PRO 2019-02

A Multicenter, Double-blind, Randomized, Controlled, Roll-over Study of the Safety and Pain Associated with Injections of PN40082, RV001 with Topical Anesthetic or RV001 for Lip Augmentation

Clinical Phase 3

Trial Sponsor:	[redacted]
Key Sponsor Contact:	[redacted]
Original Protocol Date:	01 April 2019
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Amendment 02 Date:	11 July 2019
Amendment 03 Date:	19August 2019
Amendment 04 Date:	17 October 2019

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SIGNATURE PAGE

PROTOCOL NUMBER:	PRO 2019-02
PROTOCOL VERSION:	6.0
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PROTOCOL TITLE:	A Multicenter, Double-blind, Randomized, Controlled, Roll-over Study of the Safety and Pain Associated with Injections of PN40082, RV001 with Topical Anesthetic or RV001 for Lip Augmentation

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

[redacted]

10/18/2019

Date

[redacted]

10/18/2019

Date

[redacted]

21 OCT 2019

Date

1 SYNOPSIS

Title of Study: A Multicenter, Double-blind, Randomized, Controlled, Roll-over Study of the Safety and Pain Associated with Injections of PN40082, RV001 with Topical Anesthetic or RV001 for Lip Augmentation

Name of Sponsor: Prollenium Medical Technologies Inc.

Name of Finished Product: PN40082®

Device Composition: PN40082 - Hyaluronic acid gel with lidocaine (0.3% w/w)
RV001- Hyaluronic acid gel without lidocaine

Objectives: To evaluate the safety of repeat injections and pain associated with injection of PN40082 and comparative pain associated with RV001 with a topical anesthetic and RV001 for lip augmentation.

Study Design: This is a multicenter, double-blind, randomized, controlled, roll-over clinical study of treatment of subjects seeking lip augmentation who received treatment with either PN40082 or Restylane Silk in prior Protocol PRO 2018-02, and PN40082 in prior Protocol PRO 2018-03. Subjects meeting the inclusion/exclusion criteria will receive a single additional treatment with either RV001, RV001 with a topical anesthetic, or PN40082. 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 / 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 – End of Study Visit

- Day 56 (±4 days) / Month 2 – Safety follow-up telephone call
- Day 168 (±7 days) / Month 6 – End of Study telephone call

Efficacy evaluations are:

Subject pain score (VAS) at time of injection

Subject pain score (VAS) at 15 minutes after injection

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 of repeat injections, comparing incidence of reported AEs from all three studies will be analyzed. Safety will be assessed by monitoring adverse events (AEs) at all study visits. Other safety evaluations are lip function, lip sensation, lip texture, lip firmness, lip symmetry, and lip movement/function.

Other evaluations are Investigator Ease of Use Assessment, Swelling Assessment, and Subject Satisfaction with Lips Assessment.

Number of Study Centers: Five (5) sites in the United States

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

Duration of Study: The study will require approximately 20 months from the beginning to the end of the study (first subject signing the ICF to last contact with last subject)

Number of Subjects: Eligible subjects from the PRO 2018-03 study will be encouraged to be retreated during their Day 168/Month 6 telephone call. It is anticipated that the number of subjects will be less than the 158 subjects enrolled in the PRO 2018-02 study.

Inclusion Criteria:

1. Completed Protocol PRO 2018-03

   OR

   Protocol PRO 2018-02 and did not enroll in Protocol PRO 2018-03.

2. Men or non-pregnant or non-breastfeeding women over 21 years of age
3. At PRO 2018-02 baseline visit had 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

   Had 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. If female and of childbearing potential, a negative urine pregnancy test at Visit 1/Day 1 and the subject agrees to use adequate contraception during the study period.
5. Willing to give written informed consent and read and sign the Adverse Event of Special Interest (AESI) letter dated 04JUN19.

Exclusion Criteria:

1. Women who are pregnant, lactating, or planning a pregnancy.
2. Subjects with a known history of allergy, anaphylaxis or hypersensitivity to injectable hyaluronic acid products, local anesthetics of the amide type such as lidocaine, or to latex.
3. Subjects with a significant ongoing adverse event from PRO 2018-02 or PRO 2018-03 that in the opinion of the investigator could be worsened by participation in this study.
4. Subjects that experienced an SAE, AESI, visual changes or other serious medical conditions during PRO 2018-02 or PRO 2018-03.
5. Subjects with abnormal vision evaluations (Confrontational Visual Fields, Ocular Motility) or abnormal Snellen Visual Acuity at Visit 1 pre-treatment as defined in section 7.6.5 and Appendix 5.
6. Subjects who are unable to withhold 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 before AND after any injection session.
7. Subjects with clinically significant organic disease including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the investigator, preclude participation in the trial.
8. Subjects with lip tattoos, piercings, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments.
9. Subjects with abnormal lip function, with inability to effectively sip water through a straw.
10. Subjects with abnormal lip sensation with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip.
11. Subjects with moderate or severe abnormal lip asymmetry.
12. Subjects with any mass formation on the lip.
13. Subjects with 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.
14. Subjects that have undergone facial plastic surgery or received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene, polyacrylamide, lifting threads) anywhere in the face or neck, or are planning to be implanted with any of these products during the study.

