Clinical Study Report SYM 2014-02 Appendix Table of Contents

Appendix 16.1.1 Protocol and Protocol Amendments

Protocol Amendment No. 01 Summary of Changes

Protocol No.:	SYM 2014-02
Title:	A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds
Original Protocol Date:	26 February 2015 (Version 1.0)
Amendment 01 Date:	05 May 2015 (Version 2.0)
Sponsor:	Prollenium Medical Technologies Inc. 138 Industrial Parkway North Aurora Ontario L4G 4C3 Canada

Amendments:

1. **Original text and location:** Synopsis

Study Design: Evaluations include:

Wrinkle Severity Rating Scale (WSRS)
Patient Global Aesthetic Improvement (pGAI)
Patient Comfort Rating (PCR)
Investigator Global Aesthetic Improvement (iGAI)
Safety will be assessed by monitoring adverse events (AEs) at all study visits.

Revised text and location: **Synopsis**

Study Design: Evaluations include:

Wrinkle Severity Rating Scale (WSRS)
Patient Global Aesthetic Improvement (pGAI)

Investigator Global Aesthetic Improvement (iGAI)
Safety will be assessed by monitoring adverse events (AEs) at all study visits.
Other evaluations include Patient Comfort Rating (PCR) and Investigator Ease of Use Assessment.

2. **Original text and location:** Synopsis

Efficacy Analysis:

Secondary efficacy endpoints are the responder rate, i.e. the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, iGAI score at Visit 6/Week 24, and change from baseline to Visit 6/Week 24 in PCR. For these secondary variables, the null hypothesis to be tested is that there is no difference between the two products. The variables responder rate, pGAI and iGAI scores at Visit 6/Week 24 will be tabulated with frequencies and percentage and analyzed using the Wilcoxon matched-pairs signed rank test. Change in PCR will be tabulated with numeric statistics and analyzed via the paired t-test.

Other efficacy variables include change in WSRS score, pGAI, iGAI, and change in PCR at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12. Treatment difference with respect to these variables will be examined using descriptive summaries.

Revised text and location: Synopsis

Efficacy Analysis:

Secondary efficacy endpoints are the responder rate, i.e. the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, and iGAI score at Visit 6/Week 24. For these secondary variables, the null hypothesis to be tested is that there is no difference between the two products. The variables responder rate, pGAI and iGAI scores at Visit 6/Week 24 will be tabulated with frequencies and percentage and analyzed using the Wilcoxon matched-pairs signed rank test.

Other efficacy variables include change in WSRS score, pGAI, and iGAI at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12. Treatment difference with respect to these variables will be examined using descriptive summaries.

3. Original text and location: Section 8.1 Overall Study Design, last paragraph

Evaluations include Wrinkle Severity Rating Scale (WSRS), Patient Global Aesthetic Improvement (pGAI), Patient Comfort Rating (PCR), and Investigator Global Aesthetic Improvement (iGAI). Safety will be assessed by monitoring adverse events (AEs) at all study visits. 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 for the first 2 weeks after treatment.

Revised text and location: Section 8.1 Overall Study Design, last paragraph

Evaluations include Wrinkle Severity Rating Scale (WSRS), Patient Global Aesthetic Improvement (pGAI), and Investigator Global Aesthetic Improvement (iGAI). Safety will be assessed by monitoring adverse events (AEs) at all study visits. **Other evaluations include the Patient Comfort Rating (PCR) and Investigator Ease of Use Assessment.** 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 for the first 2 weeks after treatment.

4. Original text and location: Section 3.2 Study Flow Chart

							Retreated Subjects Only			
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6[a]**	**Visit 7**	**Phone contact**	**Visit 8**	
Scheduled Day (Week)	**Day 1 (Week 0)**	**Day 7 (Week 1)**	**Day 14 (Week 2)**	**Day 28 (Week 4)**	**Day 84 (Week 12)**	**Day 168 (Week 24)**	**Day 196 (Week 28)**	**Day 280 (Week 40)**	**Day 364 (Week 52)**	**Unsched Visit**
Scheduling Window	**none**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
Patient Comfort Rating (PCR)	X					X	X		X	

a Subjects may be retreated with open-label Revanesse Ultra on both sides of the face if their WSRS score has returned to baseline; for subjects who are not retreated, Visit 6 is End of Study.
b If applicable.
c For women of childbearing potential, to be completed prior to enrollment.

Revised text and location: Section 3.2 Study Flow Chart

							Retreated Subjects Only			
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6[a]**	**Visit 7**	**Phone contact**	**Visit 8**	
Scheduled Day (Week)	**Day 1 (Week 0)**	**Day 7 (Week 1)**	**Day 14 (Week 2)**	**Day 28 (Week 4)**	**Day 84 (Week 12)**	**Day 168 (Week 24)**	**Day 196 (Week 28)**	**Day 280 (Week 40)**	**Day 364 (Week 52)**	**Unsched Visit**
Scheduling Window	**none**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
Patient Comfort Rating (PCR)	X	X[d]								

a Subjects may be retreated with open-label Revanesse Ultra on both sides of the face if their WSRS score has returned to baseline; for subjects who are not retreated, Visit 6 is End of Study.
b If applicable.
c For women of childbearing potential, to be completed prior to enrollment.
d For subjects who receive a touch-up treatment

5. Original text and location: Section 8.6.10 Patient Comfort Rating (PCR)

Overall comfort will be assessed by the patient using the NRS scale from 0 being most uncomfortable to 10 being most comfortable at Visit 1/Day 1 and Visit 6/Week 24 (End of Study/Early Termination for subjects who are not retreated). For subjects who are retreated, this will also be assessed at Visit 7/Week 28 and Visit 8/Week 52 (End of Study/Early Termination). Subjects will be asked the question "How would you rate your comfort level upon injection of the study material and will respond by circling the appropriate number on the scale with 0 being most uncomfortable to 10 being most comfortable?"

Revised text and location: Section 8.6.10 Patient Comfort Rating (PCR)

Overall comfort will be assessed by the patient using the NRS scale from 0 being most uncomfortable to 10 being most comfortable at Visit 1/Day 1 and **Visit 2/Week 2 if a touch-up treatment is administered.** For subjects who are retreated, this will also be assessed at Visit 7/Week 28 and Visit 8/Week 52 (End of Study/Early Termination). Subjects will be asked the question "How would you rate your comfort level upon injection of the study material?" and will respond by circling the appropriate number on the scale with 0 being most uncomfortable to 10 being most comfortable.

6. Original text and location: Section 8.7 Visit- Specific Procedures

Section 8.7.2 Visit 2/Day 7 (± 2 days), Visit 3/Day 14 (± 2 days), Visit 4/Day 28 (± 4 days), and Visit 5/Day 84 (± 4 days): Interim Visits

1. WSRS assessment (Section 8.6.7)
2. At Visit 2/Day 7 only, evaluation for touch-up (Section 8.6.11)
3. pGAI assessment (Section 8.6.12)
4. iGAI assessment (Section 8.6.13)
5. Assess AEs (Section 8.9)
6. Assess concomitant medications (Section 8.6.16)
7. Collect subject diary card at Visit 3/Day 14; dispense subject diary card at Visit 2/Day 7, if applicable and collect subject diary card at Visit 4/ Week 4 if applicable (Section 8.6.14)
8. Schedule next visit
9. Complete CRFs (Section 11.2.1)

Section 8.7.3 Visit 6/Day 168 (Week 24) (± 7 days): Optional Retreatment or Final Visit/Early Termination

1. WSRS assessment (Section 8.6.7)
2. PCR assessment (Section 8.6.10)
3. pGAI assessment (Section 8.6.12)
4. iGAI assessment (Section 8.6.13)
5. Assess AEs (Section 8.9)
6. Assess concomitant medications (Section 8.6.16)
7. Subjects with WSRS at baseline score may be retreated with Revanesse Ultra open-label on both sides of the face (Section 8.4.3)
8. Dispense subject diary card if subject was retreated (Section 8.6.14)
9. Schedule next visit for retreated subjects
10. Complete CRFs (Section 11.2.1)

Section 8.7.4 For Retreated Subjects Only: Visit 7/Day 196 (Week 28) (± 7 days): Follow-up

1. WSRS assessment (Section 8.6.7)
2. PCR assessment (Section 8.6.10)
3. pGAI assessment (Section 8.6.12)
4. iGAI assessment (Section 8.6.13)
5. Assess AEs (Section 8.9)
6. Assess concomitant medications (Section 8.6.16)
7. Collect subject diary card, if applicable (Section 8.6.14)
8. Schedule next visit
9. Complete CRFs (Section 11.2.1)

Section 8.7.5 For Retreated Subjects Only: Telephone Contact /Day 280 (Week 40) (± 7 days)

1. Assess AEs (Section 8.9)
2. Assess concomitant medications (Section 8.6.16)
3. Schedule next visit
4. Complete CRFs (Section 11.2.1)

Section 8.7.6 For Retreated Subjects Only: Visit 8/Day 364 (Week 52) (± 7 days): Final Visit/Early Termination

5. WSRS assessment (Section 8.6.7)
6. PCR assessment (Section 8.6.10)
7. pGAI assessment (Section 8.6.12)
8. iGAI assessment (Section 8.6.13)
9. Assess AEs (Section 8.9)
10. Assess concomitant medications (Section 8.6.16)
11. Complete CRFs (Section 11.2.1)

Section 8.7.7 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.

