3. Improved – obvious improvement in appearance from the initial condition. A touch-up might further improve the result.
4. Much improved – marked improvement in appearance from the initial condition, but not completely optimal. A touch-up might slightly improve the result.
5. Very much improved – optimal cosmetic result.

The iGAI score will be assessed by the Blinded Evaluating Investigator at Visits 2, 3, 4, and 5.

7.6.15 Investigator Ease of Use Assessment

The Treating Investigator will assess overall ease of use by the device by circling the appropriate number on the numerical rating scale from 0 being not easy to 10 being most easy at Visit 1/Day 1 and for subjects who have touch-up treatment at Visit 2/Month 1.

7.6.16 Swelling Assessment

Swelling will assessed by the Blinded Evaluating Investigator at Visits 2, 3, 4, and 5 using the 5-point scale with the categories that follow. The blinded Evaluating Investigator should examine both upper and lower lip simultaneously and recall the degree of augmentation originally provided for comparison. The subject should not be specifically questioned regarding swelling but if the subject spontaneously reports it, such information can be used to assist in selection of a grade for swelling.

0: None – No swelling noticeable. Lips appear the same as when originally augmented. Any lip enlargement is due to the implanted product only.

1: Minimal – Slight enlargement of either lip beyond the originally provided augmentation. May or may not be noticeable to the subject but is noticeable to the investigator.

2: Mild – Some enlargement of either lip beyond the original augmentation that is easily noticeable to the subject, but the lips do not appear abnormally large.

3: Moderate – Significant enlargement of either lip beyond the original augmentation. Either lip appears abnormally large.

4: Severe – Any degree of swelling that substantially interferes with lip function such as changes in speech or difficulty eating or drinking.

7.6.17 Lip Function Evaluation

Subjects' lip function will be assessed by the Blinded Evaluating Investigator by their ability to sip liquid through a straw prior to any injections and at all follow-up visits.

7.6.18 Lip Sensation Evaluation

Subjects' lip sensation will be assessed by the Blinded Evaluating Investigator and tested via: 1) the monofilament test (i.e., a subject's ability to feel the sensation of a 0.4G monofilament at three points on the upper lip and three points on the lower lip and 2) the cotton wisp test (i.e., a subject's ability to feel the sensation of a cotton wisp at three points on the upper lip and three points on the lower lip) prior to any injections and at all follow-up visits.

7.6.19 Lip Texture Evaluation

Subjects' lip texture will be assessed by the Blinded Evaluating Investigator as normal or abnormal prior to any injection and at all follow-up visits.

Table 2. Lip Texture Scoring Criteria

Normal	Abnormal		
	Mild	Moderate	Severe
Texture of the lip is even without visible undulations or excessive coarseness beyond that expected for stated age	The lip shows a single area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) can be visualized only with close inspection	The lip shows more than one area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) can be visualized only with close inspection. Or The lip shows one area of textural irregularity (less than ¼ of the lip area) at a conversational distance.	The lip shows two or more areas of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) can be visualized at a conversational distance. Or The lip shows one area of textural irregularity (more than ¼ of the lip area) at conversational distance

7.6.20 Lip Firmness Evaluation

Subjects' lip firmness will be assessed by the Blinded Evaluating Investigator as normal or abnormal prior to any injection and at all follow-up visits.

Table 3. Lip Firmness Scoring Criteria

Normal	Abnormal		
	Mild	Moderate	Severe
Lip is supple when compressed laterally and surface distorted readily with minimal pressure. Pressure with a narrow diameter instrument (cotton-tipped applicator, toothpick, etc) causes a focal depression in the surface of the lip. Upon palpation, lip is absent of abnormal structures such as scars or lumps; normal product feel without being visible.	Lip is slightly firm with lateral compression or required slightly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump is felt, but is not visible.	Lip is firm with lateral compression or requires distinctly greater than normal pressure to distort the surface or pressure with a narrow diameter instrument (cotton-tipped applicator or toothpick) causes a broader depression in the surface of the lip. Upon palpation, an abnormal structure such as a scar or lump is felt and is visible.	Lip is very firm with lateral compression or requires significantly greater than normal pressure to distort the surface. Upon palpitation, an abnormal structure such as a scar or lump is felt and is visually distracting.

7.6.21 Lip Symmetry Evaluation

Subjects' lip symmetry will be assessed by the Blinded Evaluating Investigator as normal or abnormal prior to any injection and at all follow-up visits.

Table 4. Lip Symmetry Scoring Criteria

Normal	Abnormal		
	Mild	Moderate	Severe
One side of the lip balanced or mirrored the other side	One side of the lip shows a 1 mm or less difference in height or a 1 mm or less difference in the length of the vermilion at repose.	One side of the lip shows a 1.1 mm to 2 mm difference in height or a 1.1 to 2 mm difference in the length of the vermilion at repose	One side of the lip shows a greater than 2 mm difference in the height or a greater than 2 mm difference in the length of the vermilion at repose.

7.6.22 Lip Movement/Function

Lip movement/function will be evaluated by the Blinded Evaluating Investigator as normal or abnormal prior to any injection and at all follow-up visits as the subject's ability to pucker lips, blowing and pronunciation of words that begin with the letter "W" such as water, work, week and wind.

7.6.23 Subject Satisfaction with Lips (Visual Analog Scale)

Subjects will be asked to assess their overall satisfaction with their lips at Visits 2, 3, 4, and 5 using a 100-mm VAS scale from 0 = Very Unsatisfied to 100 = Very Satisfied (Figure 1).

Figure 1. Visual Analog Scale for Subject Satisfaction

Very Unsatisfied — Very Satisfied

7.6.24 Subject Diary Card

A diary card will be dispensed to each enrolled subject at Visit 1/Day 1. The subject will be instructed to complete the diary cards to record any AEs experienced during the 2 weeks after receiving the initial treatment and the touch up treatment. The diary cards will be collected at Visit 2/Month 1 and Visit 3/Month 2 if touch up treatment was given. A new diary card will be dispensed at Visit 2/Month 1 if touch up treatment is given.

7.6.25 Adverse Events and Serious Adverse Events Assessment

See Section 7.9 for instructions on the assessment and reporting of AEs and SAEs and Section 7.9.7 for instructions on reporting SAEs to the Sponsor or designee.

7.6.26 Treatment Question

At Visit 5 or early termination, subjects and blinded evaluating investigators will be asked to identify which treatment they thought had been administered.

7.7 Visit-Specific Procedures

The following sections outline the procedures required at each visit.

7.7.1 Visit 1/Day 1: Baseline and Treatment

- Obtain written informed consent
- Obtain medical history and demographic information, including Fitzpatrick skin type classification
- Perform abbreviated physical examination, including height, weight, and vital signs (temperature, heart rate, blood pressure, and respiratory rate)
- Vision Evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Obtain/record prior and concomitant medications/treatments
- Perform urine pregnancy test for all women of childbearing potential
- LFGS assessment
- POL assessment

- Lip function evaluation prior to treatment administration
- Lip sensation evaluation prior to treatment administration
- Lip texture evaluation prior to treatment administration
- Lip firmness evaluation prior to treatment administration
- Lip symmetry evaluation prior to treatment administration
- Lip movement/function evaluation prior to treatment administration
- Evaluate inclusion/exclusion criteria
- Randomization
- Treatment administration
- Vision Evaluation (Snellen visual acuity, confrontational visual fields, ocular motility) 30 minutes after treatment
- Investigator Ease of Use assessment
- Assess AEs
- Dispense subject diary card
- Schedule next visit
- Complete CRFs

7.7.2 Telephone Contacts on Day 3 and Day 14 (± 2 days)

- Assess AEs
- Assess concomitant medications/treatments
- Confirm adherence to prohibited treatments/medications

7.7.3 Visit 2/Day 28 (± 2 days): Interim Visit at Month 1 with Possible Touch-up Treatment

- LFGS assessments
- POL assessments
- pGAI assessment
- iGAI assessment
- Lip function evaluation prior to treatment administration if applicable
- Lip sensation evaluation prior to treatment administration if applicable
- Lip texture evaluation prior to treatment administration if applicable
- Lip firmness evaluation prior to treatment administration if applicable
- Lip symmetry evaluation prior to treatment administration if applicable
- Lip movement/function evaluation prior to treatment administration if applicable
- Vision Evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Swelling Assessment
- Subject satisfaction with lips (VAS)

- Treatment administration if touch-up is needed (at Treating Investigator's discretion)
- Vision Evaluation (Snellen visual acuity, confrontational visual fields, ocular motility) 30 minutes after treatment if applicable
- Investigator Ease of Use assessment if applicable
- Assess AEs
- Assess concomitant medications/treatments
- Collect subject diary card
- Dispense new subject diary card if touch up treatment is given
- Schedule next visit
- Complete CRFs

7.7.4 Telephone Contacts on Day 33 and Day 44 (±2 days) for Subjects with Touch-up Treatment

- Assess AEs
- Assess concomitant medications/treatments
- Confirm adherence to prohibited treatments/medications

7.7.5 Visit 3/Day 56 (± 4 days) and Visit 4/Day 84 (± 4 days): Interim Visits at Month 2 and Month 3

- LFGS assessments
- POL assessments
- pGAI assessment
- iGAI assessment
- Lip function evaluation
- Lip sensation evaluation
- Lip texture evaluation
- Lip firmness evaluation
- Lip symmetry evaluation
- Lip movement/function evaluation
- Vision Evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Assess AEs
- Swelling Assessment
- Assess concomitant medications/treatments
- Subject satisfaction with lips (VAS)
- Collect subject diary card at Visit 3 if dispensed at Visit 2
- Schedule next visit
- Complete CRFs

7.7.6 Telephone Contacts on Day 112 (Month 4) and Day 140 (Month 5) ±4 days

- Assess AEs
- Assess concomitant medications/treatments
- Confirm adherence to prohibited treatments/medications

7.7.7 Visit 5/Day 168 (± 7 days): Month 6 End of Study Visit/Early Termination

- LFGS assessments
- POL assessments
- pGAI assessment
- iGAI assessment
- Lip function evaluation
- Lip sensation evaluation
- Lip texture evaluation
- Lip firmness evaluation
- Lip symmetry evaluation
- Lip movement/function evaluation
- Vision Evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Assess AEs
- Swelling Assessment
- Assess concomitant medications/treatments
- Subject satisfaction with lips (VAS)
- Treatment question
- Obtain written consent for open-label retreatment protocol
- Complete CRFs

All subjects will be evaluated for retreatment and undergo consent procedure for the subsequent open-label retreatment protocol.

7.7.8 Unscheduled Visit

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted. The following procedures may be performed at the Unscheduled Visit if required.

- LFGS assessments
- POL assessments
- pGAI assessment
- iGAI assessment
- Lip function evaluation
- Lip sensation evaluation

- Lip texture evaluation
- Lip firmness evaluation
- Lip symmetry evaluation
- Lip movement/function evaluation
- Vision Evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Assess AEs
- Swelling Assessment
- Subject Satisfaction with lips (VAS)
- Assess concomitant medications/treatments
- Complete CRFs

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is change from Baseline to Month 2 in overall lip fullness based on the Blinded Evaluating Investigator assessment using the LFGS. The LFGS is a validated scale (Carruthers et al, 2008).

7.8.2 Secondary Efficacy Analysis

Secondary analysis include

- percent of subjects with treatment success (responder: overall LFGS based on the Blinded Evaluating Investigator Assessment) at Visit 3/Month 2 where responder is defined as a subject with at least a 1-grade increase from baseline on the LFGS post augmentation,
- percent of responders overall on the POL severity scale at Visit 4/Month 3 (defined as a subject demonstrating ≥ 1-point improvement, i.e., decrease in severity, from baseline),
- change from baseline to Visit 4/Month 3 in overall LFGS based on the Blinded Evaluating Investigator Assessment
- change from baseline to Visit 5/Month 6 in overall LFGS based on the Blinded Evaluating Investigator Assessment.

7.8.3 Other Efficacy Analysis

Other efficacy analysis include

- pGAI, iGAI, and Swelling Assessment at each scheduled visit,
- percent of subjects with treatment success (responder: upper lips, lower lips LFGS) at Visit 3/Month 2 where responder is defined as a subject with at least a 1-grade increase from baseline on the LFGS post augmentation
- percent of responders (upper lips, lower lips) on the POL severity scale at Visit 4/Month 3 (defined as a subject demonstrating ≥ 1-point improvement, i.e., decrease in severity, from baseline),
- satisfaction with lips VAS at each scheduled visit,

- change from baseline to Visit 4/Month 3 and Visit 5/Month 6 in upper lips, lower lips LFGS.