15. Subjects that have 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 are planning to undergo such treatment during the study.
16. Subjects that have 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 are planning to undergo any of these procedures during the study.
17. that have used ANY lip filling agents within 12 months of study enrollment (hyaluronic acid products, collagen-based products, etc.) other than Investigational Device administered in PRO 2018-02 and PRO-2018-03.
18. Subjects that have used any lip plumping products or devices within 10 days before enrollment or are planning to use such products during the study.
19. Subjects that have 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 are 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).
20. Subjects that have a history or presence of bleeding disorders.
21. Subjects that have used systemic corticosteroids or immunosuppressive medications within 30 days prior to treatment.
22. Subjects that are on a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine)
23. Subjects that have an active inflammation (skin eruptions such as cysts, pimples, rashes, or hives), infection cancerous or precancerous lesion, or unhealed wound on the face.
24. Subjects that have a history of known susceptibility to keloid formation or hypertrophic scars.
25. Subjects that have porphyria.
26. Subjects that have active herpes labialias 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.
27. Subjects that have 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.
28. Subjects that have any uncontrolled disease, i.e., a condition that has not been appropriately diagnosed, evaluated, and received medically appropriate treatment or care

29. Subjects that have 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 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

RV001 with a topical anesthetic: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 mg/mL of stabilized hyaluronic acid to be used with LMX4 topical lidocaine

RV001: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 mg/mL of stabilized hyaluronic acid to be used alone

Statistical Methods

Safety and efficacy results will be summarized descriptively for all subjects who receive treatment in this study. Data will be summarized overall and also broken down by the treatment arm. A detailed description of statistical analysis of the data from this study will be included in a separate Statistical Analysis Plan (SAP) document.

Efficacy Analysis:

Compare subject pain scores (VAS) between PN40081, RV001 with topical anesthetic, and RV001. Change from baseline will be summarized for LFGS and POL. Other efficacy variables include pGAI, iGAI, and Swelling Assessment at Visit 2/Month 1.

Safety Analysis:

Safety of the treatment with PN40082 or RV001 with topical anesthetic or RV001 will be evaluated by 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. The frequency and type of AEs will be evaluated for each group based on the previous treatments that they received in the PRO 2018-02 and PRO 2018-03 protocols, and the difference in AEs in this protocol (PRO 2019-02) between the subjects who received injections that contained lidocaine, and the group that was treated with topical lidocaine. Safety of repeat injections, comparing incidence of reported AEs from all three studies, PRO 2018-02, PRO 2018-03, and PRO 2019-02 will be discussed in the clinical study report. 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 overall and for each treatment in PRO 2019-02 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 by preferred term.

2 SCHEDULE OF ACTIVITIES

Visit Number (Month)	**Visit 1**	**Phone Contact**	**Phone Contact**	**Visit 2 (Mo 1)**	**Phone Contact (Mo 2)**	**Phone Contact (Mo 6)**	**Unsched Visit**
Scheduled Day(s)	**Day 1**	**Day 3**	**Day 14**	**Day 28**	**Day 56**	**Day 168**	
Scheduling Window	**± 14 days of Day 168/Month 6 telephone call for PRO 2018-03**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**	**± 7 days**	
Informed consent and AESI Letter	X						
Medical history/ demographics	X[a]						
Vital Signs	X						
Vision evaluations (Snellen visual acuity, confrontational visual fields, ocular motility)[b]	X			X			X[c]
Concomitant medication/ Treatment	X	X	X	X	X	X	X
Inclusion/exclusion criteria review	X						
Urine pregnancy test[d]	X						
Reason for study participation question	X						
Lip Fullness Grading Scale (LFGS) (overall, upper lip, and lower lip)	X			X			X[c]
Perioral lines at rest severity scale (POL) (overall, upper lip, and lower lip)	X			X			X[c]
Lip function	X[e]			X			X[c]
Lip sensation	X[e]			X			X[c]
Lip texture	X[e]			X			X[c]
Lip firmness	X[e]			X			X[c]
Lip symmetry	X[e]			X			X[c]
Lip movement/function	X[e]			X			X[c]
Patient GAI (pGAI)	X[e]			X			X[c]
Swelling Assessment	X[e]			X			X[c]
Investigator GAI (iGAI)	X[e]			X			X[c]
Subject Satisfaction with Lips	X[e]			X			X[c]
Randomization	X						
Application of Lidocaine cream or inert cream 15 minutes prior to treatment	X						
Treatment with study device	X						
Investigator Ease of Use Assessment	X						
Subject Pain score VAS (immediately after treatment, 15 minutes after treatment)	X						
Subject Pain score VAS				X			X
Treatment question				X			
Adverse event assessment	X	X	X	X	X	X	X
Subject Diary	Dispense			Collect			

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

a. To be updated if/as needed for changes since Visit 1 of *PRO 2018-02*.

b. To be performed prior to any treatment and repeated 30 minutes following any treatment and all follow-up visits.

c. If/as needed
d. For women of childbearing potential, to be completed prior to enrollment.
e. To be performed prior to treatment

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	adverse event
AESI	Adverse Event of Special Interest
CFR	Code of Federal Regulations
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
IUD	intrauterine device
LFGS	Lip Fullness Grading Scale
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
pGAI	Patient Global Aesthetic Improvement
PI	principal investigator
POL	Perioral Lines Severity Scale
SAE	serious adverse event
SAR	suspected adverse reaction
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
VAS	visual analog scale

5 INTRODUCTION

PN40082 is a stabilized hyaluronic acid dermal filler with lidocaine. RV001 is a stabilized hyaluronic acid dermal filler. RV001 is highly hydrophilic and is osmolality balanced, resulting in less swelling response to injections and less pain on injection.

The purpose of this study is to evaluate the safety of repeat injections and pain associated with injection of PN40082 and comparative pain associated with RV001 with a topical anesthetic and RV001 for lip augmentation in subjects who participated in PRO 2018-02 and PRO 2018-03.

6 STUDY OBJECTIVES

To evaluate the safety of repeat lip augmentation treatment and pain associated with injection and safety of PN40082, RV001 with topical anesthetic, or RV001 for lip augmentation.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design

This is a multicenter, double-blind, randomized, controlled, roll-over study of the safety and pain associated with injections of PN40082, RV001 with topical anesthetic, or RV001 for lip augmentation.