1. WSRS assessment (Section 8.6.7)
2. PCR assessment (Section 8.6.10)
3. pGAI assessment (Section 8.6.12)
4. iGAI assessment (Section 8.6.13)
5. Assess AEs (Section 8.9)
6. Assess concomitant medications (Section 8.6.16)
7. Complete CRFs (Section 11.2.1)

Revised text and location: Section 8.7 Visit- Specific Procedures

Section 8.7.2 Visit 2/Day 7 (± 2 days), Visit 3/Day 14 (± 2 days), Visit 4/Day 28 (± 4 days), and Visit 5/Day 84 (± 4 days): Interim Visits

1. WSRS assessment (Section 8.6.7)
2. At Visit 2/Day 7 only, evaluation for touch-up (Section 8.6.11)
3. **PCR assessment if a touch-up treatment is administered (Section 8.6.10)**
4. pGAI assessment (Section 8.6.12)
5. iGAI assessment (Section 8.6.13)
6. Assess AEs (Section 8.9)

7. Assess concomitant medications (Section 8.6.16)
8. Collect subject diary card at Visit 3/Day 14; dispense subject diary card at Visit 2/Day 7, if applicable and collect subject diary card at Visit 4/ Week 4 if applicable (Section 8.6.14)
9. Schedule next visit
10. Complete CRFs (Section 11.2.1)

Section 8.7.3 Visit 6/Day 168 (Week 24) (± 7 days): Optional Retreatment or Final Visit/Early Termination

1. WSRS assessment (Section 8.6.7)
2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Subjects with WSRS at baseline score may be retreated with Revanesse Ultra open-label on both sides of the face (Section 8.4.3)
7. Dispense subject diary card if subject was retreated (Section 8.6.14)
8. Schedule next visit for retreated subjects
9. Complete CRFs (Section 11.2.1)

Section 8.7.4 For Retreated Subjects Only: Visit 7/Day 196 (Week 28) (± 7 days): Follow-up

1. WSRS assessment (Section 8.6.7)
2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Collect subject diary card, if applicable (Section 8.6.14)
7. Schedule next visit
8. Complete CRFs (Section 11.2.1)

Section 8.7.5 For Retreated Subjects Only: Telephone Contact /Day 280 (Week 40) (± 7 days)

1. Assess AEs (Section 8.9)
2. Assess concomitant medications (Section 8.6.16)

3. Schedule next visit
4. Complete CRFs (Section 11.2.1

Section 8.7.6 For Retreated Subjects Only: Visit 8/Day 364 (Week 52) (± 7 days): Final Visit/Early Termination

1. WSRS assessment (Section 8.6.7)
2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Complete CRFs (Section 11.2.1)

Section 8.7.7 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.

1. WSRS assessment (Section 8.6.7)
2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Complete CRFs (Section 11.2.1)

7. Original text and location: 8.8 Efficacy Assessments

Section 8.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are the responder rate, i.e., the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, iGAI score at Visit 6/Week 24, and change from baseline to Visit 6/Week 24 in PCR.

Section 8.8.3 Other Efficacy Endpoints

Other efficacy endpoints include change in WSRS score, pGAI, iGAI, and change in PCR at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12.

Revised text and location: 8.8 Efficacy Assessments

Section 8.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are the responder rate, i.e., the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, and iGAI score at Visit 6/Week 24.

Section 8.8.3 Other Efficacy Endpoints

Other efficacy endpoints include change in WSRS score, pGAI, and iGAI at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12.

8. Original text and location: 9.4 Efficacy Evaluations; 2nd and 3rd paragraphs

Secondary efficacy endpoints include the responder rate, i.e., the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, iGAI score at Visit 6/Week 24, and change from baseline to Visit 6/Week 24 in PCR. For these secondary variables, the null hypothesis to be tested is that there is no difference between the two products. The variables responder rate, pGAI and iGAI scores at Visit 6/Week 24 will be tabulated with frequencies and percentage and analyzed using the Wilcoxon matched-pairs signed rank test. Change in PCR will be tabulated with numeric statistics and analyzed via the paired t-test.

Other efficacy variables include change in WSRS score, pGAI, iGAI, and change in PCR at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12. Treatment difference with respect to these variables will be examined using descriptive summaries.

Revised text and location: 9.4 Efficacy Evaluations; 2nd and 3rd paragraphs

Secondary efficacy endpoints include the responder rate, i.e., the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, and iGAI score at Visit 6/Week 24. For these secondary variables, the null hypothesis to be tested is that there is no difference between the two products. The variables responder rate, pGAI and iGAI scores at Visit 6/Week 24 will be tabulated with frequencies and percentage and analyzed using the Wilcoxon matched-pairs signed rank test.

Other efficacy variables include change in WSRS score, pGAI, and iGAI at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12. Treatment difference with respect to these variables will be examined using descriptive summaries.

Reason for Amendment: All sections amended pertain to the Patient Comfort Rating (PCR). This is to correct and clarify that PCR will only be done at Visit 1 and Visit 2, if a touch-up treatment is administered. This is also to clarify that PCR is not considered an efficacy endpoint.

9. Original text and location: Section 8.4.2 Method of Treatment Assignment, Randomization, and/or Stratification, 3rd paragraph

A unique subject number will be assigned to each subject. Each site will receive a list of randomization code numbers and corresponding study product boxes with the same randomization code numbers. Each eligible subject will be assigned a unique randomization code number in ascending order.

Revised text and location: Section 8.4.2 Method of Treatment Assignment, Randomization, and/or Stratification, 3rd paragraph

A unique subject number will be assigned to each subject. Each site will receive a list of randomization code numbers and corresponding study product boxes. Each eligible subject will be assigned a unique randomization code number in ascending order.

Reason for Amendment: This is to clarify that the study product will not include the randomization code number on it.

10. Original text and location: Section 8.9.5 Reporting Safety Obesrvations

Symbio contact details:

Evyan Cord-Cruz, MD Medical Monitor Direct: 516/338-0647 or 631/474-8531 ext 5126 Cell: 516/982-0677 Fax: 631/474-8534	Kathy Schultz Director, Clinical Operations Direct: 435/772-3154 Cell: 435/632-7669	Symbio, LLC 21 Perry Street Port Jefferson, NY 11777 Tel: 631/474-8531 Fax: 631/474-8534

Revised Text and Location: Section 8.9.5 Reporting Safety Observations

Symbio contact details:

Evyan Cord-Cruz, MD Medical Monitor Direct: 516/338-0647 or 631/474-8531 ext 5126 Cell: 516/982-0677 Fax: 631/474-8534	**Shanna Smith** **Director, Clinical Operations** **Direct: 631-474-8531 ext 2456** **Cell: 215-817-0175**	Symbio, LLC 21 Perry Street Port Jefferson, NY 11777 Tel: 631/474-8531 Fax: 631/474-8534

Reason for amendment: To reflect change in one of Symbio's contact persons and phone numbers.

PROTOCOL AMENDMENT 01

The protocol amendment described herein has been incorporated in Version 2.0 Amendment 01 of Protocol No. SYM 2014-02 dated 05 May 2015.

This Protocol Amendment has been verified and approved by:

Mr. Ario Khoshbin
Managing Director
Prollenium Medical Technologies Inc.

Date

Debra A. Dow, PharmD
Vice President, Scientific Affairs
Symbio, LLC

12 May 2015
Date

PROTOCOL AMENDMENT 01

INVESTIGATOR STATEMENT

PROTOCOL TITLE: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds

I have carefully read 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 Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted 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 drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____
Principal Investigator's Printed Name

_____
Principal Investigator's Signature

_____
Date

Protocol Amendment No. 02 Summary of Changes

Protocol No.:	SYM 2014-02
Title:	A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds
Original Protocol Date:	26 February 2015 (Version 1.0)
Amendment 01 Date:	05 May 2015 (Version 2.0)
Amendment 02 Date:	04 September 2015 (Version 3.0)
Sponsor:	Prollenium Medical Technologies Inc. 138 Industrial Parkway North Aurora Ontario L4G 4C3 Canada

Amendments:

1. **Original text and location: Synopsis, Study Design**

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 – interim visit

Visit 4/Week 4 – interim visit

Visit 5/Week 12 – interim visit

Visit 6/Week 24 – optional open-label retreatment with Revanesse Ultra; End of Study for subjects not being retreated

Visit 7/Week 28 – follow-up for retreated subjects

Visit 8/Week 52 – End of Study for retreated subjects

Revised text and location: Synopsis, Study Design

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 – interim visit

Visit 4/Week 4 – interim visit

Visit 5/Week 12 – interim visit

Visit 6/Week 24 – optional open-label retreatment with Revanesse Ultra **as needed for optimal correction**; End of Study for subjects not being retreated

Visit 7/Week 28 – follow-up for retreated subjects

Visit 8/Week 52 – End of Study for retreated subjects

2. **Original text and location:** Study Flow Chart, Footnote A

Subjects may be retreated with open-label Revanesse Ultra on both sides of the face; for subjects who are not retreated, Visit 6 is End of Study.

Revised text and location: Study Flow Chart, Footnote A

Subjects may be retreated with open-label Revanesse Ultra on both sides of the face **for optimal correction**; for subjects who are not retreated, Visit 6 is End of Study.

3. Original text and location: Section 6.2 Rationale for the Study and Study Design

This study is a randomized, double-blind prospective, comparative study of the efficacy and safety of Revanesse Ultra versus the approved product Restylane in the cutaneous correction of nasolabial folds (NLFs). Randomization will follow a 1:1 within-subject control model of augmentation correction of NLFs. Given that the implants have been shown to not migrate, the within-subject model is ideal and has already been shown in previous studies to detect differences. Subjects with signs of NLFs who meet the entry criteria will be enrolled. All subjects will be followed for efficacy and safety for 6 months. The study design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used.