7.9 Assessment of Safety

7.9.1 Safety Analysis

Safety of the study devices will be compared by evaluating the nature, severity, and frequency of treatment-emergent adverse events (TEAEs). All AEs that occur during the study will be recorded whether or not they are considered to be related to treatment. A description of the AE will be recorded with the date of onset, date of resolution, severity of the AE, relationship to the study device, action taken, and the outcome.

7.9.2 Other Safety Evaluations

Lip function, lip sensation, lip texture, lip firmness, lip symmetry and lip movement/function will be assessed prior to any injections and at all follow-up visits.

7.9.3 Definitions of Terms

7.9.3.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug/device in humans, whether or not considered drug/device-related (21 Code of Federal Regulations [CFR] 312.32 (a) and 803). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug/device, without any judgment about causality.

Expected adverse events are defined as the events that appeared at injection site subsequent to the first injection. Expected adverse events may include but are not limited to bruising, swelling, erythema, edema, inflammation at injection site.

7.9.3.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is defined as any AE for which there is reasonable possibility that the drug/device caused the AE (21 CFR 312.32 (a)).

7.9.3.3 Unexpected Adverse Event

An AE or SAR is considered unexpected if it is not consistent with the risk information described in the labeling for the study devices.

7.9.3.4 Adverse Events of Special Interest

Certain events will require more detailed and timely reporting. These include:

- any changes in vision
- any events attributable to an embolic or ischemic cause (i.e., skin infarction)
- Any incidence of an event due to an embolic or ischemic cause or visual disturbances (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye, blind spot or shadow in the visual field, trouble moving eyes, etc.) MUST be immediately reported to the Medical Monitor by phone, email or fax. The investigator/coordinator must complete the AE source/CRF page and email or fax it to the Medical monitor as soon as possible after the investigator or coordinator has become aware of its occurrence. These reports will include the depth of injection, the injection volume, the symptoms that were observed, the time to onset, time

to resolution and any interventions that were implemented. The Sponsor will notify the FDA within 10 working days.

In the event of blindness or any ophthalmic signs or symptoms, subjects will undergo immediate evaluation by a retina specialist.

Refer to Appendix 1 for first aid protocol.

7.9.3.5 Serious Adverse Event

An SAE is defined as any AE or SAR that, in the view of the investigator or Sponsor, results in any of the following outcomes (21 CFR 312.32 (a)):

- Death
- Life-threatening AE (Note: the term "life-threatening" as used here refers to an event that in the view of the investigator or Sponsor places the subject at immediate risk of death at the time of the event; it does not include an AE or SAE that, had it occurred in a more severe form, might have caused death [21 CFR 312.32(a)])
- Inpatient hospitalization or prolongation of existing hospitalization. See exclusion to SAE reporting below under Planned Hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment/damage
- Any "other" important medical event. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.9.3.6 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure occurs as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the study, it must be reported as an AE.

7.9.4 Pregnancy

Pregnancies occurring after administration of study device require immediate reporting. They must be reported within 24 hours after the investigator has become aware of the pregnancy. A pregnancy report will be completed and sent by fax to the Sponsor or designee within 24 hours of becoming aware of the pregnancy. The investigator will collect follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant that must also be reported to the Sponsor or designee. Upon awareness of the outcome of the pregnancy, the Principal Investigator or designee must forward a follow-up Pregnancy Report with any relevant information to the Sponsor or designee.

If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator will report the

event by faxing a completed SAE report form to the Sponsor or designee within 24 hours of being notified of the pregnancy report.

The subject should immediately be withdrawn from the study.

7.9.5 Monitoring Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs, immediately after treatment initiation. Each subject will be followed for safety monitoring until discharged from this study. Follow-up procedures related to pregnancy or AEs or SAEs may continue beyond the end of the study.

Subjects will be questioned and/or examined by the investigator or a qualified designee for occurrence of AEs throughout the study. The presence or absence of specific AEs should not be elicited from subjects. In addition, subjects will be instructed to record AEs on the subject diary card during the 2 weeks after treatment. Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded on the CRF, as well as in the subject's source documentation.

For all AEs that require the subject to be withdrawn from the study and SAEs, relevant clinical assessments will be repeated as clinically appropriate until final resolution or stabilization of the event(s).

7.9.6 Assessment of Adverse Events

7.9.6.1 Assessment of Severity

Severity of AEs will be graded according to the following definitions:

Mild: AE that was easily tolerated

Moderate: AE sufficiently discomforting to interfere with daily activity

Severe: AE that prevented normal daily activities

7.9.6.2 Assessment of Causality

A medically qualified investigator must assess the relationship of any AE (including SAEs) to the use of the study device as unlikely related, possibly related, or probably related based on available information, using the following guidelines:

Unlikely related: no temporal association, or the cause of the event has been identified, or the study device cannot be implicated based on available information

Possibly related: temporal association but other etiologies are likely to be the cause; however, involvement of the study device cannot be excluded based on available information

Probably related: temporal association, other etiologies are possible, but unlikely based on available information

7.9.6.3 Reference Safety Information for Assessing Expectedness of Adverse Events

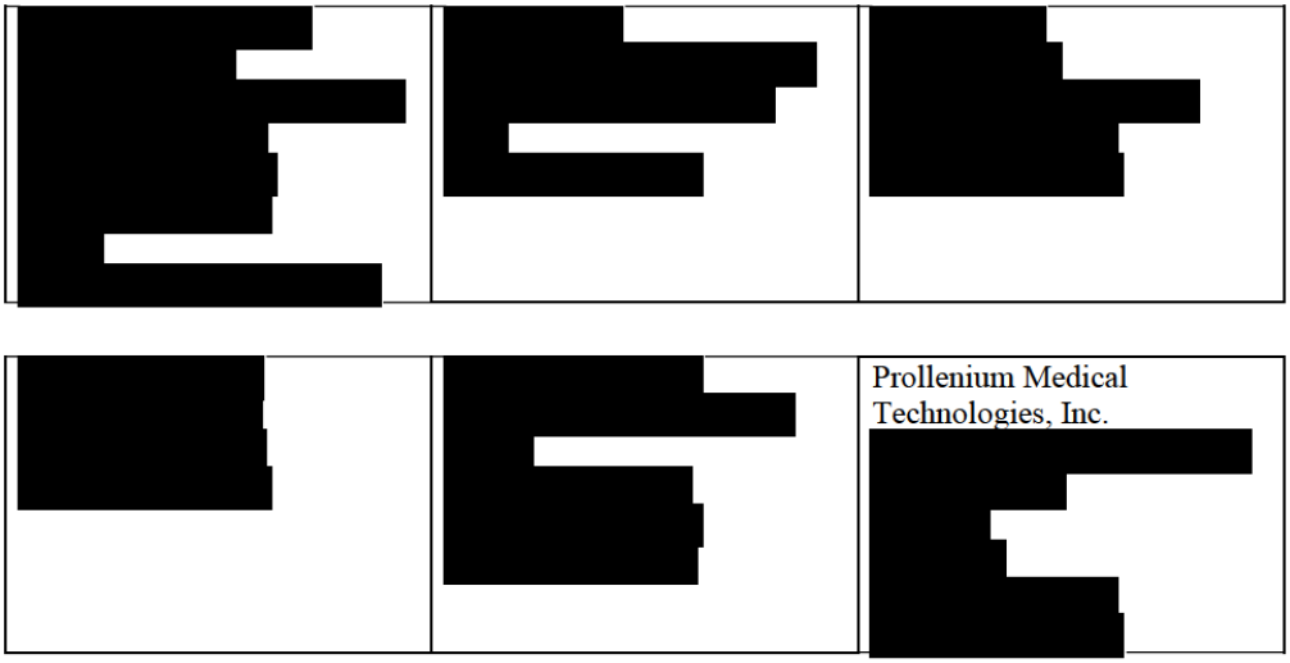
The reference safety information for assessing the expectedness of an AE for the study device in this study is the PN40082 Instructions for Use and the Restylane® Silk Instructions for Use.

7.9.7 Reporting Safety Observations

Any SAE, whether deemed device-related or not, must be reported to the Sponsor or designee by telephone, email or fax as soon as possible after the investigator or coordinator has become aware of its

occurrence. The investigator/coordinator must complete a Serious Adverse Event (SAE) Form and email or fax it to the Sponsor or designee along with the subject's Adverse Events Log and Concomitant Medications Log within 24 hours of notification of the event. The Sponsor will notify the FDA of device-related SAEs.

Designee and Sponsor contact details:



The investigator must be prepared to supply the medical monitor with the following information:

1. Investigator name and site number
2. Protocol number
3. Subject ID (screening/randomization) number
4. Subject initials and date of birth
5. Subject demographics
6. Clinical event
    a. description
    b. date of onset
    c. severity
    d. treatment (including hospitalization)
    e. relationship to study device
    f. action taken regarding study device
    g. if the AE was fatal or life-threatening:
        i. cause of death (whether or not the death was related to study device)
        ii. autopsy findings (if available)

The Sponsor must submit a written summary of the clinical course of any life-threatening SAE and related subject information to the FDA within 7 days. Serious and unexpected AEs that are not life-threatening must be reported to the FDA within 15 calendar days. Any serious and unexpected AE

(including all deaths) must also be reported to the Institutional Review Board (IRB) by the investigator according to IRB reporting requirements and documentation of this report sent to the Sponsor or designee.

The investigator must provide a follow-up written report within 5 calendar days of reporting the event to the medical monitor. The written report must contain a full description of the event and any sequelae. Subjects who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized.

7.9.8 Diary Assessments

Diaries will be reviewed by the Treating Investigator and/or unblinded staff each time they are returned by a subject. Entries will be reviewed for completeness and medical accuracy. Any diary events listed by the subject as persisting beyond the final recording day of the diary will be evaluated by the Treating Investigator at the next visit and may be recorded as an AE at the discretion of the investigator.

7.9.9 Criteria for Early Termination of the Study

The trial may be terminated because of safety concerns. Where termination is deemed appropriate, there will be timely communication with the FDA in accordance with the regulation (21 CFR 812.150 (devices)). The sponsor, Prollenium Medical Technologies, will initiate discussion as soon as possible about the appropriate course of action for the trial in question and for the investigational product. There will be immediate follow up by the company to investigate any potential safety concern.

In the event of a vascular embolic event leading to skin necrosis, vision loss, or stroke, enrollment and treatment at the investigational site will be suspended and a root cause investigation will be conducted to determine the cause of the embolic event and whether the outcome was anticipated (the investigator did not properly follow the treatment SOP) or unanticipated (the investigator did properly follow the treatment SOP). If the latter situation is observed, the entire study will be immediately suspended and no patients will be enrolled until the event can be properly characterized and an appropriate treatment strategy to avoid this unanticipated event can be devised.

7.9.10 Withdrawal, Treatment Interruption, and Unblinding of Blinded Treatment Due to Safety Observations

7.9.10.1 Withdrawal

See Section 7.3.3 for the criteria for withdrawing a subject. If a subject is withdrawn from the study, the activities specified for Visit 5/Month 6 on the schedule of study activities (Section 2) should be completed if possible.

7.9.10.2 Unblinding Treatment for a Subject During the Study

Unblinding by the investigator should occur only in the event of an AE or SAE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. In the event of an emergency that requires breaking of the study blind, the Investigator can unblind the subject without prior contact with the Medical Monitor although the Investigator will immediately notify the Medical Monitor accompanied by a written explanation of the reason why the blind was broken. In the event of an emergency that requires breaking of the study blind, the randomization code will be maintained by each unblinded Treating Investigator that can be opened to reveal the study device to the applicable staff. In the event the unblinded Treating Investigator is not available, the site should designate another unblinded staff member not involved in the study conduct to access the randomization code for that

subject. Note this can be done WITHOUT informing the blinded Evaluating Investigator and thus maintaining the study blind. If unblinding occurs, the subject must be withdrawn from the study.

8 STATISTICAL METHODS

Prior to the database lock, a detailed, finalized Statistical Analysis Plan will be completed and placed on file. The Statistical Analysis Plan will contain a more comprehensive explanation than that provided here of the methodology used in the statistical analyses, as well as the rules and data handling conventions used to perform the analyses and the procedure used to account for missing data.