Visits and telephone contacts will occur at:

Visit 1 / 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 – End of Study (EOS) Visit

- Day 56 (±4 days) - Safety follow-up telephone call
- Day 168 (±7 days) – End of Study telephone call

Efficacy evaluations are:

Subject pain score (VAS) at time of injection, 15 minutes after injection and at Visit 2.

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, including any changes in vision and any events attributable to an embolic or ischemic cause (e.g., skin infarction), will be monitored. Other safety evaluations are lip function, lip sensation, lip texture, lip firmness, lip symmetry, and lip movement/function.

Other evaluations are 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.

A subject is considered to have completed the study after he/she has completed the Day 168 Month 6/End of study telephone call.

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), starting 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 from the time he/she signs the ICF through the final contact. After determination of eligibility at Visit 1/Day 1, each subject will be treated with study device.

It is anticipated that the duration of this study will be 20 months from the beginning to the end of the study (first subject signing the ICF to last contact with last subject).

7.3 Study Population

7.3.1 Inclusion Criteria

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

1. Completed Protocol PRO 2018-03

   OR

   Protocol PRO 2018-02 and did not enroll in Protocol PRO 2018-03.
2. Men or non-pregnant or non-breastfeeding women over 21 years of age

3. At PRO 2018-02 baseline visit had 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

   Had 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. If female and of childbearing potential, a negative urine pregnancy test at Visit 1/Day 1 and the subject agrees to use adequate contraception during the study period.
5. Willing to give written informed consent and read and sign the Adverse Event of Special Interest (AESI) letter dated 04JUN19.

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. Subjects with a known history of allergy, anaphylaxis or hypersensitivity to injectable hyaluronic acid products, local anesthetics of the amide type such as lidocaine, or to latex.
3. Subjects with a significant ongoing adverse event from PRO 2018-02 or PRO 2018-03 that in the opinion of the investigator could be worsened by participation in this study.
4. Subjects that experienced an SAE, AESI, visual changes or other serious medical conditions during PRO 2018-02 or PRO 2018-03.
5. Subjects with abnormal vision evaluations (Confrontational Visual Fields, Ocular Motility) or abnormal Snellen Visual Acuity at Visit 1 pre-treatment as defined in section 7.6.5 and Appendix 5.
6. Subjects who are unable to withhold 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 before AND after any injection session.
7. Subjects with clinically significant organic disease including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the investigator, preclude participation in the trial.
8. Subjects with lip tattoos, piercings, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments.
9. Subjects with abnormal lip function, with inability to effectively sip water through a straw.
10. Subjects with abnormal lip sensation with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip.
11. Subjects with moderate or severe abnormal lip asymmetry.

12. Subjects with any mass formation on the lip.
13. Subjects with 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.
14. Subjects that have undergone facial plastic surgery or received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene, polyacrylamide, lifting threads) anywhere in the face or neck, or are planning to be implanted with any of these products during the study.
15. Subjects that have 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 are planning to undergo such treatment during the study.
16. Subjects that have 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 are planning to undergo any of these procedures during the study.
17. that have used ANY lip filling agents within 12 months of study enrollment (hyaluronic acid products, collagen-based products, etc.) other than Investigational Device administered in PRO 2018-02 and PRO-2018-03.
18. Subjects that have used any lip plumping products or devices within 10 days before enrollment or are planning to use such products during the study.
19. Subjects that have 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 are 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).
20. Subjects that have a history or presence of bleeding disorders.
21. Subjects that have used systemic corticosteroids or immunosuppressive medications within 30 days prior to treatment.
22. Subjects that are on a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine)
23. Subjects that have an active inflammation (skin eruptions such as cysts, pimples, rashes, or hives), infection cancerous or precancerous lesion, or unhealed wound on the face.
24. Subjects that have a history of known susceptibility to keloid formation or hypertrophic scars.
25. Subjects that have porphyria.

26. Subjects that have active herpes labialias 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.
27. Subjects that have 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.
28. Subjects that have any uncontrolled disease, i.e., a condition that has not been appropriately diagnosed, evaluated, and received medically appropriate treatment or care
29. Subjects that have 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
- 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 2/Month 1) should be completed and any outstanding data and study device 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 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

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. The study device will be provided by the Sponsor.

Comparator device: RV001 (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 to be used with LMX4, a topical lidocaine. The study device will be provided by the Sponsor. LMX4 will be provided in commercial stock packaging by the Sponsor

Comparator device: RV001 (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 to be used alone. The study device will be provided by the Sponsor.

7.4.2 Randomization

Subjects who satisfy all of the eligibility criterial will be randomized in a 1:1:1 ratio to treatment with RV001, RV001 with a topical anesthetic or PN40082. 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 randomization subject number will be assigned to each subject in ascending order. Each site will receive the randomization scheme.

7.4.3 Study Device Administration

Subjects are physically masked (blindfolded) just prior to and during all injection procedures including the application of the LMX4 or inert cream to prevent observation of the syringes containing study device and the topical product. Any unblinded investigators and staff should be reminded NOT to discuss the treatment in the presence of the subject. Subjects will maintain the unique subject number previously assigned in Protocol PRO 2018-02 and PRO 2018-03.

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 maintain the subject blinding, the upper and lower lip, upper and lower vermillion and any planned injection areas in or around the mouth corners should be covered with a liberal application of either the Sponsor provided inert cream or the topical anesthetic according to the randomization code. The designated cream product should be applied in a layer thick enough

that no skin or lip color is visible through the product. Investigators should use as much cream as necessary to achieve this result and not be limited to the contents of one tube of product.

Wait 15 minutes before treatment administration.

The anesthetic cream or inert cream should be removed by wiping firmly with a dry gauze before injecting. Only the area to be immediately treated should be wiped clear of cream. Areas not yet treated should remain covered with cream until moments prior to undergoing injection.