Revised text and location: Section 6.2 Rationale for the Study and Study Design

This study is a randomized, double-blind prospective, comparative study of the efficacy and safety of Revanesse Ultra versus the approved product Restylane in the cutaneous correction of nasolabial folds (NLFs). Randomization will follow a 1:1 within-subject control model of augmentation correction of NLFs. Given that the implants have been shown to not migrate, the within-subject model is ideal and has already been shown in previous studies to detect differences. Subjects with signs of NLFs who meet the entry criteria will be enrolled. All subjects will be followed for efficacy and safety for 6 months. **Subjects may have open-label retreatment as needed with Revanesse Ultra at 6 months to achieve optimal correction and will be followed for a total of 12 months.** The study design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used.

4. Original Text and Location: Section 8.1 Overall Study Design

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

Visit 1/Week 0 (Day 1) – baseline and treatment
Visit 2/Week 1 (± 2 days) – interim visit, touch-up if the iGAI score = 3 or 4
Visit 3/Week 2 (± 2 days) – interim visit
Visit 4/Week 4 (± 4 days) – interim visit
Visit 5/Week 12 (± 4 days) – interim visit

Visit 6/Week 24 (± 7 days) – optional open-label retreatment with Revanesse Ultra for subjects; End of Study for subjects not being retreated

Visit 7/Week 28 (± 7 days) – follow-up for retreated subjects

Visit 8/Week 52 (± 7 days) – End of Study for retreated subjects

Revised Text and Location: Section 8.1 Overall Study Design

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 (± 2 days) – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 (± 2 days) – interim visit

Visit 4/Week 4 (± 4 days) – interim visit

Visit 5/Week 12 (± 4 days) – interim visit

Visit 6/Week 24 (± 7 days) – optional open-label retreatment with Revanesse Ultra for subjects **as needed to achieve optimal correction**; End of Study for subjects not being retreated

Visit 7/Week 28 (± 7 days) – follow-up for retreated subjects

Visit 8/Week 52 (± 7 days) – End of Study for retreated subjects

5. Original Text and Location: Section 8.4.3 Optional Retreatment at 6 Months

Revised Text and Location: Section 8.4.3 Optional Retreatment at 6 Months

At Visit 6/Week 24, the subject may be retreated with Revanesse Ultra. Retreatment would be open-label and may be administered to both sides of the face as needed to achieve optimal correction.

6. **Original Text and Location: Section 8.7.3 Visit 6/Day 168 (week 24) Optional Retreatment**

   Subjects may be retreated with Revanesse Ultra open-label on both sides of the face.

   Revised Text and Location: Section 8.7.3 Visit 6/Day 168 (Week 24) Optional Retreatment

   Subjects may be retreated with Revanesse Ultra open-label on both sides of the face to achieve optimal correction.

Reason for Amendment: Previously the protocol offered subjects optional retreatment at Week 24 with Revanesse Ultra open-label if their NLFs had returned to their baseline scores. This amendment will allow subjects the option to be re-treated at Week 24 with Revanesse Ultra open-label on one or both sides of the face in order to achieve optimal correction, without the requirement that their NLFs have returned to their baseline score.

PROTOCOL AMENDMENT 02

The protocol amendment described herein has been incorporated in Version 3.0 Amendment 02 of Protocol No. SYM 2014-02 dated 04 SEPTEMBER 2015.

This Protocol Amendment has been verified and approved by:

28/Sept. 2015
Date

Mr. Ario Khoshbin
Managing Director
Prollenium Medical Technologies Inc.

24Sept 2015
Date

Debra A. Dow, PharmD
Vice President, Scientific Affairs
Symbio, LLC

PROTOCOL AMENDMENT 02

INVESTIGATOR STATEMENT

PROTOCOL TITLE: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds

I have carefully read 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 Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted 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 drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____
Principal Investigator's Printed Name

_____
Principal Investigator's Signature

_____
Date

Protocol Amendment No. 03 Summary of Changes

Protocol No.:	SYM 2014-02
Title:	A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds
Original Protocol Date:	26 February 2015 (Version 1.0)
Amendment 01 Date:	05 May 2015 (Version 2.0)
Amendment 02 Date:	04 September 2015 (Version 3.0)
Amendment 03 Date:	28 October 2015 (Version 4.0)
Sponsor:	Prollenium Medical Technologies Inc. 138 Industrial Parkway North Aurora Ontario L4G 4C3 Canada

Amendments:

1. **Original text and location: Synopsis, Study Design**

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 – interim visit

Visit 4/Week 4 – interim visit

Visit 5/Week 12 – interim visit

Visit 6/Week 24 – optional open-label retreatment with Revanesse Ultra as needed for optimal correction; End of Study for subjects not being retreated

Visit 7/Week 28 – follow-up for retreated subjects

Visit 8/Week 52 – End of Study for retreated subjects

Revised text and location: Synopsis, Study Design

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 – interim visit

Visit 4/Week 4 – interim visit

Visit 5/Week 12 – interim visit

Visit 6/Week 24 – optional open-label retreatment with Revanesse Ultra **for subjects who have returned to baseline WSRS score or as needed for optimal correction if WSRS scores have not returned to baseline**; End of Study for subjects not being retreated

Visit 7/Week 28 – follow-up for retreated subjects

Visit 8/Week 52 – End of Study for retreated subjects

2. **Original text and location:** Study Flow Chart, Footnote A

Subjects may be retreated with open-label Revanesse Ultra on both sides of the face for optimal correction; for subjects who are not retreated, Visit 6 is End of Study.

Revised text and location: Study Flow Chart, Footnote A

Subjects may be retreated with open-label Revanesse Ultra **if scores have returned to baseline or to achieve optimal correction if the baseline scores have not returned to baseline;** for subjects who are not retreated, Visit 6 is End of Study.

3. Original text and location: Section 6.2 Rationale for the Study and Study Design

This study is a randomized, double-blind prospective, comparative study of the efficacy and safety of Revanesse Ultra versus the approved product Restylane in the cutaneous correction of nasolabial folds (NLFs). Randomization will follow a 1:1 within-subject control model of augmentation correction of NLFs. Given that the implants have been shown to not migrate, the within-subject model is ideal and has already been shown in previous studies to detect differences. Subjects with signs of NLFs who meet the entry criteria will be enrolled. All subjects will be followed for efficacy and safety for 6 months. Subjects may have open-label retreatment as needed with Revanesse Ultra at 6 months to achieve optimal correction and will be followed for a total of 12 months. The study design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used.

Revised text and location: Section 6.2 Rationale for the Study and Study Design

This study is a randomized, double-blind prospective, comparative study of the efficacy and safety of Revanesse Ultra versus the approved product Restylane in the cutaneous correction of nasolabial folds (NLFs). Randomization will follow a 1:1 within-subject control model of augmentation correction of NLFs. Given that the implants have been shown to not migrate, the within-subject model is ideal and has already been shown in previous studies to detect differences. Subjects with signs of NLFs who meet the entry criteria will be enrolled. All subjects will be followed for efficacy and safety for 6 months. **Subjects may have open-label retreatment as needed with Revanesse Ultra at 6 months if their baseline WSRS scores have returned to baseline, or as needed to achieve optimal correction if their baseline WSRS scores have not returned to baseline and will be followed for a total of 12 months.** The study design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used.

4. Original Text and Location: Section 8.1 Overall Study Design

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 (± 2 days) – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 (± 2 days) – interim visit

Visit 4/Week 4 (± 4 days) – interim visit

Visit 5/Week 12 (± 4 days) – interim visit

Visit 6/Week 24 (± 7 days) – optional open-label retreatment with Revanesse Ultra for subjects as needed to achieve optimal correction; End of Study for subjects not being retreated

Visit 7/Week 28 (± 7 days) – follow-up for retreated subjects

Visit 8/Week 52 (± 7 days) – End of Study for retreated subjects

Revised Text and Location: Section 8.1 Overall Study Design

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 (± 2 days) – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 (± 2 days) – interim visit

Visit 4/Week 4 (± 4 days) – interim visit

Visit 5/Week 12 (± 4 days) – interim visit

Visit 6/Week 24 (± 7 days) – optional open-label retreatment with Revanesse Ultra for subjects if their baseline WSRS scores have returned to baseline, or as needed to achieve optimal correction if their baseline WSRS scores have not returned to baseline; End of Study for subjects not being retreated

Visit 7/Week 28 (± 7 days) – follow-up for retreated subjects

Visit 8/Week 52 (± 7 days) – End of Study for retreated subjects

5. **Original Text and Location: Section 8.4.3 Optional Retreatment at 6 Months**

At Visit 6/Week 24, the subject may be retreated with Revanesse Ultra. Retreatment would be open-label and may be administered to both sides of the face as needed to achieve optimal correction.

Revised Text and Location: Section 8.4.3 Optional Retreatment at 6 Months

At Visit 6/Week 24, the subject may be retreated with Revanesse Ultra, **and treatment will be open-label. Subjects will be eligible for retreatment when WSRS scores have returned to baseline for either or both NLFs. If scores have not returned to baseline, subjects are also eligible to be injected for either one or both NLFs as needed to achieve optimal correction. The retreatment group and the optimal correction group will be separated for data analysis.**

6. **Original Text and Location: Section 8.7.3 Visit 6/Day 168 (week 24) Optional Retreatment**

Subjects may be retreated with Revanesse Ultra open-label on both sides of the face to achieve optimal correction (Section 8.4.3)

Revised Text and Location: Section 8.7.3 Visit 6/Day 168 (Week 24) Optional Retreatment

Subjects may be retreated with Revanesse Ultra open-label on both sides of the face **if their WSRS scores have returned to baseline or to achieve optimal correction** (Section 8.4.3)

Reason for Amendment: Previously the protocol offered subjects optional retreatment at Week 24 with Revanesse Ultra open-label in order to achieve optimal correction. This amendment will allow subjects the option to be re-treated at Week 24 with Revanesse Ultra open-label on one or both sides of the face when their WSRS scores have returned to baseline, or in order to achieve optimal correction if their NLFs have returned to their baseline score. The retreatment group and the optimal correction group will be separated for data analysis.