8.1 Analysis Populations

Intent-to-treat (ITT) (safety) population: All randomized subjects who received study device

Modified intent-to-treat (mITT): All randomized subjects who met the inclusion/exclusion criteria, were randomized, and received study device

Per-protocol (PP): All randomized subjects who met all inclusion/exclusion criteria; received study device, completed Visit 5 within the specified window; had LFGS score by the Blinded Evaluating Investigator at Visit 3/Month 2 within the specified visit window, and had no significant protocol violations that would affect the treatment evaluation

Efficacy analyses will be performed on the mITT and PP populations, with PP as the primary population and mITT supportive.

Safety analyses will be performed on the ITT population.

8.2 Efficacy Analysis

The primary efficacy endpoint is change from baseline to Month 2 in overall lip fullness based on the Blinded Evaluating Investigator assessment using the LFGS. A 95% confidence interval (CI) will be constructed for the difference between PN40082 and Restylane Silk (i.e. PN40082 minus Restylane Silk) with respect to the primary endpoint. If the lower limit of this 95% CI is above a pre-specified NI limit -0.50, PN40082 will be claimed non-inferior to Restylane Silk.

The primary endpoint will also be analyzed for the following two subsets of subjects: (1) subjects that have injection on one lip only, and (2) subjects that have injections on both lips.

Secondary analysis include

- percent of subjects with treatment success (responder: overall LFGS based on the Blinded Evaluating Investigator Assessment) at Visit 3/Month 2 where responder is defined as a subject with at least a 1-grade increase from baseline on the LFGS post augmentation,
- percent of responders overall on the POL severity scale at Visit 4/Month 3 (defined as a subject demonstrating ≥ 1-point improvement, i.e., decrease in severity, from baseline),
- change from baseline to Visit 4/Month 3 in overall LFGS based on the Blinded Evaluating Investigator Assessment
- change from baseline to Visit 5/Month 6 in overall LFGS based on the Blinded Evaluating Investigator Assessment.

For this non-inferiority study, the null hypothesis to be tested for all the secondary endpoints is that there is no difference between the two products, and all statistical comparisons for these endpoints will be considered descriptive (non-inferential). These secondary variables will be summarized with descriptive statistics for

each treatment arm and a 95% CI for the difference between treatments. For the proportion variables, the 95% CI for treatment difference will be calculated using the Wald's method, with subjects pooled from all study sites. For the change variables, the 95% CI for treatment difference will be derived using ANCOVA with factors of treatment and site, and the corresponding baseline value for the endpoint as covariate.

Other efficacy analysis include

- pGAI, iGAI, and Swelling Assessment at each scheduled visit,
- percent of subjects with treatment success (responder: upper lips, lower lips LFGS) at Visit 3/Month 2 where responder is defined as a subject with at least a 1-grade increase from baseline on the LFGS post augmentation,
- percent of responders (upper lips, lower lips) on the POL severity scale at Visit 4/Month 3 (defined as a subject demonstrating ≥ 1-point improvement, i.e., decrease in severity, from baseline),
- satisfaction with lips VAS at each scheduled visit,
- change from baseline to Visit 4/Month 3 and Visit 5/Month 6 in upper lips, lower lips LFGS.

All other efficacy endpoints will be summarized by treatment arm using descriptive statistics.

8.3 Interim Analysis

No formal interim analysis is planned.

8.4 Safety Analyses

Adverse events will be coded to system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20 or higher).

Frequency and percentage of subjects reporting treatment-emergent adverse events (TEAEs) will be tabulated for each treatment by preferred terms and further by severity and relationship to study device. In summaries of severity and relationship, subjects reporting more than one event in a treatment arm that are mapped to the same preferred term will be counted only once in that treatment arm under the strongest severity and relationship, respectively. In addition, visual related TEAEs will be summarized separately for each treatment by preferred term.

Assessment results of lip function, lip sensitivity, lip texture, lip firmness, lip symmetry, and lip movement/function will be summarized with frequency and percentage for each scheduled visit.

Safety analyses will be conducted using the ITT population.

8.5 Sample Size Determination

For the PRO 2018-02 study, the primary variable is change from baseline to Month 3 in LFGS. The sample size was determined based on (1) both PN40082 and Restylane Silk having an equal mean value with a common standard deviation of 0.85 for change from baseline in LFGS, and (2) the non-inferiority limit of -0.50. The test:control ratio of 1:1 results in 126 (63:63) PP subjects at 90% power. Assuming 80% of randomized subjects meet the PP criteria, a total of 158 (79:79) subjects will be randomized to obtain 126 (63:63) PP subjects.

9 ETHICS

9.1 Informed Consent

The principles of informed consent, according to Food and Drug Administration (FDA) regulations and International Council on Harmonization (ICH) guidelines on GCP, will be followed. A copy of the proposed ICF must be submitted with the protocol to the IRB for approval.

The informed consent process must be conducted and the ICF must be signed before each subject undergoes any Visit 1 procedures that are performed solely for the purpose of determining eligibility for the study, in compliance with 21 CFR Part 50. Each subject's signed ICF must be kept on file by the investigator for inspection by regulatory authorities at any time. A copy of the signed ICF will be given to the subject. A notation will be made in the subject's medical record indicating the date and time informed consent was obtained.

9.2 Institutional Review Board (IRB)

The study protocol and ICF must be approved in writing by an appropriate IRB as defined by FDA regulations and other applicable requirements prior to enrollment of any study subjects.

Any changes to the protocol or a change of investigator approved by the Sponsor must also be approved by the site's IRB and documentation of that approval provided to the Sponsor or designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to inspection by regulatory authorities during or after completion of the study. SAEs must also be reported to the IRB.

Periodic status reports must be submitted to the IRB at least annually, as well as notification of completion of the study and a final report within 1 month of study completion or termination. A copy of all reports submitted to the IRB must be sent to the Sponsor or designee.

The investigator will ensure that an IRB that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the study.

9.3 Subject Confidentiality

All subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the Sponsor, the investigator must permit the study monitor, Sponsor representative or auditor, and/or FDA representative or other regulatory authority to review the portion of the subject's medical record that is directly related to the study. This shall include all study-relevant documentation including medical history to verify eligibility, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study, and autopsy reports if a death occurs during the study.

As part of the required content of informed consent, each subject must be informed that his or her medical chart may be reviewed by the Sponsor, the Sponsor's authorized representatives, FDA or other regulatory authority. If access to the medical record requires a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

9.4 Study Registration

The study will be registered by the Sponsor on an appropriate free public web site such as clinicaltrials.gov, which is a service of the United States National Institutes of Health.

10 DATA HANDLING AND RECORDKEEPING

10.1 Site Regulatory Documents Required for Initiation

The Sponsor or designee will receive the following documents prior to the initiation of the study:

- Completed, signed Form FDA 1572
- Current curricula vitae, signed and dated, for the principal investigator (PI) and co-investigators named on Form FDA 1572
- Current license(s) of the PI and co-investigators named on Form FDA 1572
- Documentation of IRB approval of the study protocol, investigator, and ICF
- Current IRB membership list
- A copy of the protocol signature page signed by the PI
- Original Non-disclosure Agreements for the PI and co-investigators named on Form FDA 1572
- Debarment Certification for the PI and co-investigators named on Form FDA 1572
- Financial Disclosure Statement for all individuals named on Form FDA 1572

10.2 Maintenance and Retention of Records

The study will be conducted according to GCP as outlined in ICH guidelines by the FDA. It is the responsibility of the investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Investigators will be instructed to retain all study records required by the Sponsor and the regulations in a secure and safe facility with limited access. Regulations require retention for a period of at least 2 years after marketing approval and notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities.

These records include documents pertaining to the receipt and return of study device, IRB, informed consent, source documents, and final signed CRFs. No documents shall be transferred from the site or destroyed without first notifying the Sponsor.

10.2.1 Case Report Forms (CRFs)

CRFs for individual subjects will be provided by the Sponsor or designee. CRFs must be legible and complete. CRFs for this study will be maintained in a study binder and data recorded on 2-part NCR paper. One copy will be kept by the investigator and the other copy will be collected by the study monitor. All forms should be completed using a black ballpoint pen. Errors should be lined out, *but not obliterated,* and the correction inserted, initialed, and dated by designated study personnel. Further data corrections will be performed on special "data correction forms" (DCFs) that will be provided to the investigator in case of erroneous or unclear data. The investigator will make the correction on the DCF and sign the DCF. The original will be sent to the study monitor and a copy retained with the CRFs.

A CRF must be completed and signed by the investigator for each subject enrolled, including those withdrawn from the study for any reason. The reason for withdrawal must be noted on a subject's study termination form.

CRFs must be kept current to reflect the subject's status at each phase during the course of the study. Subjects are not to be identified on CRFs by name; appropriately coded identification and the subject's initials must be used. The investigator must keep a separate log of the subjects' names and addresses.

Source documents such as the clinic chart are to be maintained separately from the CRF to allow data verification. Because of the potential for errors, inaccuracies, and illegibility in transcribing data onto

CRFs, originals of laboratory and other test results must be kept on file with the subject's CRF. CRFs, source documents, and copies of test results must be available at all times for inspection by the study monitor. The following should also be available for review:

- Subject Screening Log, which should reflect the reason any subject screened for the study was found to be ineligible
- Delegation of Authority Log, which will list all site personnel with their responsibilities as delegated by the PI and their signatures. This log will be maintained at the site throughout the study
- Monitoring Log, which will list the date and purpose of all monitoring visits by the Sponsor or designee
- Enrollment Log, which will list subject initials and start and end dates for all enrolled subjects
- Product Inventory/Packing Slip, which will list the total amount of study device shipped to the site and received and signed for by the investigator
- Study Device Dispensing Log, which will list the lot number and total amount of study device used for each subject
- ICF, which must be available for each subject and be verified for proper documentation
- All correspondence

10.2.2 Primary Source Documents

The investigator must maintain primary source documents supporting significant data for each subject's medical notes. These documents, which are considered "source data," should include documentation of:

- Demographic information
- Evidence supporting the indication for which the subject is being studied
- General information supporting the subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the investigator(s), occurrence (or lack) of AEs, and changes in medication usage
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible AEs
- An original, signed ICF for study participation

The investigator must also retain all subject-specific printouts/reports of tests and procedures performed as a requirement of the study. During monitoring visits the monitor will validate CRF entries against these data sources.

10.3 Study Monitoring

The Sponsor or designee will be responsible for monitoring the study according to GCP and applicable regulations. The study will be monitored by a Clinical Research Associate (CRA) in compliance with GCP, ICH guidelines, and applicable regulations. The investigator will be visited by a CRA prior to the study and at regular intervals during the course of the study. These visits are to verify adherence to the protocol. The CRA will review the ICFs and verify CRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The CRA will review the maintenance of regulatory documentation and product accountability. The monitor will review the progress of the study with the investigator and other site personnel on a regular basis. CRFs may be collected during these visits. At the end of the study, a closeout monitoring visit will be

performed. Monitoring visits will be arranged with site personnel in advance at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitoring of CRFs and relevant source documents. The coordinator and/or investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the investigator and study staff.

10.4 Audits and Inspections

During the course of the study and/or after it has been completed, 1 or more sites may be audited by authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with recognized GCP/ICH guidelines and regulations.

Additionally, the study may be inspected by regulatory authorities. These inspections may take place at any time during or after completion of the study and are based on local regulations.

10.5 Modifications to the Protocol

The procedures defined in the protocol and CRFs will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. To ensure the validity of the data, no deviations from the protocol (with minimal exceptions) may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and IRB prior to implementation. The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate an apparent immediate hazard to a subject or subjects. In such a case, however, the investigator must notify the Sponsor immediately and the IRB within 5 working days after implementation.

10.6 Completion of the Study

The investigator is required to forward CRFs and all other relevant data and records to the Sponsor or designee. The investigator will complete and report (submission of CRFs) his/her study in satisfactory compliance with the protocol as soon as possible after the completion of the study.

The investigator must submit a final report to the IRB and the Sponsor within 1 month of study completion or early termination.

11 CONFIDENTIALITY, USE OF INFORMATION, AND PUBLICATION

All information related to this study that is supplied by the Sponsor and not previously published is considered confidential information. This information includes but is not limited to data, materials (protocol, CRFs), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists, and technical and commercial information relating to customers or business projections used by the Sponsor in its business. Any data, inventions, or discoveries collected or developed as a result of this study are considered confidential. This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of the Sponsor, and shall not be used except in the performance of the study.