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. Efforts should be made to keep the injection procedure similar between subjects. It is understood that each subject is somewhat different but each investigator should strive to use the same techniques for each subject. Additionally, the number of needle insertions should be kept to the minimum necessary for each subject.
8. 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.
9. If excessive material is implanted or irregularly implanted, massage the area somewhat more firmly than for the usual implantation procedure to obtain optimal results.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.

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.

For RV001 with topical anesthetic, one 1.0 mL syringe is packaged along with two fine-gauge needles (27G) in an easy-open tray. 30G fine-gauge needles will be provided in bulk by the Sponsor for use instead of the 27G needles. 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. Bulk commercial supplies of LMX4 will be provided.

For RV001, one 1.0 mL syringe is packaged along with two fine-gauge needles (27G) in an easy-open tray. 30G fine-gauge needles will be provided in bulk by the Sponsor for use instead of the 27G needles. 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. To confirm use of the 30G needles, the 27G needles should remain in the retained packaging for reconciliation.

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. The 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 investigational product 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 Concomitant Medications

All medications and other treatments taken by the subject during the study and 6 months prior to Visit 1 for subjects who did not participate in PRO 2018-03 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 over-the-counter (OTC) medications and dietary supplements. All medications taken on a regular basis, including vitamins, aspirin, and acetaminophen, should be recorded prior to 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 During the Study

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 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 below.

- 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)
- 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 stable regimen of such products for at least 90 days must continue their regimen throughout the study.)

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 treated in PRO 2019-02.

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 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.

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 who is either a board certified dermatologist or board certified plastic surgeon 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 and topical product is administered in accordance with the protocol and other study instructions. 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 Written Informed Consent

The study personnel will review the ICF for this study 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. The study personnel will review the letter regarding AESI dated 04JUN19, have the subject sign the letter. A copy of the signed letter will be given to every subject and the original will be maintained with the subject's records.

7.6.3 Significant Medical History/Demographic Information

Medical history and demographic information will be updated if/as needed at Visit 1/Day 1 to record any changes since Visit 1 in Protocol PRO 2018-02.

7.6.4 Vital Signs

Vital signs will be recorded. Vital signs will include sitting blood pressure, temperature, heart rate, and respiratory rate.

7.6.5 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 at Visit 1/Day 1 prior to treatment and repeated 30 minutes following treatment and at Visit 2/Month 1. Normal and abnormal findings are summarized in Appendix 5.

7.6.5.1 Snellen Visual Acuity

Site staff trained on conducting visual acuity will hold the provided Snellen chart 6 feet from the subject. The subject will be instructed to wear any usual corrective eyewear and cover one eye with the provided occlude. The subject will read each line until no longer capable. The best readable line will be recorded for each eye.

Normal finding: The same Snellen Visual Acuity results as the Snellen Visual Acuity results recorded pre-treatment at Visit 1/baseline in PRO 2018-02.

Abnormal finding: Any change from the Snellen Visual Acuity results recorded pre-treatment at Visit 1/Baseline in PRO 2018-02 will be considered abnormal.

7.6.5.2 Confrontational Visual Fields

The Blinded Evaluating Investigator will:

- Sit face to face with the subject
- Have the subject cover their left eye with hand or occlude
- The investigator covers their right eye
- Instruct the subject to continuously stare at the investigator's nose
- The investigator stares continuously at the subject's nose
- The investigator extends their left arm with finger pointed inward from far left side and gradually moves their finger toward the midline
- Ask the subject to indicate when they see the finger
- Repeat test for top of visual field (arm and finger up high)
- Repeat test for bottom of visual field (arm and finger down low)
- Repeat all three tests for the other eye

Normal finding: Subject reports seeing the finger at about the same time or location as the investigator.

Abnormal finding: Subject does not see the finger at about the same time or location as the investigator.

7.6.5.3 Ocular Motility

The Blinded Evaluating Investigator will:

- Have the subject stare at the investigator

- Ask the subject to "follow my finger"
- The investigator will move their finger to extremes of gaze on left, right, top and bottom

Normal finding: Observe eyes to ensure consistent conjugate gaze throughout the test

Abnormal finding: subject does not have consistent conjugate gaze throughout the test

7.6.6 Prior and Concomitant Medication/Treatment Review

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 at each study visit and telephone contact. For subjects who did not participate in PRO 2018-03, prior medications/treatments, including the necessary washout times 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 will be obtained at Visit 1/Day 1.

7.6.7 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.

7.6.8 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 Reason for Study Participation Question

Subjects will be provided with the Study Participation Question which asks, "Why did you choose to enroll in this study?" with the following choices:

- Was happy with results and wanted a little more product
- Fullness has diminished and lips are back to original condition
- Other

7.6.10 Lip Fullness Grading Scale

The LFGS is a validated 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 at each study visit by the Blinded Evaluating Investigator.

7.6.11 Perioral Lines at Rest Severity Scale

The POL is a 4-point rating scale that 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 at each study visit by the Blinded Evaluating Investigator.

7.6.12 Lip Function Evaluation

Lip function will be assessed by the Blinded Evaluating Investigator by the subject's ability to sip liquid through a straw prior to treatment at each study visit.

7.6.13 Lip Sensation Evaluation

Lip sensation will be assessed by the Blinded Evaluating Investigator and tested via: 1) the monofilament test (a subject's ability to feel the sensation of a 0.4G monofilament at 3 points on the upper lip and 3 points on the lower lip), and 2) the cotton wisp test (a subject's ability to feel the sensation of a cotton wisp at 3 points on the upper lip and 3 points on the lower lip) prior to treatment at each study visit.

7.6.14 Lip Texture Evaluation

Lip texture will be assessed by the Blinded Evaluating Investigator as normal or abnormal prior to treatment at each study visit (Table 1 Lip Texture Scoring Criteria).