PROTOCOL AMENDMENT 03

The protocol amendment described herein has been incorporated in Version 4.0 Amendment 03 of Protocol No. SYM 2014-02 dated 28 OCTOBER 2015.

This Protocol Amendment has been verified and approved by:

Mr. Ario Khoshbin
Managing Director
Prollenium Medical Technologies Inc.

Date

Debra A. Dow, PharmD
Vice President, Scientific Affairs
Symbio, LLC

29Oct2015
Date

PROTOCOL AMENDMENT 03

INVESTIGATOR STATEMENT

PROTOCOL TITLE: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds

I have carefully read 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 Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted 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 drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____
Principal Investigator's Printed Name

_____
Principal Investigator's Signature

_____
Date

1 TITLE PAGE

Title:	A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds
Protocol No.:	SYM 2014-02
Sponsor:	Prollenium Medical Technologies Inc. 138 Industrial Parkway North Aurora Ontario L4G 4C3 Canada
Protocol Version:	4.0
Amendment No.:	03
Current Protocol Version Date:	28 October 2015
Previous Versions of the Protocol:	Version 1.0 dated 26 February 2015 Version 2.0 dated 05 May 2015 Version 3.0 dated 03 September 2015

2 SPONSOR/CRO SIGNATURE PAGE

PROTOCOL NUMBER: SYM 2014-02

PROTOCOL VERSION: 4.0

AMENDMENT NO.: 03

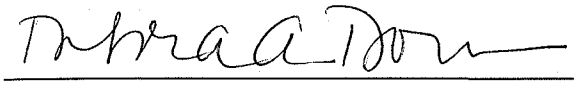
PROTOCOL DATE: 28 October 2015

PROTOCOL TITLE: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds

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

Mr. Ario Khoshbin
Managing Director
Prollenium Medical Technologies Inc.

Date



29Oct 2015

Debra A. Dow, PharmD
Vice President, Scientific Affairs
Symbio, LLC

Date

3 SYNOPSIS AND STUDY FLOW CHART

3.1 Synopsis

Title of Study: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds

Name of Sponsor: Prollenium Medical Technologies Inc.

Name of Finished Product: Revanesse® Ultra

Device Composition: Hyaluronic acid gel

Objectives: To compare the safety and efficacy profiles of Revanesse® Ultra to Restylane® for subjects undergoing correction of nasolabial folds (NLFs)

Study Design: This is a randomized, multicenter, double-blind, split-face study in subjects seeking nasolabial fold correction. Subjects will be treated with Revanesse Ultra in the NLF on one side of the face and Restylane in the NLF on the other side of the face. The side of the face for each study product will be randomly assigned. The investigator and the subject will be blinded to the treatment; injections of the study product will be performed by an unblinded injecting investigator.

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 – interim visit

Visit 4/Week 4 – interim visit

Visit 5/Week 12 – interim visit

Visit 6/Week 24 – optional open-label retreatment with Revanesse Ultra for subjects who have returned to baseline WSRS score or as needed for optimal correction if WSRS scores have not returned to baseline; End of Study for subjects not being retreated

Visit 7/Week 28 – follow-up for retreated subjects

Visit 8/Week 52 – End of Study for retreated subjects

Evaluations include:

Wrinkle Severity Rating Scale (WSRS)

Patient Global Aesthetic Improvement (pGAI)

Investigator Global Aesthetic Improvement (iGAI)

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

Other evaluations include Patient Comfort Rating (PCR) and Investigator Ease of Use Assessment.

A telephone contact will also be performed at Week 40 for subjects who have been re-treated.

Number of Study Centers: Approximately 5 sites in the United States

Duration of Participation: Subjects who are not retreated will participate in the study for approximately 24 weeks and subjects who are retreated at 24 weeks will participate in the study for approximately 52 weeks from the time they sign the informed consent form (ICF) through the final contact.

Duration of Study: The study will require approximately 24 months from the beginning to the end of the study (first subject signing the ICF to last contact with last subject).

Number of Subjects: Approximately 163 subjects will be randomized.

Inclusion Criteria

1. Men or women 22 years of age or older.
2. Two fully visible bilateral nasolabial folds each with a Wrinkle Severity Rating Scale Score of 3 or 4 that may be corrected with an injectable dermal filler.
3. If female and of childbearing potential, a negative urine pregnancy test and agree to use adequate contraception.
4. Ability to understand and comply with the requirements of the study.
5. Willingness and ability to provide written informed consent.
6. Agree to refrain from seeking other treatment for this condition during the study.

Exclusion Criteria

1. Wrinkle Severity Rating Scale Score of ≤ 2 on the right or left nasolabial fold.
2. Women who are pregnant or lactating.
3. Received prior dermabrasion, facelift, or Botox under the orbital rim within 6 months (180 days) prior to entry into the study.
4. Previous tissue augmentation (bulking agents) for facial wrinkles and scars within 6 months (180 days) at the proposed injection sites.
5. Previous tissue augmentation with permanent implants.
6. Evidence of scar-related disease or delayed healing activity within the past 1 year.
7. Scars at the intended treatment sites.
8. History of keloid formation or hypertrophic scars.
9. Any infection or wound on the face.
10. Allergic history including anaphylaxis or multiple severe allergies to natural rubber latex or lidocaine.
11. Aspirin or nonsteroidal anti-inflammatory drugs within 1 week (7 days) prior to treatment.
12. Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders or connective tissue disorders.
13. Over-the-counter (OTC) wrinkle products or prescription wrinkle treatments within 4 weeks (28 days) prior to treatment and throughout the study.
14. Immunocompromised or immunosuppressed.
15. 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.

16. Received any investigational product within 30 days.
17. Facial tattoo that may interfere with diagnosis.
18. Systemic (oral/injectable) corticosteroids or immunosuppressive medications within 30 days prior to treatment and topical steroids on the face within 14 days prior to treatment start and throughout the study.

Test product: Revanesse Ultra: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 mg/mL of stabilized hyaluronic acid.

Comparator product: Restylane: a clear, colorless gel in 1.0 mL pre-filled syringes with 20 mg/mL of stabilized hyaluronic acid.

The injection will be given intradermally and for best results should be injected in the mid-dermis.

Statistical Methods:

Sample Size Determination: Approximately 63 per-protocol (PP) subjects will supply a power of 85% with respect to change from baseline to Month 6 in WSRS score based on the following:

- The non-inferiority limit is 0.50. If the upper bound of the 95% confidence interval (CI) treatment difference (Comparator – Test) is less than 0.50 for the PP population, the Test product will be claimed to be non-inferior to the Comparator product.
- The difference between Comparator and Test (i.e., Comparator – Test) has a mean value of 0, with a standard deviation of 1.30.

A total of 163 subjects will be randomized in the study to provide adequate data for monitoring safety of the study product.

Analysis Populations:

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

Modified intent-to-treat (mITT): All randomized subjects who met the inclusion/exclusion criteria, were randomized, received both study products, and returned for at least 1 post-injection assessment of WSRS score from both sides of the face.

Per-protocol (PP): All randomized subjects who met all inclusion/exclusion criteria; received both study products; completed Visit 6/Week 24 within the specified window, had data on WSRS score from both sides of the face, and had no significant protocol violations that would affect the treatment evaluation.

Efficacy analyses will be performed on the mITT and PP populations. Safety analyses will be performed on the ITT population.

Efficacy Analysis:

The primary efficacy variable is change from Baseline to Visit 6/Week 24 in WSRS score. Summary statistics (mean, SD, minimum, median, maximum) and 95% CI will be presented for the changes scores for each treatment and for the difference in change scores between the two treatment groups (Comparator minus Test). The 95% CI for the difference between

treatments will be constructed using the paired t-test. If the upper bound of this 95% CI is less than the pre-specified non-inferiority limit (i.e. 0.50), the Test product will be claimed to be non-inferior to the Comparator product.

Secondary efficacy endpoints are the responder rate, i.e. the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, and iGAI score at Visit 6/Week 24. For these secondary variables, the null hypothesis to be tested is that there is no difference between the two products. The variables responder rate, pGAI and iGAI scores at Visit 6/Week 24 will be tabulated with frequencies and percentage and analyzed using the Wilcoxon matched-pairs signed rank test.

Other efficacy variables include change in WSRS score, pGAI, and iGAI at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12. Treatment difference with respect to these variables will be examined using descriptive summaries.

All efficacy analyses will be performed for both the PP and mITT populations. For the primary endpoint, the results from PP are considered definitive and those from mITT supportive.

Safety Analysis:

Adverse events will be coded to system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA, Version 15.1 or higher).

Frequency and percent of subjects reporting treatment-emergent adverse events (TEAEs) of injection site reactions will be tabulated for each treatment by preferred terms, and further by severity. In summaries of severity, 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.

For other AEs where an association with either treatment may not be clearly identified, including systemic TEAEs, frequency and percent of subjects will be tabulated to treated subjects as one group by preferred terms and system organ class, and further by severity and relationship to study device. In summaries of severity and relationship, subjects who reported more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship.