The information developed during the course of this study is also considered confidential and will be used by the Sponsor in the development of the study medication. The information may be disclosed as deemed necessary by the Sponsor. To allow the use of the information derived from this study, the investigator is obliged to provide the Sponsor with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of the Sponsor. If the investigator wants to publish or present the results of this study, he or she agrees to provide the Sponsor with an abstract, manuscript, and/or presentation for review 60 days prior to submission for publication or presentation. The Sponsor retains the right to delete confidential information and to object to suggested publication/presentation and/or its timing (at the Sponsor's sole discretion).

12 LIST OF REFERENCES

Carruthers A, Carruthers J, Hardas B, et al. A validated lip fullness grading scale. Dermatol Surg. 2008;34 Suppl 2: S161-S166.

Cohen JL, Thomas J, Paradkar D, et al. An interrater and intrarater reliability study of 3 photographic scales for the classification of perioral aesthetic figures. Dermatol Surg. 2014;40:663-670.

Wolters Kluwer Health, Inc. Restoration of Visual Loss with Retrobulbar Hyaluronidase Injection After Hyaluronic Acid Filler. Dermatol Surg 2018;44:435-446.

13 INVESTIGATOR AGREEMENT

Protocol Number: PRO 2018-02

Protocol Title: A Multicenter, Double-blind, Randomized, Controlled Study of the Safety and Effectiveness of PN40082 for Lip Augmentation

I have carefully read and understand the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for Good Clinical Practice, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA), and local regulatory guidelines. I will ensure that the requirements for obtaining informed consent are met. I will attempt to complete the study within the time designated. I will ensure that the rights, safety, and welfare of subjects under my care are protected. I will ensure control of the devices under investigation in this study. I will supervise all testing of the devices involving human subjects. I will provide copies of the protocol and all other study-related information supplied by the sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the device and conduct of the study. I agree to keep records on all subject information (case report forms, shipment and device return forms, and all other information collected during the study) and device disposition in accordance with FDA regulations. I will not enroll any subjects into this protocol until IRB approval and sponsor approval are obtained.

_____

Investigator Name (Print)

_____ _____

Investigator Signature Date

14 APPENDIX 1

Filler First Aid Protocol (Wolters Kluwer Health, Inc, 2018)

Materials that are needed on-site:

- Hyaluronidase (Hylenex)
- Aspirin 325mg
- Nitroglycerin paste

Provide the following contacts to subjects and these contacts also posted on-site for easy reference:

- Ophthalmologist "on call"
- Closest ER with stroke management capability with directions to ER

Preparation:

- The above materials should be gathered and labeled for emergency use only (to ensure they are available should an urgent situation arise).
- Staff should be educated regarding the urgent nature of such an event and the location of all materials and contact information.
- Investigators may wish to familiarize themselves with the retrobulbar injection technique via literature or on line training.

It is critical to recognize any intravascular events during injections and act quickly to maximize likelihood of reversal. As soon as an intravascular is recognized, **stop any further injections**.

If a skin infarction is identified:

- Apply nitroglycerin paste – apply liberally to the affected area and massage in gently, expect headache complaint from subject but do not withhold the treatment.
- Massage area to help promoted blood flow
- Dispense Aspirin 325 mg - Have patient chew this or the aspirin may be placed sublingually for maximum rapid absorption
- If blanching persists, consider infiltration with hyaluronidase
    - Infiltrate in the area where material was being injected – this may allow hyaluronidase to enter the same vessel that was inadvertently cannulated.
    - Infiltrate in the area of blanching or ischemia as well
    - Inject a minimum of 50 units into each area; investigators are free to use larger doses as they see fit.
    - Hyaluronidase may be repeated as needed.
- Hot Packs – Towels or gel packs warmed in a microwave can be applied to the area of decreased blood flow.
- Monitor the subject and the area of blanching ischemia. If blanching persists after 24 hours,– consider hyperbaric oxygen treatments.

If signs/symptoms of visual changes, opthalmoplegia, blindness, ocular pain (usually immediately)

occur:

- Dispense Aspirin 325 mg - Have patient chew or place the tablet sublingually for maximum rapid absorption
- Massage the globe with repeated inward compression and release – this may free any embolic material
- Infiltration with hyaluronidase into area being corrected or augmented
- Have staff call ophthalmology: *Insert physician and cell phone number* or on-call ophthalmology at *nearest center with on-call ophthalmology*, and arrange transport
    - Bring hyaluronidase with the subject to the ophthalmologist – at least 300 units.
- If transport time to ophthalmology or ER is more than 60 minutes, consider performing retrobulbar hyaluronidase administration, 300-600 units at inferior, lateral orbital rim through orbital septum with 1-1.5 inch 27 gauge needle avoiding globe

After above measures, expedite to emergency room, the retina can tolerate approximately 90 minutes of ischemia until damage becomes permanent.

If stroke symptoms are recognized:

- Dispense Aspirin 325 mg - Have patient chew this or the aspirin may be placed sublingually for maximum rapid absorption
- Infiltration with hyaluronidase into area being corrected or augmented
- Call for transport to ER immediately
- Inform local stroke team during transport

PN40082 INSTRUCTIONS FOR USE

PN40082 Injectable Hyaluronic Acid Gel with 0.3% Lidocaine

Caution: Federal Law restricts this device to investigational use. This device is limited by Federal (or United States) law to investigational use

DESCRIPTION

PN40082 is a gel of hyaluronic acid generated by Streptococcus species of bacteria, chemically crosslinked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 with 0.3% lidocaine.

INDICATION

PN40082 is indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.

CONTRAINDICATIONS

- *PN40082* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *PN40082* contains trace amounts of gram positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- *PN40082* is contraindicated for patients with bleeding disorders.
- *PN40082* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.
- *PN40082* should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

WARNINGS

- Defer use of *PN40082* at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the process has been controlled.
- Injection site reactions (e.g., lip swelling, lip pain, and contusion) to *PN40082,* including short-term minor or moderate inflammatory symptoms starting shortly after treatment of lips
- *PN40082* must not be implanted into blood vessels. Localized superficial necrosis and scarring may occur after injection in or near vessels, such as in the lips, nose, or glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules that may occur rarely should be considered and treated as a soft tissue infection.
- Injections of 4.0 mL or greater (upper and lower lip combined) per treatment session increases the occurrence of injection site reactions. If a volume of more than 3 mL is needed to achieve optimal correction, a follow-up treatment session is recommended.
- As with all dermal filler procedures, *PN40082* should not be used in vascular rich areas. Use of similar products in these areas, such as glabella and nose, has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion, such as blindness.

PRECAUTIONS

- *PN40082* is packaged for single use. Do not resterilize. Do not use if package is opened or damaged.
- The safety or effectiveness of *PN40082* for the treatment of anatomic regions other than lips or perioral rhytids has not been established in controlled clinical studies.
- As with all transcutaneous procedures, *PN40082* implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of *PN40082* for use during pregnancy, in breastfeeding females or in patients under 22 years has not been established, and these individuals are excluded from this study.
- Subjects with known susceptibility to keloid formation are excluded from this study. Formation of keloids may occur after dermal filler injections.
- Hyperpigmentation may occur after dermal filler injections. Subjects with known hyperpigmentation are excluded from this study.
- *PN40082* should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *PN40082* injection sites. Patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the 3 weeks preceding treatment with *PN40082* have not been studied.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.
- The safety of *PN40082* with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least until any initial swelling and redness has resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *PN40082*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *PN40082* is administered before the skin has healed completely after such a procedure.
- Injection of *PN40082* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.

HOW SUPPLIED

PN40082 is supplied in a disposable glass syringe with a Luer-Lok® fitting. *PN40082* is packed with two 1.0 mL syringes and two sterilized needle(s) 30 G x ½" in a peel tray contained in a carton. A patient record label is a part of the syringe label. This label is to be attached to patient records to ensure traceability of the product. The contents of the syringe are sterile.

SHELF LIFE AND STORAGE

PN40082 must be used prior to the expiration date printed on the package. Store at a temperature of 5 to 25° C (77° F). Do not freeze. Protect from sunlight.

Do not use if the package is damaged.

INJECTION TECHNIQUES

1. Study device can be injected by a number of different techniques that depend on the treating investigator's experience and preference, and patient characteristics.
2. **Serial puncture** involves multiple, closely spaced injections along wrinkles, folds or the vermillion border. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
3. **Linear threading (includes retrograde and antegrade)** is accomplished by fully inserting the needle into the center of the area to be corrected or augmented and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle has been fully inserted and is being withdrawn, it can also be performed while advancing the needle - antegrade technique). To enhance the lip, the retrograde linear threading technique is the most advisable.
4. Serial threading is a technique that utilizes elements of both approaches.

   Note! The correct injection technique is crucial for the final result of the treatment.
5. The following techniques should be avoided as they may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site:
   - Dissection of the sub-epidermal plane with lateral movement of the needle – "fanning"
   - Rapid flow rate (>0.3 mL/min) of implant material injection
   - High injection volumes
   - The use of needles other than those provided in the treatment kit
6. The use of cannulas is prohibited
7. When the injection is completed, the treated site should be **gently** massaged so that it conforms to the contour of the surrounding tissues. Massaging that substantially deforms the lips, or causes blanching of compressed tissues, is excessive, and should be avoided except as described below.
8. If excessive material is implanted or irregularly implanted, massage the area somewhat more firmly than for the usual implantation procedure to obtain optimal results.
9. If blanching of the tissues is observed during or directly after injection, pause the procedure and massage the area gently until the color returns. If the condition persists, contact the Medical Monitor.
10. The lips should be augmented to achieve the maximum desirable appearance for both the treating investigator and the subject. Subjects should be provided a small hand mirror to observe the results and further injections conducted until maximum benefit has been obtained. Care should be taken to ensure that the lips are symmetric from right to left and that the upper and lower lips have relative proportionality.
11. The perioral area should be corrected AFTER the upper and lower lips have been corrected. Some correction of perioral rhytids may occur with lip augmentation, thus it is best to address any remaining perioral correction needs after the lip injections have been completed.
12. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period. Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
13. Subjects should be encouraged to avoid a recumbent position for several hours after injections to reduce swelling. The use of ice, cold packs or other therapies to reduce swelling should only be

performed at instruction of the investigator. The subject should be instructed to contact the site if substantial swelling occurs.

RESTYLANE® SILK INSTRUCTIONS FOR USE

Restylane® Silk
Injectable Gel with 0.3% Lidocaine

Caution: Federal Law restricts this device to sale by or on the order of a physician or licensed practitioner.

DESCRIPTION
Restylane Silk is a gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically crosslinked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine.

INDICATION
Restylane Silk is indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.

CONTRAINDICATIONS
- *Restylane Silk* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane Silk* contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *Restylane Silk* is contraindicated for patients with bleeding disorders.
- *Restylane Silk* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.
- *Restylane Silk* should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

WARNINGS
- Defer use of *Restylane Silk* at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the process has been controlled.
- Injection site reactions (e.g., lip swelling, lip pain, and contusion) to *Restylane Silk* have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting shortly after treatment, with an average of less than 18 days duration in the lips. In some cases delayed onset of these events has been observed with a range of 21 to 142 days after treatment. Most events with delayed onset resolved within 18 days. Injection site swelling appears to occur more frequently with the linear antegrade method of injection. Rare post-market Restylane reports of immediate post-injection reactions included extreme swelling of lips, the whole face and symptoms of hypersensitivity such as anaphylactic shock.
- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the *intravascular* injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly

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evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

- *Restylane Silk* must not be implanted into blood vessels. Localized superficial necrosis and scarring may occur after injection in or near vessels, such as in the lips, nose, or glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules that may occur rarely should be considered and treated as a soft tissue infection.
- Injections of 3.0 mL or greater (upper and lower lip combined) per treatment session increases the occurrence of injection site reactions. If a volume of more than 3 mL is needed to achieve optimal correction, a follow-up treatment session is recommended.
- As with all dermal filler procedures, *Restylane Silk* should not be used in vascular rich areas. Use of similar products in these areas, such as glabella and nose, has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion, such as blindness. For additional information please see the Post-Marketing Surveillance in Adverse Events.