Table 1. 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

7.6.15 Lip Firmness Evaluation

Lip firmness will be assessed by the Blinded Evaluating Investigator as normal or abnormal prior to treatment at each study visit (Table 2. Lip Firmness Scoring Criteria).

Table 2. 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.

7.6.16 Lip Symmetry Evaluation

Lip symmetry will be assessed by the Blinded Evaluating Investigator as normal or abnormal prior to treatment at each study visit (Table 3. Lip Symmetry Scoring Criteria).

Table 3. 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.

7.6.17 Lip Movement/Function Evaluation

Lip movement/function will be evaluated by the Blinded Evaluating Investigator as normal or abnormal prior to treatment at each study visit 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.

7.6.18 Patient Global Aesthetic Improvement (pGAI) Score

The pGAI score will be recorded at each study visit. Subjects will be asked the question "How would you rate improvement in your appearance compared to your initial condition prior to enrolling in Protocol PRO 2018-02 using the scale below?"

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.

7.6.19 Investigator Global Aesthetic Improvement (iGAI) Score

The iGAI score will be assessed at each study visit by the Blinded Evaluating Investigator.

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.

7.6.20 Swelling Assessment

Swelling will be assessed by the Blinded Evaluating Investigator at each study visit using the 5-point scale with the categories that follow. The 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.

7.6.21 Subject Satisfaction with Lips (Visual Analog Scale [VAS])

Subjects will be asked to assess their overall satisfaction with their lips by using a 100 mm VAS scale from 0 = Very Unsatisfied to 100 = Very Satisfied at Visit 2/Month 1 (Figure 1).

Figure 1 Visual Analog Scale for Subject Satisfaction

Very Unsatisfied — Very Satisfied

7.6.22 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. (Figure 2)

Figure 2 Investigator Ease of Use

0 1 2 3 4 5 6 7 8 9 10
Not Easy Most Easy

7.6.23 Subject Pain Score – Visual Analog Scale

Pain from the injection session will be assessed by the subject using a 100-mm VAS scale from 0 = no pain to 100 = worst possible pain at Visit 1/Day 1 immediately after the injection, 15 minutes post the last injection of the session, and at Visit 2. Subjects will be asked the question "How would you rate your pain from the injection of study material?" and will respond by placing a mark on the VAS. (Figure 3)

Figure 3 Visual Analog Scale for Subject Assessment of Pain

7.6.24 Treatment Question

At Visit 2 or early termination, subjects and blinded evaluating investigators will be asked to identify which treatment they thought had been administered.

7.6.25 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 card to record any AEs experienced during the 2 weeks after receiving treatment. The diary card will be collected at Visit 2/Month 1.

7.6.26 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.

7.7 Visit-Specific Procedures

The following sections outline the procedures required at each visit.

7.7.1 Visit 1/Day 1: Treatment

Visit is ±14 days of Day 168/Month 6 telephone call for PRO 2018-03 or for subjects enrolled from PRO 2018-02, Visit 1 is Day 1.

- Obtain written informed consent and read and sign the AESI letter dated 04JUN19.
- Update the medical history and demographic information as needed from entry to Protocol PRO 2018-02 and PRO 2018-03
- Perform vital signs (temperature, heart rate, blood pressure, and respiratory rate)
- Vision evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Obtain/record concomitant medications/treatments

- Evaluate inclusion/exclusion criteria
- Perform urine pregnancy test for all women of childbearing potential
- Reason for study participation question
- 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 prior to treatment administration
- pGAI assessment prior to treatment administration
- iGAI assessment prior to treatment administration
- Swelling assessment prior to treatment administration
- Subject satisfaction with lips (VAS) prior to treatment administration
- Treatment administration waiting 15 minutes after lidocaine cream or inert cream application
- Investigator Ease of Use assessment
- Subject Pain Score immediately after treatment (VAS)
- Subject Pain Score 15 minutes after treatment (VAS)
- Vision evaluation (Snellen visual acuity, confrontational visual fields, ocular motility) 30 minutes post treatment.
- 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
- Ask whether the subject is experiencing or has experienced any signs/symptoms of vision changes or stroke since the injection
- Confirm adherence to prohibited treatments/medications

7.7.3 Visit 2/Day 28 (± 2 days): Month 1 End of Study Visit

- Vision evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Assess concomitant medications/treatments
- LFGS assessment
- POL assessment
- Lip function evaluation
- Lip sensation evaluation
- Lip texture evaluation
- Lip firmness evaluation
- Lip symmetry evaluation
- Lip movement/function
- pGAI assessment
- iGAI assessment
- Swelling assessment
- Subject satisfaction with lips (VAS)
- Subject Pain Score (VAS)
- Assess AEs
- Treatment Question
- Collect/Review subject diary card
- Complete CRFs

7.7.4 Telephone Contact on Day 56 (Month 2) ± 4 days

- Assess AEs
- Assess concomitant medications/treatments
- Ask whether the subject is experiencing or has experienced any signs/symptoms of vision changes or stroke since the injection
- Confirm adherence to prohibited treatments/medications

7.7.5 End of Study Telephone Contact on Day 168 (Month 6) ±7 days

- Assess AEs
- Assess concomitant medications/treatments
- Ask whether the subject is experiencing or has experienced any signs/symptoms of vision changes or stroke since the injection

- Confirm adherence to prohibited treatments/medications

7.7.6 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.

- Vision evaluation (Snellen visual acuity, confrontational visual fields, ocular motility)
- Assess concomitant medications/treatments
- LFGS assessment
- POL assessment
- Lip function evaluation
- Lip sensation evaluation
- Lip texture evaluation
- Lip firmness evaluation
- Lip symmetry evaluation
- Lip movement/function
- pGAI assessment
- iGAI assessment
- Swelling assessment
- Subject satisfaction with lips (VAS)
- Subject Pain score (VAS)
- Assess AEs
- Complete CRFs

7.8 Efficacy Endpoints

Efficacy will be evaluated by the Subject Pain Score immediately after treatment, 15 minutes after treatment, and at Visit 2. Efficacy will also be evaluated by LFGS, POL, pGAI, iGAI, and Swelling Assessment.