Adverse events will be summarized using the ITT population.

Interim Analysis: No formal interim analysis is planned.

3.2 Study Flow Chart

							Retreated Subjects Only			
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6[a]**	**Visit 7**	**Phone contact**	**Visit 8**	
Scheduled Day (Week)	**Day 1 (Week 0)**	**Day 7 (Week 1)**	**Day 14 (Week 2)**	**Day 28 (Week 4)**	**Day 84 (Week 12)**	**Day 168 (Week 24)**	**Day 196 (Week 28)**	**Day 280 (Week 40)**	**Day 364 (Week 52)**	**Unsched Visit**
Scheduling Window	**none**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
Informed consent	X									
Medical history/ demographics	X									
Physical examination (including vital signs)	X									
Concomitant Medication/ Treatment	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria review	X									
Urine pregnancy test[c]	X									
Wrinkle Severity Rating Scale (WSRS)	X	X	X	X	X	X	X		X	X[b]
Randomization	X									
Treatment with study products	X					X[a]				
Investigator Ease of Use	X									
Patient Comfort Rating (PCR)	X	X[d]								
Evaluation for touch-up		X								
Patient GAI (pGAI)		X	X	X	X	X	X		X	X[b]
Investigator GAI (iGAI)		X	X	X	X	X	X		X	X[b]
Adverse event assessment	X	X	X	X	X	X	X	X	X	X
Subject Diary	Dispense	Review/ Dispense[b]	Collect	Collect [b]		Dispense[b]	Collect[b]			
Schedule/confirm next visit	X	X	X	X	X	X[a]	X	X		X[b]

a Subjects may be retreated with open-label Revanesse Ultra if scores have returned to baseline or to achieve optimal correction if the baseline scores have not returned to baseline; for subjects who are not retreated, Visit 6 is End of Study.
b If applicable.
c For women of childbearing potential, to be completed prior to enrollment.
d For subjects who receive a touch-up treatment

4 TABLE OF CONTENTS

5 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	adverse event
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
DCF	data correction form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	hyaluronic acid
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
iGAI	Investigator Global Aesthetic Improvement
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mITT	modified intent-to-treat
NI	non-inferiority
NLF	nasolabial fold
OTC	over-the-counter
PCR	Patient Comfort Rating
pGAI	Patient Global Aesthetic Improvement
PI	principal investigator
PP	per-protocol
SAE	serious adverse event
SAR	suspected adverse reaction
SD	standard deviation

Term	Definition
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization
WSRS	Wrinkle Severity Rating Scale

6 INTRODUCTION

6.1 Background

Revanesse Ultra is a stabilized hyaluronic acid (HA) dermal filler that is commercially available in Canada and several European countries. The purpose of this study is to compare the efficacy and safety of Revanesse Ultra versus Restylane, which is also a commercially available stabilized HA dermal filler.

Details about specific benefits and risks for subjects participating in this study may be found in the Appendix (product labeling) and consent documents for this study.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

6.2 Rationale for the Study and Study Design

This study is a randomized, double-blind prospective, comparative study of the efficacy and safety of Revanesse Ultra versus the approved product Restylane in the cutaneous correction of nasolabial folds (NLFs). Randomization will follow a 1:1 within-subject control model of augmentation correction of NLFs. Given that the implants have been shown to not migrate, the within-subject model is ideal and has already been shown in previous studies to detect differences. Subjects with signs of NLFs who meet the entry criteria will be enrolled. All subjects will be followed for efficacy and safety for 6 months. Subjects may have open-label retreatment as needed with Revanesse Ultra at 6 months if their baseline WSRS scores have returned to baseline, or as needed to achieve optimal correction if their baseline WSRS scores have not returned to baseline and will be followed for a total of 12 months. The study design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used.

7 STUDY OBJECTIVES

The objectives of this study are to compare the safety and efficacy profiles of Revanesse Ultra to Restylane for subjects undergoing correction of NLFs.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design

This is a randomized, multicenter, double-blind, split-face study in subjects seeking NLF correction. Subjects will be treated with Revanesse Ultra in the NLF on one side of the face and Restylane in the NLF on the other side of the face. The side of the face for each product will be randomly assigned. The investigator performing the evaluations and the subject will be blinded to the treatment; injections of the study product will be performed by an unblinded injecting investigator.

Approximately 163 subjects will be randomized at approximately 5 study sites in the United States (US).

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:

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

Visit 2/Week 1 (± 2 days) – interim visit, touch-up if the iGAI score = 3 or 4

Visit 3/Week 2 (± 2 days) – interim visit

Visit 4/Week 4 (± 4 days) – interim visit

Visit 5/Week 12 (± 4 days) – interim visit

Visit 6/Week 24 (± 7 days) – optional open-label retreatment with Revanesse Ultra for subjects if their baseline WSRS scores have returned to baseline, or as needed to achieve optimal correction if their baseline WSRS scores have not returned to baseline; End of Study for subjects not being retreated

Visit 7/Week 28 (± 7 days) – follow-up for retreated subjects

Visit 8/Week 52 (± 7 days) – End of Study for retreated subjects

A telephone contact will also be performed at Week 40 (± 7 days) for retreated subjects to assess adverse events and concomitant medications.

Evaluations include Wrinkle Severity Rating Scale (WSRS), Patient Global Aesthetic Improvement (pGAI), and Investigator Global Aesthetic Improvement (iGAI). Safety will be assessed by monitoring adverse events (AEs) at all study visits. Other evaluations include the Patient Comfort Rating (PCR) and Investigator Ease of Use Assessment. 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 for the first 2 weeks after treatment.

8.2 Beginning and End of Study

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

A subject who is not retreated at Week 24 is considered to have completed the study after he/she has completed Visit 6/Week 24. A subject who is retreated at Week 24 is considered to have completed the study after he/she has completed Visit 8/Week 52.

A subject is considered to have withdrawn after he/she has withdrawn consent or has been withdrawn under the conditions specified in Section 8.3.3.

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 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 the subject has signed the informed consent form (ICF). 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 24 weeks (if not retreated at Week 24) or approximately 52 weeks (if retreated at Week 24) 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 Revanesse Ultra and Restylane.

It is anticipated that the duration of this study will be 24 months.

8.3 Study Population

Approximately 163 healthy males and females at least 22 years of age and with NLFs will be selected to participate in the study.

8.3.1 Inclusion Criteria

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

1. Men or women 22 years of age or older.
2. Two fully visible bilateral nasolabial folds each with a Wrinkle Severity Rating Scale Score of 3 or 4 that may be corrected with an injectable dermal filler.
3. If female and of childbearing potential, a negative urine pregnancy test and agree to use adequate contraception. Female subjects of childbearing potential (excluding women who are surgically sterilized or postmenopausal for at least 2 years) must have a negative urine pregnancy test and must be willing to use a medically accepted method of contraception 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®), intrauterine device (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.
4. Ability to understand and comply with the requirements of the study.
5. Willingness and ability to provide written informed consent.
6. Agree to refrain from seeking other treatment for this condition during the study.

8.3.2 Exclusion Criteria

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

1. Wrinkle Severity Rating Scale Score of ≤ 2 on the right or left nasolabial fold.
2. Women who are pregnant or lactating.
3. Received prior dermabrasion, facelift, or Botox below the orbital rim within 6 months (180 days) prior to entry into the study.

4. Previous tissue augmentation (bulking agents) for facial wrinkles and scars within 6 months (180 days) at the proposed injection sites.
5. Previous tissue augmentation with permanent implants.
6. Evidence of scar-related disease or delayed healing activity within the past 1 year.
7. Scars at the intended treatment sites.
8. History of keloid formation or hypertrophic scars.
9. Any infection or wound on the face.
10. Allergic history including anaphylaxis or multiple severe allergies to natural rubber latex or lidocaine.
11. Aspirin or nonsteroidal anti-inflammatory drugs within 1 week (7 days) prior to treatment.
12. Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders or connective tissue disorders.
13. Over-the-counter (OTC) wrinkle products or prescription wrinkle treatments within 4 weeks (28 days) prior to treatment and throughout the study.
14. Immunocompromised or immunosuppressed.
15. 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.
16. Received any investigational product within 30 days of signing the Informed Consent Form.
17. Facial tattoo that may interfere with diagnosis.
18. Systemic (oral/injectable) corticosteroids or immunosuppressive medications within 30 days prior to treatment and topical steroids on the face within 14 days prior to treatment start and throughout the study.

8.3.3 Subject Withdrawal Criteria

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

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

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

- The subject or legal representative withdraws consent
- The subject's product code is unblinded
- There is a significant protocol violation

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 End of Study or Early Termination procedures (Visit 6/Week 24 for subjects who are not retreated at Week 24 or Visit 8/Week 52 for subjects who are retreated at Week 24) should be completed and any outstanding data and study product should be collected. Data, including the date and primary reason for withdrawal, must be documented on the End of Study 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 8.9.5

8.3.4 Replacement of Subjects

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

8.4 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.

8.4.1 Dosage and Formulations

The test and comparator products will be provided by the sponsor as follows.

Test product: Revanesse Ultra: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 mg/mL of stabilized hyaluronic acid.

Comparator product: Restylane: a clear, colorless gel in 1.0 mL pre-filled syringes with 20 mg/mL of stabilized hyaluronic acid.

8.4.2 Method of Treatment Assignment, Randomization, and/or Stratification

Every subject will receive Revanesse Ultra on one side of the face and Restylane on the other side of the face. The side of the face treated with either product will vary from subject to subject based on the randomization assignment made at Visit 1/Day 1.