PRECAUTIONS

- Restylane Silk is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- The safety or effectiveness of *Restylane Silk* for the treatment of anatomic regions other than lips or perioral rhytids has not been established in controlled clinical studies. Refer to the clinical studies section for more information on implantation sites that have been studied.
- The safety and effectiveness of cannula injection of *Restylane Silk* have only been clinically evaluated in two brands of blunt-tip cannulas (DermaSculpt and Softfil) that are 25G-27G and 1½ inches in length.
- The safety or effectiveness of *Restylane Silk* for the treatment of perioral rhytids with a small bore, blunt tip cannula has not been established in controlled clinical studies.
- The safety and effectiveness of *Restylane Silk* for lip augmentation has not been established in patients under the age of 22 years. There is limited information on the safety of *Restylane Silk* in patients less than 36 years of age. In a premarket study of *Restylane Silk* with needle injection (MA-1700-04), the incidence of injection site reactions in 60 patients less than 36 years was similar to the 157 patients between the ages of 36 and 65 years. The majority of these injection site reactions were mild in severity. In the premarket study of *Restylane Silk* with cannula injection (43USC1505), 17 subjects less than 36 years of age were studied, and the incidence of injection site reactions were similar to the 43 subjects between the ages of 36 and 72 years.
- As with all transcutaneous procedures, *Restylane Silk* implantation carries a risk of infection. Standard precautions associated with injectable materials should be

followed.

- The safety of *Restylane Silk* for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established
- The safety in patients with known susceptibility to keloid formation has not been studied. Formation of keloids may occur after dermal filler injections including *Restylane Silk*. In a premarket study of *Restylane Silk* with needle injection (MA-1700-04), the incidence and severity of adverse events in 51 subjects with Fitzpatrick Skin Types IV (n=48) and V (n=3) was similar to that reported in the general population and no unique adverse events associated with these patient subgroups was observed. In the premarket study of *Restylane Silk* with cannula injection (43USC1505), the incidence and severity of adverse events in 13 subjects with Fitzpatrick Skin Types IV (n=8), V (n=3), and VI (n=2) were similar to those reported in the general population and no unique adverse events associated with these patient subgroups was observed.
- Hyperpigmentation may occur after dermal filler injections including *Restylane Silk*. Hyperpigmentation was not observed in the two *Restylane Silk* studies of 281 total subjects including subjects with Fitzpatrick Skin Types IV (n=56), V (n=6), and VI (n=2).
- The safety profile for Restylane Silk lip augmentation in persons of color is based upon information from 64 total subjects with Fitzpatrick Skin Types IV, V and VI from two clinical studies (MA-1700-04 and 43USC1505). Within this population, the incidence of adverse events was similar to the overall study population.
- *Restylane Silk* should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *Restylane Silk* injection sites. Patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the 3 weeks preceding treatment with *Restylane Silk* have not been studied.
- After use, syringes and needles/blunt cannula should be handled as potential biohazards.
- Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.
- The safety of *Restylane Silk* with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least until any initial swelling and redness has resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Restylane Silk*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane Silk* is administered before the skin has healed completely after such a procedure.
- Injection of *Restylane Silk* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *Restylane Silk* is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe and notify Galderma Laboratories, L.P. at 1-855-425-8722. Glass is subject to breakage under a variety of unavoidable conditions. Care should be taken with the handling of the glass syringe and with disposing of broken glass to avoid laceration or

other injury.

- *Restylane Silk* should not be mixed with other products before implantation of the device.

ADVERSE EXPERIENCES

There were two U.S. studies that reported adverse experiences. One study was conducted in support of the indication for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids, and one study was conducted in support of using a small bore, blunt-tip cannula for submucosal implantation for lip augmentation.

Study conducted for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids

The U.S. pivotal study (MA-1700-04) involved 221 subjects at 14 centers. At baseline, subjects were randomized to receive *Restylane Silk* injections in the lips and perioral rhytids (as needed) or no treatment (control group). At 6 months, all subjects were eligible to receive treatment or re-treatment in the lips and perioral rhytids with *Restylane Silk*.

Of the 221 subjects enrolled in the study, 218 subjects received their first treatment with *Restylane Silk* at either baseline/Day 0 or at 6 months, and 133 subjects received a second treatment at 6 months. Safety was also evaluated for subjects with Fitzpatrick skin types IV and V (n=52) and for the subgroup of subjects ≤ 35 years of age (n=60).

An adverse event (AE) was defined as any untoward medical occurrence or an unintended sign, symptom, or disease temporally associated with the use of the device, whether or not considered related to the device. An AE was further defined as:
• any diagnosis, sign, symptom, or abnormal laboratory value not present, detected or complained of at the baseline assessment.
• any diagnosis, sign, symptom, or abnormal laboratory value noted at baseline that worsened in severity or intensity or increased in frequency during the study.

An AE that occurred during the study was considered a treatment emergent adverse event (TEAE) if:
• it was not present prior to receiving treatment (as determined by onset date of event and date treatment was received), or
• it was present prior to receiving treatment but the severity increased after treatment (as determined by onset date of the severity increase of the event and date treatment was received).

The investigator was to classify the severity of an adverse event according to the following definitions:
• Mild: did not interfere with routine activities, could perform daily functions
• Moderate: interfered with routine activities, could perform daily functions, but with concerted effort
• Severe: unable to perform routine activities

A Serious Adverse Device Event (SADE) was defined as an AE that:
• results in death;
• is life-threatening;
• results in permanent impairment of a body function;

• results in permanent damage to a body structure; or,
• necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Subjects were asked to grade symptoms of bruising, redness, swelling, pain, tenderness and itching. Subject's scores for the severity of these events are presented in Table 2 and durations are provided in Table 3. The majority of events (>85%) were mild in intensity and resolved in 2 – 7 days. Eight patients reported diary symptoms of "Affects Daily Activities" and "Disabling" that lasted longer than 7 days. These events were: Swelling (n=6), pain (n=2), tenderness (n=3), bruising (n=3), itching (n=2), and redness (n=1).

Table 1: MA-1700-04 Maximum Intensity of Symptoms after Initial Treatment from Subject Diary (N=218)

	None n (%)	Tolerable n (%)	Affected Daily Activities n (%)	Disabling n (%)
Upper and Lower Lip Combined (N=215)				
Bruising	39 (18%)	142 (66%)	25 (12%)	9 (4%)
Redness	63 (29%)	129 (60%)	19 (9%)	4 (2%)
Swelling	2 (<1%)	111 (52%)	84 (39%)	18 (8%)
Pain	48 (22%)	123 (57%)	38 (18%)	6 (3%)
Tenderness	16 (7%)	146 (68%)	48 (22%)	5 (2%)
Itching	151 (70%)	59 (27%)	5 (2%)	0

Table 2: MA-1700-04 Duration of Symptoms from Patient Diary

		No Treatment at Baseline (N=44) Number of Days			
	Any N (%)	1 n (%)	2 - 7 n (%)	8 - 13 n (%)	14 n (%)
Upper and Lower Lip Combined					
Bruising	0	0	0	0	0
Redness	0	0	0	0	0
Swelling	1 (2%)	0	1 (100%)	0	0
Pain (includes Burning)	1 (2%)	1 (100%)	0	0	0
Tenderness	1 (2%)	1 (100%)	0	0	0
Itching	0	0	0	0	0
		First Treatment with Restylane Silk (N=218) Number of Days			
	Any N (%)	1 n (%)	2 - 7 n (%)	8 - 13 n (%)	14 n (%)
Upper and Lower Lip Combined					
Bruising	176 (81%)	10 (6%)	130 (74%)	34 (19%)	2 (1%)
Redness	152 (70%)	40 (26%)	97 (64%)	15 (10%)	0
Swelling	213 (98%)	9 (4%)	149 (70%)	40 (19%)	15 (7%)
Pain (includes Burning)	167 (77%)	43 (26%)	110 (66%)	13 (8%)	1 (<1%)
Tenderness	199 (91%)	17 (9%)	132 (66%)	41 (21%)	9 (5%)
Itching	64 (29%)	21 (33%)	34 (53%)	7 (11%)	2 (3%)
		Second Treatment with Restylane Silk (N=133) Number of Days			
	Any N (%)	1 n (%)	2 - 7 n (%)	8 - 13 n (%)	14 n (%)
Upper and Lower Lip Combined					
Bruising	89 (67%)	6 (7%)	65 (73%)	17 (19%)	1 (1%)
Redness	89 (67%)	18 (20%)	64 (72%)	7 (8%)	0
Swelling	124 (93%)	2 (2%)	96 (77%)	20 (16%)	6 (5%)
Pain (includes Burning)	100 (75%)	26 (26%)	70 (70%)	4 (4%)	0
Tenderness	118 (89%)	8 (7%)	88 (75%)	19 (16%)	3 (3%)
Itching	37 (28%)	8 (22%)	21 (57%)	8 (22%)	0

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The treatment-emergent adverse events (TEAEs) reported during the study are presented in Table 1. The number of events and subjects reporting TEAEs decreased between the first and second treatments. Seventy-eight percent (169/281) of subjects receiving their first treatment reported a total of 632 TEAEs while 63% (84/133) of subjects that received a second treatment reported a total of 196 TEAEs. Furthermore, an overwhelming majority of these TEAEs were mild in intensity (540/632; 85%, and 178/196; 91%; first and second treatment respectively), and were transient in nature, resolving in a mean of 17.4 days (median 10 days).

The most common TEAEs occurring after initial treatment with *Restylane Silk* were lip swelling (43%), contusion (44%), and lip pain (10%). There was no increased risk with additional treatment with *Restylane Silk*. After the second treatment, the reported incidence decreased to 35%, 31%, and 7%, respectively.

In the overall population of subjects receiving their initial treatment with *Restylane Silk*, 12 severe events occurred in 6 subjects. Ten of the severe events were Lip Swelling which occurred in 5 subjects. There were 80 moderate events which occurred in 34 subjects (16%). There were 5 serious adverse events in three patients during the study. In the No Treatment group there were incidences of Clostridial Infection (n=1), and Urinary Tract Obstruction (n=1). In the *Restylane Silk* group there were Cystitis (n=1), Intervertebral Disc Protrusion (n=1), and Nephrolithiasis (n=1). None of the serious events were reported as related to treatment with *Restylane Silk*.

Nineteen subjects reported AEs associated with treatment of the lip whose onset was more than 3 weeks after a *Restylane Silk* injection. There were a total of 35 events in the lip reported in these 19 subjects. Most of the events were Lip Swelling (26/35; 745) and also included Lip Disorder (6/35; 17%), Lip Pain/Pain 2/35; 6%), and Contusion (1/35; 3%). None of the events were reported as serious and all of the events were reported as either mild (24/35; 69%) or moderate (11/35; 31%).

Table 3: MA-1700-04 Summary of Treatment Emergent Adverse Events

System Organ Class/ Preferred Term	Severity	No Treatment at Baseline (N=44)		First Treatment with Restylane Silk (N=218)		Second Treatment with Restylane Silk (N=133)	
Any TEAE		Events	Subjects	Events	Subjects	Events	Subjects
	Total	20	12 (27%)	632	169 (78%)	196	84 (63%)
	Mild	16	10 (23%)	540	129 (59%)	178	73 (55%)
	Moderate	2	1 (2%)	80	34 (16%)	18	11 (8%)
	Severe	2	1 (2%)	12	6 (3%)	0	0
Gastrointestinal Disorders							
Lip Disorder	Total	0	0	17	11 (5%)	1	1 (<1%)
	Mild	0	0	17	11 (5%)	1	1 (<1%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Lip Pain	Total	0	0	34	21 (10%)	12	9 (7%)
	Mild	0	0	30	19 (9%)	12	9 (7%)
	Moderate	0	0	4	2 (<1%)	0	0
	Severe	0	0	0	0	0	0
Lip Swelling	Total	0	0	186	94 (43%)	74	46 (35%)
	Mild	0	0	154	77 (35%)	65	41 (31%)
	Moderate	0	0	22	12 (6%)	9	5 (4%)
	Severe	0	0	10	5 (2%)	0	0
General Disorders and Administrative Site Conditions							
Pain	Total	0	0	32	18 (8%)	6	4 (3%)
	Mild	0	0	24	13 (6%)	4	3 (2%)
	Moderate	0	0	8	5 (2%)	2	1 (<1%)
	Severe	0	0	0	0	0	0
Injury, Poisoning, and Procedural Complication							
Contusion	Total	0	0	145	96 (44%)	55	41 (31%)
	Mild	0	0	134	87 (40%)	53	39 (29%)
	Moderate	0	0	11	9 (4%)	2	2 (2%)
	Severe	0	0	0	0	0	0
Nervous System Disorders							
Headache	Total	7	4 (9%)	11	10 (5%)	3	2 (2%)
	Mild	7	4 (9%)	10	9 (4%)	2	1 (<1%)
	Moderate	0	0	1	1 (<1%)	1	1 (<1%)
	Severe	0	0	0	0	0	0

The vast majority of all symptoms reported in subject diaries resolved within 2-7 days of treatment. Furthermore, the duration profiles are similar between first treatment and second treatments with *Restylane Silk*.