7.9 Assessment of Safety

7.9.1 Safety Endpoints

Safety of the treatment with PN40082 or RV001 with topical anesthetic, or RV001 will be evaluated by 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. The frequency and type of AEs will be evaluated for each group based on the previous

treatments that they received in the PRO 2018-02 and PRO 2018-03 protocols, and the difference in AEs in this protocol (PRO 2019-02) between the subjects who received injections that contained lidocaine, and the group that was treated with topical lidocaine.

7.9.2 Other Safety Evaluations

Adverse events of special interest, including any changes in vision and any events attributable to an embolic or ischemic cause (e.g., skin infarction), will be evaluated. Other safety evaluations are lip function, lip sensation, lip texture, lip firmness, lip symmetry, and lip movement/function.

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, and 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 device.

7.9.3.4 Adverse Events of Special Interest

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

- any significant changes in vision. A one-line change in the Snellen chart is considered significant and requires reporting as an AESI.
- any events attributable to an embolic or ischemic cause (e.g., 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 regardless of relation to investigational device.

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

Refer to Appendix 1: Filler 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.

The FDA considers events such as detached retina and Bell's Palsy serious adverse events.

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 the 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, and on the subject diary card dispensed at Visit 2 for the remainder of the study. 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

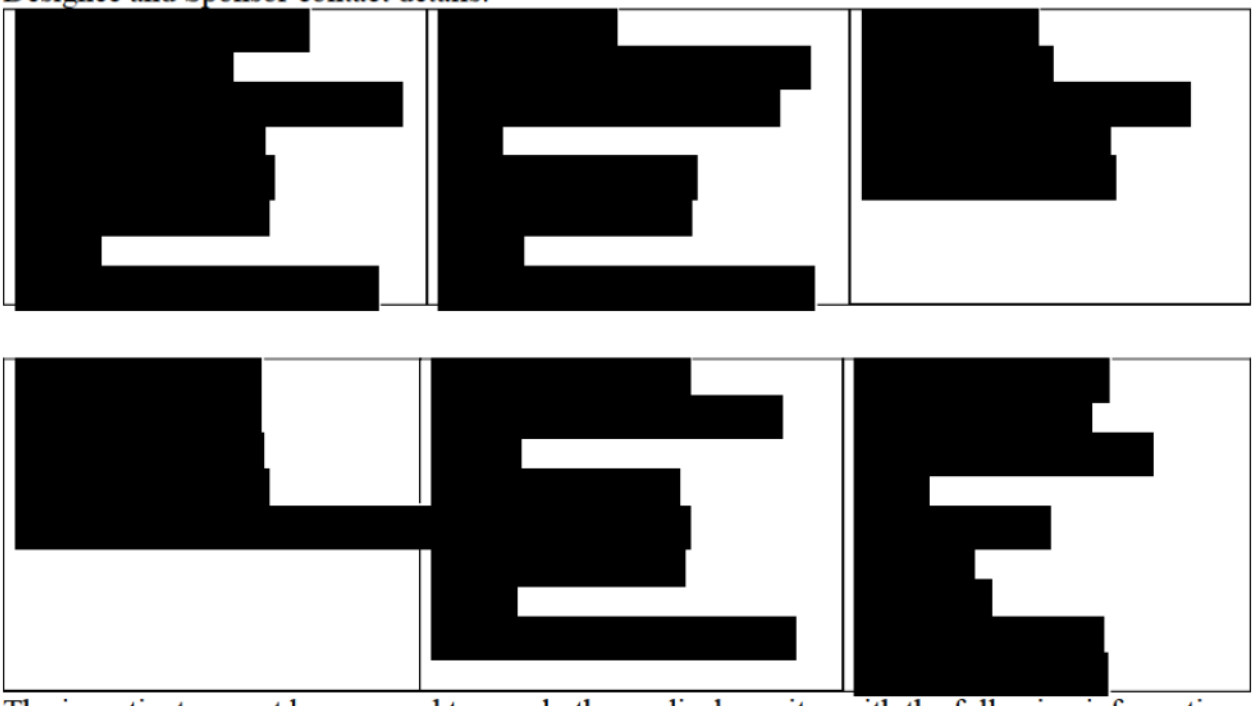
7.9.6.3 Reference Safety Information for Assessing Expectedness of Adverse Events

For reference safety information for assessing the expectedness of an AE for the study device in this study, see Appendix 2: PN40082 Instructions for Use and Appendix 3: RV001 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 study 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 Investigator 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. If termination is deemed appropriate, there will be timely communication with the FDA in accordance with the regulations (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 subjects 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 and Unblinding of 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 2/Month 1 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. Data will be summarized overall and also broken down by the treatment arm.

8.1 Analysis Populations

Safety and efficacy results will be summarized descriptively for all subjects who receive treatment in this study.

8.2 Efficacy Analysis

Compare subject pain scores (VAS) between PN40082 and RV001 with topical anesthetic and RV001. Change from baseline will be summarized for LFGS and POL. Other efficacy variables include pGAI, iGAI, and Swelling Assessment at Visit 2/Month 1.

8.3 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 TEAEs will be tabulated overall and for each treatment in PRO 2019-02 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 by preferred term.

8.4 Sample Size Determination

The maximum sample size was determined by the number of subjects who competed Protocol PRO 2018-02 and the number of subjects who rolled over into PRO 2018-03.

9 ETHICS

9.1 Informed Consent

The principles of informed consent, according to Food and Drug Administration (FDA) regulations and International Council for Harmonization (ICH) guidelines on Good Clinical Practice (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 website 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 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.