Subjects who satisfy all of the inclusion and none of the exclusion criteria will be randomized with respect to which side of the face receives which treatment. Randomization will be performed according to a computer-generated randomization scheme. The randomization scheme will be generated and maintained by an independent third party. A sealed copy of the randomization scheme should be retained at each site and should be available to regulatory authorities at the time of site inspection to allow for verification of the treatment identity for each subject.

A unique subject number will be assigned to each subject. Each site will receive a list of randomization code numbers and corresponding study product boxes. Each eligible subject will be assigned a unique randomization code number in ascending order.

No stratification based on age, sex, or other characteristics will be performed.

8.4.3 Administration of Dose for Each Subject

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

Injections of the study product are performed by the unblinded injecting investigator. The blinded evaluator is not allowed to retrieve study supplies or to be present during opening of the study supplies or during the injections. The injecting investigator is not to have any discussion with the blinded evaluator or subjects regarding the treatments.

Up to a maximum of 2.0 mL (2 pre-filled syringes) will be used per treatment on each nasolabial fold similar to the comparator agent based on previous studies and common clinical practice.

The injection will be given intradermally and for best results should be injected in the mid-dermis. The treatment technique and the volume per treatment should be as similar as possible on both sides of the face.

For many patients with moderate NLFs, one syringe will be adequate per NLF. Based on the iGAI score at that time, a touch-up treatment may be administered at Visit 2/Week 1.

For this study, topical anesthetic will not be used. Ice may be applied before the treatment if the injecting investigator deems it necessary. The same technique should be used on both sides of the face. Using the nondominant hand to apply gentle downward traction to the inferiormost aspect of the fold to immobilize it, the dominant hand is used to inject filler. Steadying the injecting hand on the mandible or the other hand, the linear threading technique is most easily used to deposit the filler beneath the fold and efface it.

The peri-alar sulcus, a triangular shaped concavity at the upper end of the fold, may be more effectively filled with the fanning technique of implantation, where two or three threads are deposited in a fan-like array. Wide portions of the fold may require several threads placed side by side, with gentle massage after each thread is placed.

Treatment of this area is generally easy and straightforward. Notice that the fold is partially formed by prominent cheek tissue that is lateral to it, with the fold becoming more prominent as the cheek becomes more protuberant. Therefore, injections should stay medial to the fold to fill it. Injecting lateral to the fold, in the excessive cheek tissue, can actually tend to accentuate the fold.

Bruising is the most common side effect in this area and usually resolves in 5 to 7 days. The facial artery runs below the fold and necrosis is possible, although rare.

Implantation Technique

After removing any make-up, the area to be treated should be cleansed with an alcohol prep pad or some other antiseptic. It is useful to avoid having the subject completely recline as the contours of some facial folds change in the supine position.

The viscosity of stabilized HA gel fillers decreases with increasing temperature. The syringe should be warmed in the hand for a few minutes prior to injection. Use the syringes labeled LEFT to treat the left NLF and the syringe labeled RIGHT to treat the right NLF.

Before injecting the subject, push the plunger forward to feel the intrinsic resistance of the filler moving through the needle, until a small droplet appears at the needle tip. Wipe off the droplet with a sterile pad and begin injection.

The linear threading technique is probably the most commonly used. Holding the syringe parallel to the length of the NLF to be treated, pierce the skin and advance the needle to its fullest extent. Then, while slowly withdrawing the needle, apply even pressure on the plunger to dispense material into dermis. Relieve pressure just before withdrawing the needle from the skin to avoid leakage. Several successive "threads" below, above, or beside previous injections may be required to fill larger folds.

Enter the skin with a needle angle of 30°, 45°, or parallel to the skin. It is recommended to keep the needle bevel up so the tip of the needle is seen and more precisely controlled where the skin is pierced. Keep the tip of the needle at constant depth during implantation, depositing all filler material within the same plane to get even results. The depth of needle placement (and thus filler implantation) should be mid-dermis for NLFs, where the needle's contour should be visible through the subject's skin, but the needle's color is not visible.

After injection, manually massage the area gently to smooth out any nodular or uneven areas, and ensure the implanted material conforms to the contour of surrounding tissues. Using an ice pack or other cold compress can help to minimize swelling and alleviate post injection discomfort.

The subject should be injected so that an optimal correction is achieved. If overcorrected, massage firmly between fingers or against underlying bone to obtain optimal results. Approximately 20% overcorrection can be massaged out; more will lead to a persistent unwanted cosmetic result.

Optional Retreatment at 6 Months

At Visit 6/Week 24, the subject may be retreated with Revanesse Ultra, and treatment will be open-label. Subjects will be eligible for retreatment when WSRS scores have returned to baseline for either or both NLFs. If scores have not returned to baseline, subjects are also eligible to be injected for either one or both NLFs as needed to achieve optimal correction. The retreatment group and the optimal correction group will be separated for data analysis.

8.4.4 Blinding of Study Product

Injections of the study product prior to Week 24 are performed by the unblinded injecting investigator. The blinded evaluator is not allowed to retrieve study supplies or to be present during opening of the study supplies or during the injections. The injecting investigator is not to have any discussion with the blinded evaluator or subjects regarding the treatments.

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

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, randomization code envelopes will be maintained by each investigator that can be opened to reveal the study product.

See Section 8.9.6.2 for a description of the method of unblinding a subject during the study if such action is warranted.

Retreatment with Revanesse Ultra at Week 24 is unblinded. Subjects being retreated do not need to be masked and retreatment may be administered by a qualified investigator or evaluator.

8.4.5 Method of Packaging, Labeling, Storage, and Dispensing

Study products will be supplied to the sites in their standard packaging. A label that includes the protocol number and Sponsor name will be attached to each pouch of the Revanesse study product. Restylane study product will be supplied by the sites for their subjects. Investigators will be instructed to follow instructions regarding storage in accordance with the product's Instructions for Use.

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

The investigator agrees to store and administer the study product 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 product will be administered only to subjects who have provided written informed consent and have met all entry criteria. Study product may not be used for any purpose other than as stated in the protocol.

8.4.6 Study Product Accountability

Study product will be available on site for each subject. Receipt of study product will be documented and confirmed via the Investigational Product Receipt Form. All study product 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 product will be recorded on the Study Product Dispensing Log. The site monitor will periodically check the supply of study product held by the investigator or pharmacist to ensure accountability. At study conclusion, all unused study 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.

8.4.7 Prior and Concomitant Medications/Treatments

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

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

8.4.7.1 Medications, Supplements, and Other Substances Prohibited Before Study Entry and During the Study

The medications prohibited prior to Visit 1/Day 1 are listed in the exclusion criteria (Section 8.3.2).

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

- Botox® in the study treatment areas
- Any chemical peel (light, medium or deep) in the study treatment areas
- Soft tissue augmentation anywhere on the face
- Dermabrasion or laser abrasion anywhere on the face
- Silicone injections or implants anywhere on the face
- Facial wrinkle therapies, including Accutane® and Renova®
- Aesthetic facial surgery (i.e., facelift)
- Oral corticosteroids or immunosuppressive medications
- Topical corticosteroids on the face

8.4.7.2 Concomitant Medications, Supplements, and Other Substances Allowed During the Study

Permitted medications/treatments include any concomitant medication/treatment not listed in the exclusion criteria (Section 8.3.2).

8.4.8 Assessment of Compliance

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

8.5 Study Schedule

The visit-by-visit schedule of study activities is provided in the Study Flow Chart in Section 3.2. The timing of each visit is relative to Day 1, which is defined as the day the subject is randomized and treated.

All visits should be performed within the windows specified on the Study Flow Chart. 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.

8.6 Study Procedures

The Study Flow Chart in Section 3.2 summarizes the study procedures to be performed at each visit. Individual study procedures are described below.

All clinical assessments (WSRS and iGAI) must be conducted by qualified investigators listed on the Form FDA 1572 who have been delegated these tasks by the principal investigator (PI). The PI may delegate this task to physicians, physician assistants, or nurse practitioners who have documented training and past experience conducting the assessment.

The WSRS and iGAI evaluations are to be performed by a research team member who does not participate in treatment and who is blinded to the treatment assignment of each NLF (blinded evaluator).

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.

8.6.1 Study Initiation

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

8.6.2 Written Informed Consent

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

8.6.3 Significant Medical History/Demographic Information

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

Table 1 Fitzpatrick Classification Scale

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

8.6.4 Physical Examination (Including Vital Signs)

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

8.6.5 Prior and Concomitant Medication/Treatment Review

Prior medications/treatments, including the necessary washout times, and concomitant medications will be reviewed with the subject. A record of prior medications/treatments taken or

used by the subject within 6 months before signing the ICF and concomitant medications/treatments will be obtained at Visit 1/Day 1. Concomitant medications or treatments will be reviewed with the subject at each study visit.

8.6.6 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.

8.6.7 Wrinkle Severity Rating Scale (WSRS)

The WSRS Score is a 5-point scale with the following categories:

1. Absent - No visible fold; continuous skin line.
2. Mild - Shallow but visible fold with a slight indentation; minor facial feature; implant is expected to produce a slight improvement in appearance.
3. Moderate - Moderately deep folds; clear facial feature visible at normal appearance but not when stretched; excellent correction is expected from injectable implant.
4. Severe - Very long and deep folds; prominent facial feature; less than 2 mm visible when stretched; significant improvement is expected from injectable implant.
5. Extreme - Extremely deep and long folds, detrimental to facial appearance; 2 to 4 mm visible V-shaped fold when stretched; unlikely to have satisfactory correction with injectable implant alone.