Table 4: Duration of Commonly Occurring Treatment Emergent Adverse Events

System Organ Class/ Preferred Term	No Treatment at Baseline (N=44)	First Treatment with *Restylane Silk* (N=218)	Second Treatment with *Restylane Silk* (N=133)
All TEAEs			
n	11	168	83
Mean (S.D.)	15.2 (28.8)	17.7 (29.0)	9.7 (8.3)
Median (min, max)	6.0 (1, 101)	10.0 (1, 174)	7.0 (1, 38)
Gastrointestinal Disorders			
Lip Disorder			
n	0	10	1
Mean (S.D.)	- (-)	49.1 (44.4)	27.0 (-)
Median (min, max)	-	38.5 (1, 124)	27.0
Lip Pain			
n	0	21	9
Mean (S.D.)	- (-)	10.6 (14.5)	5.2 (2.3)
Median (min, max)	-	7.0 (3, 71)	6.0 (2, 8)
Lip Swelling			
n	0	94	46
Mean (S.D.)	- (-)	7.3 (4.1)	7.4 (8.1)
Median (min, max)	-	6.0 (2, 21)	5.0 (1, 38)
General Disorders and Administrative Site Conditions			
Pain			
n	0	18	4
Mean (S.D.)	- (-)	3.6 (2.3)	3.5 (1.9)
Median (min, max)	-	3.0 (1, 9)	3.0 (2, 6)
Injury, Poisoning, and Procedural Complication			
Contusion			
n	0	96	41
Mean (S.D.)	- (-)	8.4 (3.9)	8.6 (5.9)
Median (min, max)	-	8.0 (2, 20)	7.0 (3, 32)
Nervous System Disorders			
Headache			
n	4	10	2
Mean (S.D.)	2.8 (2.9)	1.6 (1.1)	1.0 (0.0)
Median (min, max)	1.5 (1, 7)	1.0 (1, 4)	1.0 (1, 1)

In addition, subjects with Fitzpatrick skin types IV and V and subjects ≤ 35 years of age had safety results similar to the general study population.

Concomitant treatment of perioral rhytids with lip augmentation does not increase the risk for adverse events. TEAEs for subjects receiving treatment for perioral rhytids were similar in type and frequency to those in the overall population for the common events of lip disorder (bumps), lip pain, lip swelling and contusion. No important differences were noted between those subjects receiving treatment for perioral rhytids and those not receiving treatment for perioral rhytids for first and second injections of *Restylane Silk*.

Study conducted for the use of a small bore, blunt tip cannula for submucosal implantation for lip augmentation

Clinical study 43USC1505 was a multicenter, open-label, single-arm prospective study designed to assess adverse experiences identified with the use of Restylane Silk when used in conjunction with a small blunt tip cannula (in the range of 25G-27G) for lip augmentation. Two brands of cannulas, DermaSculpt and Softfil, were evaluated and all were 25G-27G and 1½ inches in length.

The study was conducted at 4 sites in the U.S. with sixty (60) subjects enrolled and treated. Thirteen (13) subjects with Fitzpatrick skin types IV, V and VI were included in the safety analysis. Subjects with these FST were not required to meet the inclusion criterion for MLFS score.

Adverse experiences were assessed by collecting Adverse Events (AEs) throughout the study. A subject diary was used for documentation of pre-defined, expected post-treatment injection site reactions (i.e. bruising, redness, swelling, pain, tenderness, and itching) during the first two (2) weeks after the treatment.

An adverse event (AE) was defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects (whether or not considered related to the device or procedure), users or other persons (definition restricted to events related to the investigational device or procedure).

The investigator was to classify the severity of an adverse event according to the following definitions:

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

A Serious Adverse Event (SAE) was defined as an AE that:

- led to death;
- led to serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or body function
    - in-patient or prolonged hospitalization
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death, or a congenital abnormality or birth defect

Pre-defined, expected post-treatment events occurring after lip treatment were collected in a subject diary by day during a 14-day period, starting on the day of treatment. Except for swelling, which was primarily assessed as moderate or severe in intensity, the majority of subjects assessed all other diary symptoms as mild. Of the subjects that reported a severe upper and/or lower lip symptom, the majority of the severe diary symptoms started on day 1 of the diary and lasted 2-7 days.

Table 5: Duration of symptoms by maximum intensity (mild, moderate, severe) recorded from the patient diary

Duration of Symptoms from Patient Diary						
Max Intensity	Event	Number of days, Upper and Lower Lip combined				
		Any n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Mild	Bruising	25 (41.7)	4 (16.0)	20 (80.0)	1 (4.0)	0 (0.0)
	Redness	32 (53.3)	9 (28.1)	23 (71.9)	0 (0.0)	0 (0.0)
	Swelling	12 (20.0)	1 (8.3)	8 (66.7)	2 (16.7)	1 (8.3)
	Pain	27 (45.0)	13 (48.1)	14 (51.9)	0 (0.0)	0 (0.0)
	Tenderness	33 (55.0)	6 (18.2)	22 (66.7)	5 (15.2)	0 (0.0)
	Itching	12 (20.0)	6 (50.0)	5 (41.7)	1 (8.3)	0 (0.0)
Moderate	Bruising	10 (16.7)	0 (0.0)	8 (80.0)	2 (20.0)	0 (0.0)
	Redness	12 (20.0)	1 (8.3)	11 (91.7)	0 (0.0)	0 (0.0)
	Swelling	28 (46.7)	0 (0.0)	18 (64.3)	9 (32.1)	1 (3.6)
	Pain	16 (26.7)	2 (12.5)	14 (87.5)	0 (0.0)	0 (0.0)
	Tenderness	19 (31.7)	0 (0.0)	11 (57.9)	5 (26.3)	3 (15.8)
	Itching	5 (8.3)	0 (0.0)	5 (100.0)	0 (0.0)	0 (0.0)
Severe	Bruising	1 (1.7)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
	Redness	4 (6.7)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)
	Swelling	20 (33.3)	0 (0.0)	11 (55.0)	6 (30.0)	3 (15.0)
	Pain	1 (1.7)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
	Tenderness	5 (8.3)	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)
	Itching	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Apart from the expected post-treatment events collected in subject diaries, the majority of subjects (49/60 [81.7%]) had no treatment emergent adverse event (TEAE). In total, there were 27 TEAEs occurring in 11 subjects.

No severe TEAEs were observed and there were no serious adverse events (SAEs). The TEAEs are presented by MedDRA System Organ class (SOC) and Preferred Term (PT) in Table 6. Of these events, six (6) were classified as not related to product or injection procedure.

Table 6: Summary of TEAEs by Severity – Safety Population

System Organ Class/ Preferred Term	Severity	Treatment with Restylane Silk (N=60)	
		Events	Subjects
Any TEAE	**Total**	**27**	**11* (18.3%)**
	Mild	22	11 (18.3%)
	Moderate	5	3 (5.0%)
	Severe	0	0
Gastrointestinal Disorders			
Chapped lips	**Total**	**2**	**1 (1.7%)**
	Mild	2	1 (1.7%)
	Moderate	0	0
Colitis ulcerative	**Total**	**1**	**1 (1.7%)**
	Mild	0	0
	Moderate	1	1 (1.7%)
General Disorders and Administration Site Conditions			
Injection site bruising	**Total**	**5**	**4 (6.7%)**
	Mild	5	4 (6.7%)
	Moderate	0	0
Injection site pain	**Total**	**2**	**1 (1.7%)**
	Mild	2	1 (1.7%)
	Moderate	0	0
Injection site swelling**	**Total**	**14**	**8 (13.3%)**
	Mild	10	6 (10.0%)
	Moderate	4	2 (3.3%)
Infections and Infestations			
Sinusitis	**Total**	**1**	**1 (1.7%)**
	Mild	1	1 (1.7%)
	Moderate	0	0
Upper respiratory tract infection	**Total**	**2**	**1 (1.7%)**
	Mild	2	1 (1.7%)
	Moderate	0	0

*Eleven (11) subjects had TEAEs of mild intensity and three (3) of these also had TEAEs of moderate intensity.
**One of the TEAEs categorized as 'Injection site swelling', was described in the case report form as 'Swelling secondary to cold sore/herpes simplex', and was re- assessed by the Sponsor from unrelated to study product and injection procedure, to be possibly related to the injection procedure.

The time to onset and duration of related TEAEs are presented in Table 7. Most events related to treatment with *Restylane Silk* using cannula emerged on the day of treatment and resolved in a mean of 6.2 days (median 5 days).

Table 7: Summary of related TEAEs by Time to Onset and Duration - Safety population (N=60)

System Organ Class/ Preferred Term	Time to Onset (Days)	Duration (Days)
Any related TEAE (n=21)		
Mean (SD)	0.4 (0.6)	6.0 (2.3)
Median (min, max)	0 (0, 2)	5 (2, 10)
General Disorders and Administration Site Conditions		
Injection site bruising (n=5)		
Mean (SD)	0.2 (0.4)	6.2 (1.3)
Median (min, max)	0 (0, 1)	6 (5, 8)
Injection site pain (n=2)		
Mean (SD)	1.0 (0.0)	5.0 (0)
Median (min, max)	1 (1, 1)	5 (5, 5)
Injection site swelling (n=14)		
Mean (SD)	0.4 (0.6)	6.1 (2.7)
Median (min, max)	0 (0, 2)	5 (2, 10)

Evaluation of adverse events for subjects with Fitzpatrick skin types IV- VI showed no unique TEAEs associated with this subgroup.

One device deficiency associated with injection procedure occurred: at the beginning of injecting, the cannula disconnected from the syringe prior to injecting into the patient.

POST-MARKETING SURVEILLANCE

The adverse event reports received from post-marketing surveillance (from voluntary reporting and published literature) of *Restylane Silk* in the U.S. most commonly included reports of transient swelling/edema of the lip or, inflammatory reactions with immediate or delayed onset, up to several weeks after treatment. The following events were also reported: mass/induration, pain/tenderness, lack of effect, bruising/hematoma, erythema, papules/nodules, discoloration/hyperpigmentation, hypersensitivity, angioedema, injection site reactions including exfoliation, burning sensation, irritation, warmth, discomfort, dryness, presumptive bacterial infections and abscess formation, ischemia and necrosis due to unintentional intravascular injection, vascular compression or embolisation, reactivation of herpes infection, pruritus, inflammation, neurological symptoms such as hypoaesthesia and paresthesia, blisters/vesicles, eye disorders including eye swelling, eye irritation and visual disturbance such as transient vision blurred, increased lacrimation, eyelid ptosis and visual impairment, rash, device dislocation, urticaria, fistula/discharge, atrophy/scarring, capillary disorders such as telangiectasia, acne, dermatitis, muscular weakness, and other dermatological events such as dry lips, skin wrinkling, dry skin and skin exfoliation and non-dermatological events such as pyrexia, anxiety, fatigue, insomnia and headache.

When required, treatments for these events included corticosteroids, antibiotics, antihistamines, NSAIDs, aspiration/incision and drainage, surgery or enzymatic degradation

(with hyaluronidase) of the product.

Reports of serious adverse events for *Restylane Silk* are rare. The most commonly reported serious adverse events were ischemia/necrosis, infection/abscess and hypersensitivity. Other serious events included concomitant symptoms; swelling, pain/tenderness, erythema and bruising.

In addition to the events listed above, the following adverse events were received from post-marketing surveillance for *Restylane* filler range of products: encapsulation, vasovagal reactions, extrusion of device, granuloma and dermaphytosis.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolisation. Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments have been reported.

Vision abnormalities including blindness have been reported following injection of hyaluronic acid fillers into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to a few days following injection. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, steroid treatment and hyperbaric oxygen. Outcomes ranged from resolved to ongoing at the time of last contact. Events requiring medical intervention, and events where resolution information is not available were reported. In these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (See Warnings section).

Adverse reactions should be reported to Galderma Laboratories, L.P. at 1-855-425-8722.

CLINICAL TRIALS

U.S. Clinical Study

MA-1700-04

The safety and effectiveness of *Restylane Silk* for lip fullness augmentation and treatment of perioral rhytids was evaluated in a randomized, evaluator blinded, no treatment controlled study.