Chestnut C. Restoration of visual loss with retrobulbar hyaluronidase injection after hyaluronic acid filler. Dermatol Surg. 2018;44:435-446.

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.

13 INVESTIGATOR AGREEMENT

Protocol Number: PRO 2019-02

Protocol Title: A Multicenter, Double-blind, Randomized, Controlled, Roll-over Study of the Safety and Pain Associated with Injections of PN40082 or RV001 with Topical Anesthetic or RV001 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 (CHESTNUT C., 2018)

Materials that are needed on-site:

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

Provide the following contacts to subjects and these contacts should also be 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

15 APPENDIX 2: 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.

16 APPENDIX 3: RV001 INSTRUCTIONS FOR USE

RV001 Injectable Hyaluronic Acid Gel

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

DESCRIPTION

RV001 (Revanesse Versa without lidocaine) 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. The product was previously approved on August 4, 2017 for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. The product is injected by qualified, trained physicians into the dermis of patients, using a variety of techniques. The injections place a small portion of the gel beneath a crease or wrinkle in the skin and the augmentation of the tissue produces a smoothing effect on the surface.

INDICATION

RV001 is indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.

CONTRAINDICATIONS

- *RV001* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *RV001* contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *RV001* is contraindicated for patients with bleeding disorders.
- *RV001* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.
- *RV001* should not be used with a topical anesthetic in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

WARNINGS

- Defer use of *RV001* 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 *RV001,* including short-term minor or moderate inflammatory symptoms starting shortly after treatment of lips

- *RV001* 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, *RV001* 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

- *RV001* is packaged for single use. Do not resterilize. Do not use if package is opened or damaged.
- The safety or effectiveness of *RV001* 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, *RV001* implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of *RV001* 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.
- *RV001* should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *RV001* injection sites. Patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the 3 weeks preceding treatment with *RV001* 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 *RV001* 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 *RV001*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *RV001* is administered before the skin has healed completely after such a procedure.
- Injection of *RV001* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.

HOW SUPPLIED

RV001 is supplied in a disposable glass syringe with a Luer-Lok® fitting. *RV001* is packed with two 1.0 mL syringes and two sterilized needle(s) 27 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. Sterilized needles, 30 G x ½", will be supplied and used for the study.

SHELF LIFE AND STORAGE

RV001 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.

Prollenium Medical Technologies Inc.
138 Industrial Parkway N., Aurora, L4G 4C3 Ontario Canada
Ph: 905-508-1469
Toll free: 866-353-3015
Fax: 905-508-6716

INJECTION TECHNIQUES

15. Study device can be injected by a number of different techniques that depend on the treating investigator's experience and preference, and patient characteristics. The topical anesthetic supplied in bulk should be applied 15 minutes prior to injection for subjects randomized to receive the topical anesthetic.
16. **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.
17. **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.
18. 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.

19. The following techniques should be avoided:
    - 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
- The use of a topical anesthetic other than that provided in the kit

As they may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.

20. The use of cannulas is prohibited
21. 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.
22. If excessive material is implanted or irregularly implanted, massage the area somewhat more firmly than for the usual implantation procedure to obtain optimal results.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.

17 APPENDIX 4: LMX4 PACKAGE INSERT

1. LMX4 – LIDOCAINE CREAM FERNDALE LABORATORIES, INC.

Disclaimer: Most OTC drugs are not reviewed and approved by FDA; however they may be marketed if they comply with applicable regulations and policies. FDA has not evaluated whether this product complies.

2. Drug Facts
Active ingredient

Lidocaine 4% w/w

3. Purpose

Topical anesthetic

4. Uses

temporarily relieves pain and itching due to

- minor cuts
- minor scrapes
- minor burns
- sunburn
- minor skin irritations
- insect bites

5. Warnings

For external use only.

Do not use

- in or near the eyes
- in large quantities, particularly over raw surfaces or blistered areas

6. Stop use and ask a doctor if:

- allergic reaction occurs
- condition worsens or does not improve within 7 days symptoms clear up and return within a few days
- redness, irritation, swelling, pain or other symptoms begin or increase

7. Keep out of reach of children.

If swallowed, get medical help or contact a Poison Control Center right away.

8. Directions

- Adults and children 2 years and older: Apply externally to the affected area up to 3 to 4
-

times a day Children under 2 years: Consult a doctor

9. Other Information

- May be applied under occlusive dressing.
- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