The WSRS score will be assessed for each NLF at every study visit through Visit 6/Week 24 (Visit 1/Day 1, Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, Visit 5/Week 12, and Visit 6/Week 24 [End of Study/Early Termination for subjects who are not retreated]) by a blinded evaluator (blinded to the treatment assignment of each NLF). For subjects who are retreated, this will also be assessed at Visit 7/Week 28 and Visit 8/Week 52 (End of Study/Early Termination) but the evaluator does not need to be blinded for those assessments.

8.6.8 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.

8.6.9 Investigator Ease of Use Assessment

The Investigator will assess overall ease of use by the device by circling the appropriate number on the Numerical Rating Scale (NRS) from 0 being not easy to 10 being most easy at Visit 1/Day 1.

8.6.10 Patient Comfort Rating (PCR)

Overall comfort will be assessed by the patient using the NRS scale from 0 being most uncomfortable to 10 being most comfortable at Visit 1/Day 1 and Visit 2/Week 1 if a touch-up treatment is administered. Subjects will be asked the question "How would you rate your comfort level upon injection of the study material?" and will respond by circling the appropriate number on the scale with 0 being most uncomfortable to 10 being most comfortable.

8.6.11 Evaluation for Touch-up

If the iGAI score = 3 or 4 at Visit 2/Week 1 a touch-up treatment will be administered.

8.6.12 Patient Global Aesthetic Improvement (pGAI) Score

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

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

The pGAI score will be assessed for each NLF at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, Visit 5/Week 12, Visit 6/Week 24 (End of Study/Early Termination for subjects who are not retreated). For subjects who are retreated, this will also be assessed at Visit 7/Week 28 and Visit 8/Week 52 (End of Study/Early Termination). Subjects will be asked the question "How would you rate improvement in your appearance compared to your initial condition using the scale below?"

8.6.13 Investigator Global Aesthetic Improvement (iGAI) Score

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

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

The iGAI score will be assessed for each NLF at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, Visit 5/Week 12, Visit 6/Week 24 (End of Study/Early Termination for subjects who are not retreated) by a blinded evaluator (blinded to the treatment assignment of each NLF). For subjects who are retreated, this will also be assessed at Visit 7/Week 28 and Visit 8/Week 52 (End of Study/Early Termination) but the evaluator does not need to be blinded for those assessments.

8.6.14 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 3/Week 2. A diary card will be dispensed at Visit 2/ Week 1 if a touch-up treatment is administered and at Visit 6/ Week 24 if retreatment is done. The diary card will be collected at Visit 4/Week 4 and Visit 7/Week 28 if applicable.

8.6.15 Adverse Events and Serious Adverse Events Assessment

See Section 8.9 for instructions on the assessment and reporting of AEs and SAEs and Section 8.9.5 for instructions on reporting SAEs to the sponsor or designee.

8.6.16 Concomitant Medication/Treatment Review

Medications, including prescription, over-the-counter, and dietary supplements taken and other treatments and cosmetic products used by the subject during the study will be reviewed at each study visit.

8.7 Visit-Specific Procedures

The following sections outline the procedures required at each visit.

8.7.1 Visit 1/Day 1: Baseline and Treatment

1. Obtain written informed consent (Section 8.6.2)
2. Obtain medical history and demographic information, including Fitzpatrick skin type classification (Section 8.6.3)
3. Perform physical examination, including height, weight, and vital signs (temperature, heart rate, blood pressure, and respiratory rate) (Section 0)
4. Obtain/record prior and concomitant medications/treatments (Section 8.6.5)
5. Perform urine pregnancy test for all women of childbearing potential (Section 8.6.6)
6. WSRS assessment (Section 8.6.7)
7. Evaluate inclusion/exclusion criteria (Section 8.3)
8. Randomization (Section 8.4.2)
9. Treatment administration (Section 8.4.3)
10. Investigator Ease of Use assessment (Section 8.6.9
11. PCR assessment (Section 8.6.10)

12. Assess AEs (Section 8.9)
13. Dispense subject diary card (Section 8.6.14)
14. Schedule next visit
15. Complete CRFs (Section 11.2.1)

8.7.2 Visit 2/Day 7 (± 2 days), Visit 3/Day 14 (± 2 days), Visit 4/Day 28 (± 4 days), and Visit 5/Day 84 (± 4 days): Interim Visits

1. WSRS assessment (Section 8.6.7)
2. At Visit 2/Day 7 only, evaluation for touch-up (Section 8.6.11)
3. PCR assessment if a touch-up treatment is administered (Section 8.6.10)
4. pGAI assessment (Section 8.6.12)
5. iGAI assessment (Section 8.6.13)
6. Assess AEs (Section 8.9)
7. Assess concomitant medications (Section 8.6.16)
8. Collect subject diary card at Visit 3/Day 14; dispense subject diary card at Visit 2/Day 7, if applicable and collect subject diary card at Visit 4/ Week 4 if applicable (Section 8.6.14)
9. Schedule next visit
10. Complete CRFs (Section 11.2.1)

8.7.3 Visit 6/Day 168 (Week 24) (± 7 days): Optional Retreatment or Final Visit/Early Termination

1. WSRS assessment (Section 8.6.7)
2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Subjects may be retreated with Revanesse Ultra open-label on both sides of the face if their WSRS scores have returned to baseline or to achieve optimal correction (Section 8.4.3)
7. Dispense subject diary card if subject was retreated (Section 8.6.14)
8. Schedule next visit for retreated subjects
9. Complete CRFs (Section 11.2.1)

8.7.4 For Retreated Subjects Only: Visit 7/Day 196 (Week 28) (± 7 days): Follow-up

1. WSRS assessment (Section 8.6.7)

2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Collect subject diary card, if applicable (Section 8.6.14)
7. Schedule next visit
8. Complete CRFs (Section 11.2.1)

8.7.5 For Retreated Subjects Only: Telephone Contact /Day 280 (Week 40) (± 7 days)

1. Assess AEs (Section 8.9)
2. Assess concomitant medications (Section 8.6.16)
3. Schedule next visit
4. Complete CRFs (Section 11.2.1)

8.7.6 For Retreated Subjects Only: Visit 8/Day 364 (Week 52) (± 7 days): Final Visit/Early Termination

1. WSRS assessment (Section 8.6.7)
2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Complete CRFs (Section 11.2.1)

8.7.7 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.

1. WSRS assessment (Section 8.6.7)
2. pGAI assessment (Section 8.6.12)
3. iGAI assessment (Section 8.6.13)
4. Assess AEs (Section 8.9)
5. Assess concomitant medications (Section 8.6.16)
6. Complete CRFs (Section 11.2.1)

8.8 Efficacy Assessments

8.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline to Visit 6/Week 24 in WSRS score. The WSRS is a validated scale (Day et al, 2004).

8.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are the responder rate, i.e., the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, and iGAI score at Visit 6/Week 24.

8.8.3 Other Efficacy Endpoints

Other efficacy endpoints include change in WSRS score, pGAI, and iGAI at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12.

8.9 Assessment of Safety

8.9.1 Safety Endpoints

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

8.9.2 Definitions of Terms

8.9.2.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related (21 Code of Federal Regulations [CFR] 312.32 (a)). 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, without any judgment about causality.

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

8.9.2.2 Suspected Adverse Reaction

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

8.9.2.3 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 products.

8.9.2.4 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
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- 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.

8.9.2.5 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.

8.9.2.6 Pregnancy

Pregnancies occurring after the administration of study product 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 Symbio 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 PI or designee must forward a follow-up Pregnancy Report with any relevant information to Symbio.

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 Symbio within 24 hours of being notified of the pregnancy report.

The subject should immediately be withdrawn from the study.

8.9.2.7 Monitoring

8.9.3 Monitoring Adverse Events and Laboratory Evaluations

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. 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 and laboratory tests will be repeated as clinically appropriate until final resolution or stabilization of the event(s).

8.9.4 Assessment of Adverse Events

8.9.4.1 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

8.9.4.2 Assessment of Causality

A medically-qualified investigator must assess the relationship of any AE (including SAEs) to the use of the study product, 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 drug, biological, or 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 drug, biological, or device cannot be excluded based on available information

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

8.9.4.3 Reference Safety Information for Assessing Expectedness of Adverse Events

The reference safety information for assessing the expectedness of an AE for the study product in this study is the Restylane package insert (2011). As reported by the subjects following injection with Restylane in 3 clinical studies, the most frequent injection-site responses were

bruising (47% to 78% of subjects by study), redness (58% to 85%), swelling (83% to 89%), pain (57% to 76%), tenderness (78% to 87%), and itching (30% to 47%).

8.9.5 Reporting Safety Observations

Any SAE, whether deemed product-related or not, must be reported to Symbio by telephone 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 fax it to Symbio along with the subject's Adverse Events Log and Concomitant Medications Log within 24 hours of notification of the event. Symbio will notify the sponsor immediately upon notification of the event from a study site to allow for reporting to the United States Food and Drug Administration (FDA) in a timely fashion. The sponsor will notify the FDA of drug-related SAEs.

Symbio contact details:

Evyan Cord-Cruz, MD Medical Monitor Direct: 516/338-0647 or 631/474-8531 ext 5126 Cell: 516/982-0677 Fax: 631/474-8534	Shanna Smith Director, Clinical Operations Direct: 631-474-8531 ext 2456 Cell: 215-817-0175	Symbio, LLC 21 Perry Street Port Jefferson, NY 11777 Tel: 631/474-8531 Fax: 631/474-8534

Sponsor contact details:

Mr. Ario Khoshbin Managing Director Prollenium Medical Technologies Inc. 138 Industrial Parkway North Aurora Ontario L4G 4C3 CANADA Tel: 905/508-1469 Fax: 905/508-6716

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 product
    f. action taken regarding study product
    g. if the AE was fatal or life-threatening:
        i. cause of death (whether or not the death was related to study product)
        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 IRB/IEC by the investigator according to IRB reporting requirements and documentation of this report sent to Symbio.