MA-1700-04 Randomized Clinical study

Design	This was a randomized, evaluator-blinded, no treatment as a control study of 221 subjects who were seeking lip fullness augmentation at 14 U.S. investigational centers. At entry to the study, subjects were randomized 3:1 to (1) Restylane Silk or (2) no treatment. The study recruited a minimum of 30 subjects with Fitzpatrick skin types IV, V, or VI. An additional 40 subjects seeking lip fullness augmentation who were ≤ 35 years of age at study entry and met all except the Medicis Lip Fullness Scales (MLFS) thin/very thin lip criterion were to be enrolled; these subjects were not randomized. Subjects may have returned at 2 weeks after the initial injection for touch-up treatment (if necessary). Subjects were also given the opportunity to have their perioral rhytids treated along with the lip augmentation. Each lip that was treated for augmentation was analyzed for effectiveness and all lips were analyzed for safety. Subjects randomized to treatment at baseline were re-treated at 6 months and subjects randomized to no treatment at baseline received their first treatment at 6 months. The safety of all subjects was then monitored for one month after the 6 month treatment. There were a total of 177 subjects that received treatment with SPHAL at the Baseline Visit. Of these subjects, 44 subjects did not receive treatment at the Month 6 treatment visit (Visit 10). Of these 44 subjects, 11 subjects were lost to follow-up (LTFU) and six subjects withdrew consent (see response to Question 8) prior to Visit 10

Endpoints	Effectiveness Primary: The Primary effectiveness objective was to identify whether Restylane Silk was more effective in lip augmentation than no treatment. This was determined by the change from baseline in blinded evaluator assessments of lip fullness at 8 weeks after the first treatment, separately in the upper and lower lips (co-primary effectiveness endpoints) in the randomized subjects using separate five grade MLFS with photoguides for each lip. Treatment success was defined as at least a one grade increase from baseline in the MLFS for the blinded evaluator assessment at Week 8 (compared to the baseline assessment). The primary safety objective was to determine the incidence of reported treatment emergent adverse events at 72 hours, 2, 4, 8, 12, 16, 20 and 24 weeks after the initial injection(s) and 72 hours, 2 weeks and 4 weeks after the 6 month treatment. Subjects maintained diaries for 14 days after the initial and 6 month treatments to record the severity and duration of bruising, redness, swelling, pain, tenderness and itching. Secondary: Secondary effectiveness objectives included: • Assessment of lip fullness augmentation after treatment with Restylane Silk compared to no treatment as assessed by the blinded evaluator, treating investigator, and independent photographic reviewer (IPR) at post-baseline time points as compared to the baseline assessment. Response was defined as at least one grade improvement from baseline in the upper and lower lips using MLFS. • Identification of lip improvement at each time point after treatment with Restylane Silk as compared to no treatment using the Global Aesthetic Improvement Scale (GAIS) by the treating investigator and the subjects. Response was defined as a GAIS rating of • "improved" or better in the upper and lower lips. • Improvement in the appearance of upper perioral rhytids compared to no treatment at each time point using the Wrinkle Assessment for Upper Lip Lines (WASULL) by the assessment of the blinded evaluator and the treating investigator. • Proportion of responders for the co-primary and secondary endpoints for subjects with pre-treatment Fitzpatrick scores IV, V, and VI as well as for subjects ≤ 35 years old at baseline. Secondary safety objectives included assessment of lip texture, firmness, symmetry, product palpability, mass formation, lip movement, lip function, and lip sensation.

Outcomes

Demographics

The study enrolled an adult population of predominately Caucasian healthy females.

Characteristics	Total (N=221)
Age (years)	
n	221
Mean (S.D.)	45.5 (12.3)
Median	48.0
Minimum	18
Maximum	65
Gender	
Male	6 (3%)
Female	215 (97%)
Race	
American Indian/Alaskan Native	1 (<1%)
Black/African American	1 (<1%)
Native Hawaiian/Pacific Islander	0
Asian	3 (1%)
White	211 (95%)
Other	5 (2%)
Ethnicity	
Not Hispanic or Latino	178 (81%)
Hispanic or Latino	43 (19%)
Fitzpatrick Skin Type	
I, II, and III	169 (76%)
IV, V, and VI	52 (24%)

Volume of *Restylane Silk* used

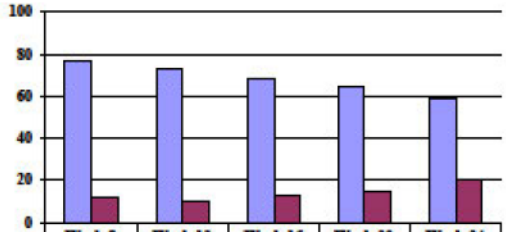
	Initial Treatment		6 Month Treatment	
	No Treatment (N=43)	*Restylane Silk* (1st Treatment)	No Treatment (1st Treatment)	*Restylane Silk* (2nd Treatment)
Volume of Injection (mL) for upper and lower lip(s) (includes treatment and touch up)				
n	--	176	41	133
Mean	--	2.18 (1.07)	2.12 (0.74)	1.50 (0.81)
Median	--	1.00	2.00	1.25
Minimum	--	0.10	1.00	0.20
Maximum	--	6.80	4.00	4.40
Volume of Injection (mL) for perioral rhytids (includes treatment and touch up)				
n	--	65	18	32
Mean	--	0.48 (0.44)	0.89 (0.70)	0.70 (0.53)
Median	--	0.30	0.90	0.60
Minimum	--	0.03	0.02	0.10
Maximum	--	1.70	1.90	2.00

It was recommended in the study protocol that the investigator treating the subject not exceed injections of 1.5 mL of *Restylane Silk* per lip per treatment session.

Effectiveness

The purpose of this study was to evaluate the safety and effectiveness of *Restylane Silk* for soft tissue augmentation of the lips and improvement of perioral rhytids. The results of assessments confirm that *Restylane Silk* is effective for adding fullness to both the upper and lower lips for at least 6 months

Proportion (%) of MLFS Responders Measured by the Blinded Evaluator (Upper and Lower Lip Combined)

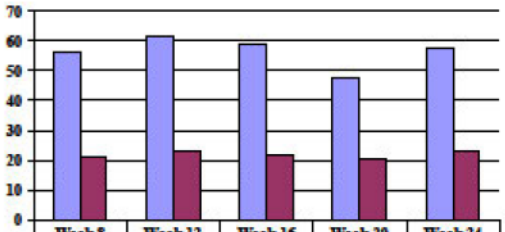


	Week 8	Week 12	Week 16	Week 20	Week 24
Restylane Silk Treatment	76.7	73.1	68.3	64	58.8
No Treatment	11.9	10	12.5	14.6	20

p<0.001 for all time points

The study also showed that the appearance of upper perioral rhytids improved in patients whose perioral rhytids were treated with *Restylane Silk* as assessed by the blinded evaluator.

Proportion (%) of Responders Measured by the Blinded Evaluator for Upper Perioral Rhytids



	Week 8	Week 12	Week 16	Week 20	Week 24
Treatment of Rhytids + Lip	56,5	61,3	59	47,5	57,6
Treatment of Lip Only	20,9	22,9	21,4	20,6	22,8

p<0.001 for all time points

	Subjects assessed lip improvement at each time point after treatment with a 7-point GAIS. When upper and lower lip outcomes were combined, the study showed that subjects were pleased with the visual improvement in their lips. No patients in the No Treatment group assessed themselves as improved from baseline at any visit. Subjects assessed lip improvement at each time point after treatment with a 7-point non-validated GAIS. When upper and lower lip outcomes were combined, the following percentage of Restylane Silk subjects assessed themselves as improved or better from Baseline: 97.7% (Week 2), 95.3% (Week 4), 90.1% (Week 8), 87.5% (Week 12), 79.4 % (Week 16), 76.5% (Week 20), and 76.5% (Week 24). No patients in the No Treatment group assessed themselves as improved from Baseline at any visit. 76% of the eligible subjects elected to receive re-treatment at Week 24 which suggests that subjects believed that the safety concerns associated with Restylane Silk lip and perioral injections were less than the aesthetic value provided by the device. Of the subjects that elected to not receive re-treatment at Week 24, six (3%) reported refusal due to adverse events experienced during their initial treatment. Lip safety assessments, such as lip texture, firmness, symmetry, movement, function, sensation, mass formation, and device palpability were evaluated at the screening visit and throughout the study. None of the lip assessments were remarkable or presented any safety concerns.

U.S. Clinical Study

43USC1505

The study was conducted to assess adverse experiences identified with the use of Restylane® Silk in conjunction with a small blunt tip cannula (in the range of 25G-27G) for lip augmentation.

43USC1505 Multicenter, Open-Label, Prospective Study

Design	This was a multicenter, open-label, 12-week prospective study of cannula injection of Restylane Silk for lip augmentation in 60 subjects. Subjects with Fitzpatrick skin types (FST) I, II, or III were required to have the MLFS scores of 1 (very thin) or 2 (thin) on both the upper and lower lips to be eligible for the study. Thirteen (13) subjects with FST IV, V, or VI were enrolled, of which six were exempt from meeting the inclusion criteria for MLFS scores per protocol. Eligible subjects were injected by the investigator at baseline; the subject's lips and perioral rhytids (if elected) were treated to optimal augmentation. After the initial treatment, follow-up visits occurred at day 3, week 2, week 4, and week 12. Safety was evaluated by collecting AEs throughout the study. A subject diary was used for documentation of pre-defined, expected post-treatment injection site reactions (i.e. bruising, redness, swelling, pain, tenderness, and itching) during the first two weeks after the treatment. Other safety assessments included evaluation by a qualified study staff member of lip palpation, texture, symmetry, movement, function, and sensation. Effectiveness was evaluated by a change from baseline in the MLFS as assessed by the investigator, and an improvement using the Global Aesthetic Improvement Scale (GAIS) as assessed by the investigator and subject.

Endpoints	Primary: The primary objective of the study was to assess adverse experiences identified with the use of Restylane Silk in conjunction with a small blunt tip cannula (in the range of 25G-27G) for lip augmentation. Adverse experiences were assessed by collecting Adverse Events (AEs) throughout the study. A subject diary was used for documentation of pre-defined, expected post-treatment injection site reactions (i.e. bruising, redness, swelling, pain, tenderness, and itching) during the first two weeks after the treatment. Other safety assessments included evaluation of lip palpation, movement, function, sensation, texture, and symmetry. Secondary: The secondary objective of the study was to characterize the effectiveness of Restylane Silk, used in conjunction with a small blunt-tip cannula, for augmentation of soft tissue fullness of the lip as determined by: • investigator assessed global aesthetic improvement at 4 and 12 weeks, • subject assessed global aesthetic improvement at 4 and 12 weeks, and • change from baseline in Investigator assessed Medicis Lip Fullness Scale (MLFS) at 4 and 12 weeks.

Outcomes

Demographics

Table 8. Demographic summary, all subjects

Characteristics	Total (N=60)
Age (Years)	
n	60
Mean (SD)	46.5 (14.1)
Median	48.0
Minimum	23.0
Maximum	72.0
Gender	
Male	4 (7%)
Female	56 (93%)
Race	
American Indian/Alaska Native	1 (2%)
Black/African American	2 (3%)
Native Hawaiian/Other Pacific Islander	1 (2%)
Asian	2 (3%)
White	53 (88%)
Other	1 (2%)
Ethnicity	
Not Hispanic or Latino	55 (92%)
Hispanic or Latino	5 (8%)
Fitzpatrick skin type	
I, II and III	47 (78%)
IV, V and VI	13 (22%)

Table 9. Fitzpatrick classification, all subjects.