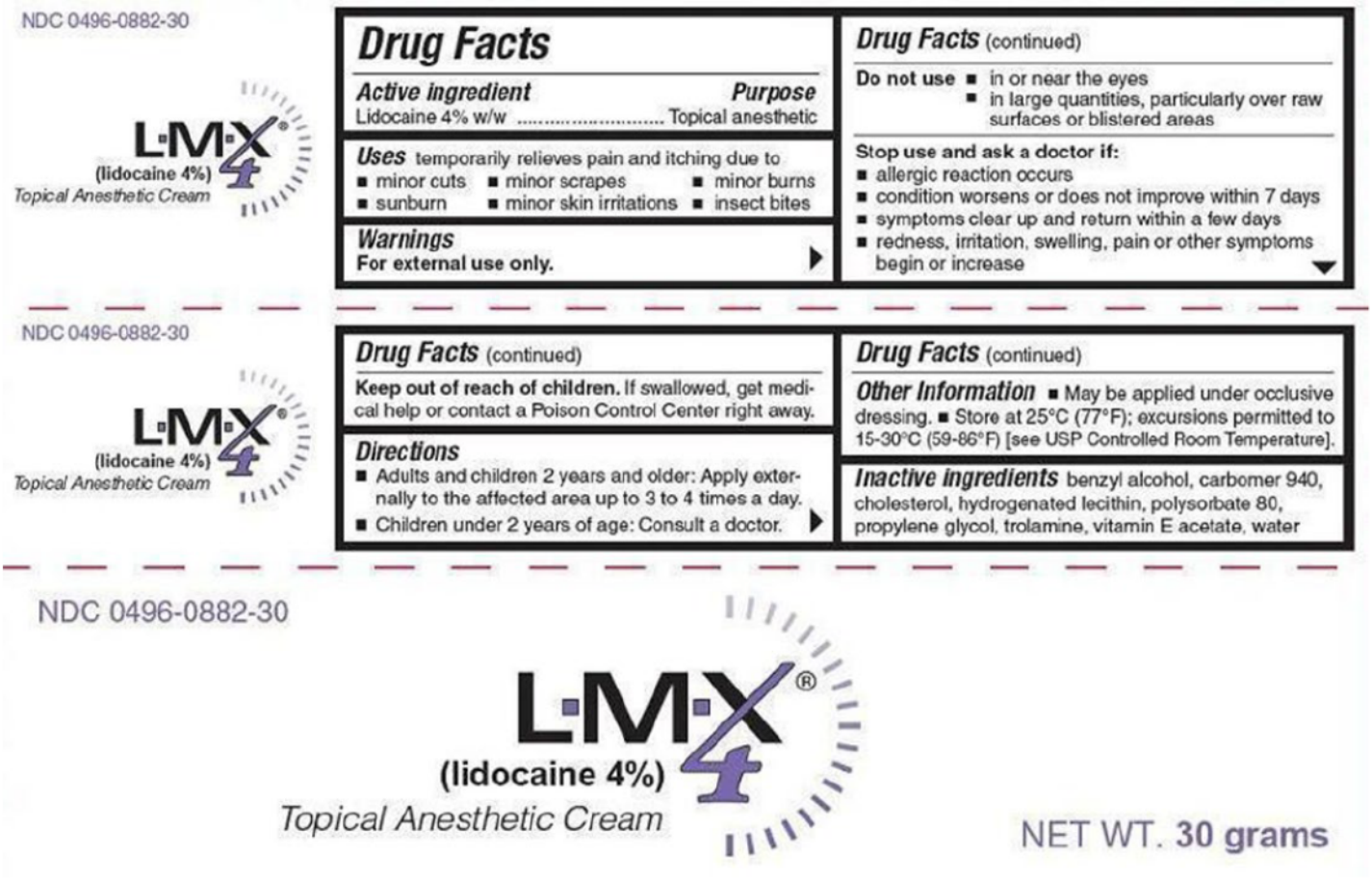
10. Inactive ingredients

benzyl alcohol, carbomer 940, cholesterol, hydrogenated lecithin, polysorbate 80, propylene glycol, trolamine, vitamin E acetate, water

11. Package Labels-Principal Display Panels

Manufactured by Ferndale
Laboratories, Inc. Ferndale, MI
48220 U.S.A.
Toll free (888) 548-0900
www.ferndalelabs.com

L.M.X.4® is a registered trademark of Ferndale IP, Inc. Tegaderm™ is a trademark of 3M Corporation.



Product Type	HUMAN OTC DRUG	**Item Code (Source)**	NDC:0 49 6 -0 8 8 2
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIDO CAINE (UNII: 9 8 PI20 0 9 8 7) (LIDOCAINE - UNII:9 8 PI20 0 9 8 7)	LIDOCAINE	40 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
BENZYL ALCO HO L (UNII: LKG8 49 4WBH)	
CARBO MER HO MO PO LYMER TYPE C (UNII: 4Q 9 3RCW27E)	
CHO LESTERO L (UNII: 9 7C5T2UQ 7J)	
PO LYSO RBATE 8 0 (UNII: 6 OZP39 ZG8 H)	
PRO PYLENE GLYCO L (UNII: 6 DC9 Q 16 7V3)	
TRO LAMINE (UNII: 9 O 3K9 3S3TK)	
ALPHA-TO CO PHERO L ACETATE (UNII: 9 E8 X8 0 D2L0)	
WATER (UNII: 0 59 QF0 KO 0 R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0496-0882-06	5 in 1 CARTON		
1	NDC:0496-0882-05	5 g in 1 TUBE		
2	NDC:0496-0882-07	5 in 1 BOX		
2	NDC:0496-0882-05	5 g in 1 TUBE		
3	NDC:0496-0882-15	15 g in 1 TUBE		
4	NDC:0496-0882-30	30 g in 1 TUBE		
5	NDC:0496-0882-05	5 g in 1 TUBE		
6	NDC:0496-0882-71	1 in 1 BOX		
6	NDC:0496-0882-30	30 g in 1 TUBE		

Marketing Information

Marketing Cate gory	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph not final	part348	0 1/0 3/20 11	

Labeler - Ferndale Laboratories, Inc. (005320536)

Establishment

Name	Address	ID/FEI	Business Operations
Ferndale Laboratories, Inc.		0 0 5320 536	manufacture(0 49 6 -0 8 8 2)

Revised: 6/2014 Ferndale Laboratories, Inc.

18 APPENDIX 5: VISION EVALUATION RESULTS

Snellen Visual Acuity

Normal findings: The same Snellen Visual Acuity results as the Snellen Visual Acuity results recorded pre-treatment at Visit 1/baseline in PRO 2018-02.

Abnormal findings: Any change from the Snellen Visual Acuity results recorded pre-treatment at Visit 1/baseline in PRO 2018-02 will be considered abnormal.

Confrontational Visual Fields

Normal finding: Subject reports seeing the finger at about the same time or location as the investigator.

Abnormal finding: Subject does not see the finger at about the same time or location as the investigator.

Ocular Motility

Normal finding: Observe eyes to ensure consistent conjugate gaze throughout the test

Abnormal finding: Subject does not have consistent conjugate gaze throughout the test