Site	Fitzpatrick classification													
	I		II		III		IV		V		VI		Total (N)	
	n	%	n	%	n	%	n	%	n	%	n	%	N	%
8302	0	0.0	5	33.3	5	33.3	2	13.3	2	13.3	1	6.7	15	100.0
8476	0	0.0	9	64.3	5	35.7	0	0.0	0	0.0	0	0.0	14	100.0
8551	1	6.7	6	40.0	3	20.0	4	26.7	1	6.7	0	0.0	15	100.0
8552	0	0.0	4	25.0	9	56.3	2	12.5	0	0.0	1	6.3	16	100.0
Total	1	1.7	24	40.0	22	36.7	8	13.3	3	5.0	2	3.3	60	100.0

	Extent of exposure The mean volume of Restylane Silk injected per lip was 1.1mL. The mean total volume for both lips was 2.2mL. The depth of injection for the upper and lower lips for all subjects was submucosal, and a majority of subjects received a combination of injection methods including linear retrograde and linear antegrade, Investigators used the same gauge of cannula when treating the upper and lower lips, and in this study 55.0% of subjects received treatment with a 27G cannula and 45.0% received treatment with a 25G cannula. Treatment of perioral rhytids was optional, and was performed by Investigators at two of the four investigational sites. Six (6) subjects had mid-dermal injections using cannula in both upper and lower perioral rhytids, and three (3) subjects had treatment in the upper perioral rhytids only. The mean total volume for both the upper and lower perioral rhytids was 0.3mL. None of the subjects with Fitzpatrick Skin Types IV, V, and VI were treated in the perioral rhytids with cannula. Safety results (For tabulated data, see Section ADVERSE EXPERIENCES) Of those subjects that reported an event, all AEs occurred after treatment at baseline. A total of 27 TEAEs were reported by 11 of the 60 enrolled subjects (18.3%). The vast majority of subjects (81.7%) reported no TEAEs during the study period. The most commonly reported TEAEs by preferred term were: injection site swelling (13.3%) and injection site bruising (6.7%). All other TEAEs (i.e., chapped lips, colitis ulcerative, injection site pain, sinusitis, and upper respiratory tract infection) were reported by 1 subject each (1.7%). No serious AEs (SAEs) were reported, The median time to onset for any related TEAEs was the same day as treatment and median duration was 5 days (mean = 6.2 days). Following treatment at baseline, all subjects completed a 14-day diary. The daily diary listed specific questions about certain pre-defined, expected events for the upper and lower lips separately, including, bruising, itching, pain, redness, swelling, and tenderness. All subjects reported at least one diary symptom in the upper and/or lower lip. The most commonly reported post-treatment symptoms were: swelling (60/60 subjects, 100%), tenderness (57/60 subjects, 95.0%), and redness (48/60 subjects, 80.0%). With the exception of swelling, which was primarily assessed as moderate or severe in intensity, the majority of all other reported diary symptoms were assessed as mild by the subject. Of the subjects that reported a severe upper and/or lower lip symptom, the majority of the diary symptoms started on day 1 of the diary and lasted 2-7 days. As expected and as diary symptoms resolved, the proportion of subjects reporting diary symptoms at any intensity level decreased over time. All subjects with FST IV-VI reported at least one diary symptom in the upper and/or lower lip. The most commonly reported post-treatment symptoms were swelling (13/13 subjects, 100%), tenderness (12/13 subjects, 92.3%), and redness (11/13 subjects, 84.6%). Maximum intensity for swelling was assessed as mild, moderate, and severe. Only one subject assessed tenderness intensity as severe. Apart from swelling, the majority of all other reported diary symptoms were assessed as mild by the subject. The majority of the symptoms reported by subjects with FST IV-VI lasted 7 days or less. All lip safety assessments, with the exception of lip texture, were assessed as normal at all study time points for all subjects. Two subjects had mild abnormal upper or lower lip texture post-treatment that returned to a normal assessment before the end of study.

Effectiveness results:

Assessment of lip fullness included subjects with a baseline MLFS score of 1 or 2. Scoring was based on visual live assessment by the Investigator. Results of the assessment at Baseline, Week 4 and Week 12 are presented in Table 10. All subjects in the ITT population had a clinically significant improvement, i.e. at least one grade improvement from baseline for the upper lip, and the majority (49/51 [96%]) of lower lips were improved at 12 weeks.

Table 10: MLFS by visit - ITT population

MLFS	Baseline				4 weeks				12 weeks			
	Upper lip		Lower lip		Upper lip		Lower lip		Upper lip		Lower lip	
	n	%	n	%	n	%	n	%	n	%	n	%
1 – Very thin	26	48.1	22	40.7	0	0.0	1	1.9	0	0.0	2	3.9
2 – Thin	28	51.9	32	59.3	4	7.5	2	3.8	8	15.7	3	5.9
3 – Medium	0	0.0	0	0.0	24	45.3	13	24.5	29	56.9	25	49.0
4 – Full	0	0.0	0	0.0	17	32.1	29	54.7	12	23.5	19	37.3
5 – Very Full	0	0.0	0	0.0	8	15.1	8	15.1	2	3.9	2	3.9
Total (N)	54	100.0	54	100.0	53	100.0	53	100.0	51	100.0	51	100.0

% = n/N*100

Further, the Investigator evaluated the degree of improvement from baseline in the visual appearance of the subject's lips using the 7-point non-validated GAIS at Weeks 4 and 12. Improvement (defined as "Improved", "Much improved" or "Very much improved") was noted for the upper and lower lips combined at Weeks 4 and 12 (98.1% and 98.0%, respectively).

Table11: Investigator assessment of improvement using GAIS - ITT population

GAIS Investigator assessment	4 weeks				12 weeks			
	Upper lip		Lower lip		Upper lip		Lower lip	
	n	%	n	%	n	%	n	%
Very Much Improved	34	64.2	45	84.9	23	45.1	32	62.7
Much Improved	12	22.6	6	11.3	13	25.5	13	25.5
Improved	6	11.3	2	3.8	14	27.5	6	11.8
No Change	1	1.9	0	0.0	0	0.0	0	0.0
Worse	0	0.0	0	0.0	1	2.0	0	0.0
Much Worse	0	0.0	0	0.0	0	0.0	0	0.0
Very Much Worse	0	0.0	0	0.0	0	0.0	0	0.0
Total (N)	53	100.0	53	100.0	51	100.0	51	100.0

% = n/N*100

Subjects also rated improvement of their lip fullness, relative to pretreatment appearance, using the GAIS at Weeks 4 and 12. For the upper and lower lips combined, the proportion of subjects that assessed themselves as improved or better from baseline was 94.3% at Week 4, and 84.3% at Week 12.

HOW SUPPLIED

Restylane Silk is supplied in a disposable glass syringe with a luer-lock fitting.

Restylane Silk is co-packed with sterilized needle(s) 30 G x ½" as indicated on the carton. A patient record label is a part of the syringe label. Remove it by pulling the flap marked with three small arrows. This label is to be attached to patient records to ensure traceability of the product.

The contents of the syringe are sterile.

The volume in each syringe and needle gauge is as stated on the syringe label and on the carton.

SHELF LIFE AND STORAGE

Restylane Silk must be used prior to the expiration date printed on the package. Store at a temperature of up to 25° C (77° F). Do not freeze. Protect from sunlight. Refrigeration is not required.

Do not resterilize *Restylane Silk* as this may damage or alter the product.

Do not use if the package is damaged. Immediately return the damaged product to Galderma Laboratories, L.P.

Rx only

U.S. PATENT 5,827,937; 8,455,459; 8,778,909; 8,357,795; 8,450,475; 8,822,676

Manufactured for
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Made in Sweden

Restylane and *Galderma* are trademarks of Nestlé Skin Health S.A.

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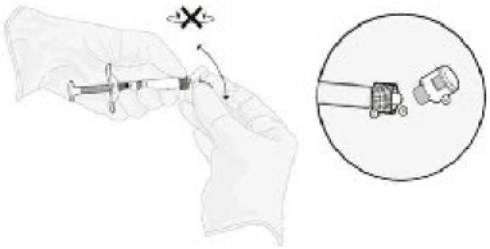
DIRECTIONS FOR ASSEMBLY

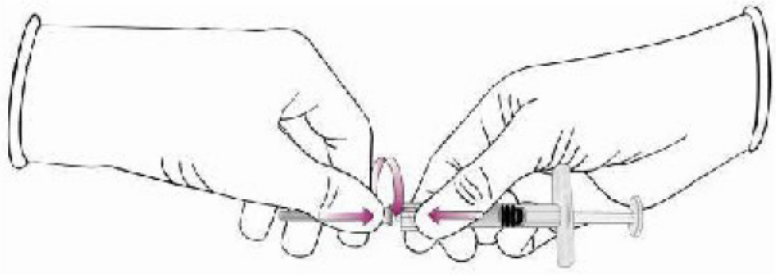
For safe use of *Restylane Silk*, it is important that the needle/blunt cannula is properly assembled.

Hold the syringe on the ribbed part (C) of the white closure system (luer-lock adapter).
With your other hand, take hold of the white cap (A) at the end of the closure system and gently tilt back and forth carefully until cap disconnects and can be pulled off (seal will be broken).
Do not rotate.
Do not touch the syringe tip (B) to keep it sterile.



ASSEMBLY OF NEEDLE TO SYRINGE

Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the luer-lock adapter. Grasp the needle shield (or hub if using a cannula) with the other hand. To facilitate proper assembly, both push and rotate firmly.



PRE-TREATMENT GUIDELINES

Prior to treatment, the patient should avoid taking aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements. These agents may increase bruising and bleeding at the injection site.

TREATMENT PROCEDURE

1. It is necessary to counsel the patient and discuss the appropriate indication, risks, benefits and expected responses to the *Restylane Silk* treatment.
   Advise the patient of the necessary precautions before commencing the procedure.

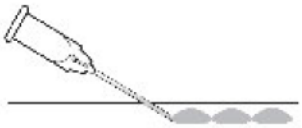
2. Assess the patient's need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
3. The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
4. Sterile gloves are recommended while injecting *Restylane Silk*.
5. Before injecting, press rod carefully until a small droplet is visible at the tip of the needle.
6. When using needle, after insertion, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular.
7. *Restylane Silk* is administered using a thin gauge needle (30 G x ½") or as an alternative a blunt tip cannula (recommended gauge sizes 25-27G) can be used. Please note use of a cannula is intended for lip augmentation only whereas needles may be used to treat both lips and perioral rhytids.
8. When using a needle, the needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle, fold, or lip. For rhytids, *Restylane Silk* should be injected into the mid-to-deep dermis. *Restylane Silk* should be injected into the submucosal layer for lip augmentation, care should be taken to avoid intramuscular injection. If *Restylane Silk* is injected too superficially this may result in visible lumps and/or bluish discoloration. When using a cannula for lip augmentation, an entry point is made in the skin, e.g. with a sharp needle of appropriate size. Inject slowly.
9. Inject *Restylane Silk* applying even pressure on the plunger rod. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
10. Only correct to 100% of the desired volume effect. Do not overcorrect. With cutaneous deformities the best results are obtained if the defect can be manually stretched to the point where it is eliminated. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique.
11. Typical usage for each treatment session is specific to the site as well amount of augmentation or rhytids correction desired. Based on U.S. clinical studies, the maximum recommended dose per treatment is 1.5 mL per lip per treatment or 1.0 mL for perioral rhytid correction.

INJECTION TECHNIQUES

1. *Restylane Silk* can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
2. **Serial puncture (only recommended for needle)** (A) involves multiple, closely spaced injections along wrinkles or folds. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
3. **Linear threading (includes retrograde and antegrade)** (B) is accomplished by fully inserting the needle/cannula into the middle of the wrinkle or fold and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle/cannula has been fully inserted and is being withdrawn, it can also be performed while advancing the needle/cannula ("push-ahead" technique). To enhance the vermillion of the lip, the retrograde linear threading technique is the most advisable.
4. Serial threading is a technique that utilizes elements of both approaches

Note! The correct injection technique is crucial for the final result of the treatment.

A. Serial Puncture (only recommended for needle)



B. Linear Threading (includes retrograde and antegrade)

5. Dissection of the sub-epidermal plane with lateral movement of the needle, rapid flows (>0.3 mL/min), rapid injection or high volumes may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.
6. When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
7. If so called "blanching" is observed, i.e., the overlying skin turns a whitish color, the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with the American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection[1].
8. If the wrinkles or lips need further treatment, the same procedure should be repeated until a satisfactory result is obtained. Additional treatment with *Restylane Silk* may be necessary to achieve the desired correction.
9. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period. Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
10. Patients may have mild to moderate injection site reactions, which typically resolve in less than 18 days in the lip.

STERILE NEEDLE(S)
Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury occurs.

- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.

- Discard unshielded needles in approved sharps collectors.
- *Restylane Silk* is provided with a needle that does not contain engineered injury protection. Administration of *Restylane Silk* requires direct visualization and complete and gradual insertion of the needle making engineered protections infeasible. Care should be taken to avoid sharps exposure by proper environmental controls.

Ordering Information
Galderma Laboratories, L.P. and its distributor, McKesson Specialty, are your only sources for FDA-approved Restylane Silk. Purchasing from any other agent is illegal.
To order call 1-855-425-8722

Revised: October 2017
Part Number: 90-17406-02

[1]Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. Dermatol Surg. 2008;34(suppl 1):S115-S148.

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