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.

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

8.9.6.1 Withdrawal

See Section 8.3.3 for the criteria for withdrawing a subject. If a subject is withdrawn from the study, the activities specified for Visit 6/Week 24 on the Study Flow Chart (Section 3.2) should be completed if possible.

8.9.6.2 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, randomization code envelopes will be maintained by each investigator that can be opened to reveal the study product.

Envelopes that have been opened at the study site must be returned to the sponsor accompanied by a written explanation of the reason why the blind was broken.

If unblinding occurs, the subject must be withdrawn from the study.

8.10 Criteria for Early Termination of the Study

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

The clinical study may be stopped if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is

unacceptable. In the event of an unanticipated serious adverse event or death, the sponsor, Prollenium Medical, will submit to the agency, and to the reviewing IRB, a report as soon as possible, but in no event later than 10 working days after the investigator / sponsor first learns of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

The following conditions are considered as cause for termination of the study:

Any death related to the study treatment

Unanticipated treatment emergent related AEs reported as severe in the opinion of the Investigator in > 7 of the subjects

Unanticipated treatment emergent related AEs reported as moderate in the opinion of the Investigator in > 43 of the subjects

Unanticipated treatment emergent related AEs reported as mild in the opinion of the Investigator and unresolved at 14 days in > 98 of the subjects

Duration of AEs lasting more than 4 weeks

Increased incidence of Physician diagnosed unexpected AEs

Increased occurrence of extreme swelling of the face, hypersensitivity reactions/anaphylaxis

Anticipated Adverse Effects: The following conditions are expected following injection, the data in the table below is the adverse effect incidence in the Restylane studies (see Restylane P020023b Table 1, Table 2). They will not be cause for early stopping of the study, unless the AE rate is deemed too high during the weekly reviews, or they are severe, or unresolved:

Condition	Anticipated rate of occurrence at 24 hours /14 days
Redness / Erythema	13.8 % / 8.7 %
Swelling and / or edema	11.6 % / 2.9 %
Ecchymosis and / or bruising	5.1 % / 2.2 %
Tenderness	15.2 % / 1.4 %

Pain	21.0 % / 0.0 %
Itching	8.0 % / 0.0 %
Other	5.1 % / 0.7 %

Unanticipated adverse events related to the injection will be evaluated as they occur by the sponsor and physician (* these may include injection site adverse events not listed above, such as Hyperpigmentation, Pruritus, Papule, Burning, Hypopigmentation, Injection Site Scab). These events will be evaluated based on their severity and duration, and if deemed necessary, the study will be stopped.

Any serious adverse event, and / or systemic response, or condition, that requires hospitalization following injection, in particular those deemed related to the injection, will be evaluated based on their severity and duration, and if deemed necessary, the study will be stopped.

All reported events will be reviewed on a weekly basis during the clinical study team meeting.

In addition, further recruitment in the study or at (a) particular site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

9 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.

9.1 Analysis Populations

Three populations are defined for the analyses.

- Intent-to-treat (ITT) (safety population): All randomized subjects who received study product.
- Modified intent-to-treat (mITT): All randomized subjects who met the inclusion/exclusion criteria, were randomized, received both study products, and returned for at least 1 post-injection assessment of WSRS score from both sides of the face.
- Per-protocol (PP): All randomized subjects who met all inclusion/exclusion criteria; received both study products; completed Visit 6/Week 24 within the specified window, had data on WSRS score from both sides of the face, and had no significant protocol violations that would affect the treatment evaluation.

Efficacy analyses will be performed on the mITT and PP populations. Safety analyses will be performed on the ITT population.

9.2 General Considerations

Two-sided hypothesis testing will be conducted for all tests. Resulting p-values less than 0.05 will be considered statistically significant unless noted otherwise. No adjustments of p-values for multiple comparisons will be made. SAS software (version 9.1.3) will be used for all data analyses and tabulations.

Missing efficacy data will be imputed via the last observation carried forward (LOCF) method in the mITT analysis. For the PP population, efficacy analysis will be performed using all the available data without imputation for the missing values.

For demographic and baseline characteristics and the safety profile, each variable will be analyzed using the existing data. Subjects with missing data will be excluded only from the analyses for which data are not available.

9.3 Comparability of Subjects at Baseline (or Demographics, Medical History, Baseline Characteristics, and Concomitant Medications)

Baseline and demographic characteristic variables (including date of birth, sex, race, ethnicity, and Fitzpatrick skin type) will be tabulated using descriptive statistics. For each continuous variable, the summary will include the mean, standard deviation, median, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages.

9.4 Efficacy Evaluations

The primary efficacy variable is change from Baseline to Week 6/Week 24 in WSRS score. Summary statistics (mean, SD, minimum, median, maximum) and 95% confidence interval (CI) will be presented for the changes scores for each treatment and for the difference in change scores between the two treatment groups (Comparator minus Test product, i.e., Restylane minus Revanesse). The 95% CI for difference between treatments will be constructed assuming a normal distribution of the change scores. If the upper bound of this 95% CI is less than the pre-specified non-inferiority (NI) limit (i.e. 0.50), the Test product will be claimed to be non-inferior to the Comparator product.

Secondary efficacy endpoints include the responder rate, i.e., the percentage of subjects with treatment success (defined as at least a 1-grade improvement in WSRS from baseline to Week 24), pGAI score at Visit 6/Week 24, and iGAI score at Visit 6/Week 24. For these secondary variables, the null hypothesis to be tested is that there is no difference between the two products. The variables responder rate, pGAI and iGAI scores at Visit 6/Week 24 will be tabulated with frequencies and percentage and analyzed using the Wilcoxon matched-pairs signed rank test.

Other efficacy variables include change in WSRS score, pGAI, and iGAI at Visit 2/Week 1, Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 12. Treatment difference with respect to these variables will be examined using descriptive summaries.

All efficacy analyses will be performed for both the PP and mITT populations. For the primary endpoint, the results from PP are considered definitive and those from mITT supportive.

9.4.1 Interim Analysis

No formal interim analysis is planned.

9.5 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 15.1 or higher).

TEAEs are defined as events that appear subsequent to the first injection or that were present prior to the first injection but worsened in intensity after the first injection. TEAEs may include, but are not limited to, injection site bruising, injection site discoloration, injection site edema, injection site erythema, injection site inflammation, injection site pain, and injection site swelling.

Frequency and percent of subjects reporting TEAEs of injection site reactions will be tabulated for each treatment by preferred terms, and further by severity. In summaries of severity, subjects who reported 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.

For other AEs where an association with either treatment may not be clearly identified, including systemic TEAEs, frequency and percent of subjects will be tabulated to treated subjects as one group by preferred terms and system organ class, and further by severity and relationship to study device. In summaries of severity and relationship, subjects who reported more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship.

Adverse events will be summarized using the ITT population.

SAEs will be discussed within the clinical study report. Data collected pertaining to SAEs will be presented in data listings.

Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary (March 2013 edition) and will be presented in data listings.

9.6 Sample Size Determination

In a previous Prollenium split-face study of Revanesse Ultra versus Restylane, following were achieved with respect to the Investigator WSRS score:

	N	**Revanesse** (Mean ± SD)	**Restylane** (Mean ± SD)
WSRS Before Injection	110	3.22 ± 0.42	3.20 ± 0.50
WSRS at Month 6	110	2.34 ± 0.79	2.41 ± 0.81

From these statistics, the difference between Revanesse and Restylane (Restylane minus Revanesse) in change from baseline WSRS to Month 6 is estimated to have a mean value of -0.095 with an approximate standard deviation (SD) of 1.30.

Therefore, about 63 per-protocol (PP) subjects will supply a power of 85% with respect to change from baseline to Month 6 in WSRS score based on the following:

- The non-inferiority limit is 0.50. If the upper bound of the 95% confidence interval (CI) treatment difference (Comparator – Test) is less than 0.50 for the PP population, the Test product will be claimed to be non-inferior to the Comparator product.

- The difference between Comparator and Test (i.e., Comparator – Test) has a mean value of 0, with a standard deviation of 1.30.

A total of 163 subjects will be enrolled into the study to provide adequate data for monitoring the safety of the study product.

10 ETHICS

10.1 Informed Consent

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

10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol and ICF must be approved in writing by an appropriate IRB/IEC 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/IEC and documentation of that approval provided to the sponsor or designee. Records of the IRB/IEC 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/IEC.

Periodic status reports must be submitted to the IRB/IEC 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/IEC must be sent to the sponsor or designee.

The investigator will ensure that an IRB/IEC 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.

10.3 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.

10.4 Study Registration

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

11 DATA HANDLING AND RECORDKEEPING

11.1 Site Regulatory Documents Required for Initiation

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

- Completed, signed Form FDA 1572
- Current curricula vitae, signed and dated, for the principal investigator (PI) and co-investigators named on Form FDA 1572
- Current license(s) of the PI and co-investigators named on Form FDA 1572
- Documentation of IRB/IEC approval of the study protocol, investigator, and ICF
- Current IRB/IEC 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

11.2 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 drug supplies, IRB/IEC, informed consent, source documents, and final signed CRFs. No documents shall be transferred from the site or destroyed without first notifying the sponsor.

11.2.1 Case Report Forms (CRFs)

CRFs for individual subjects will be provided by Symbio. 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 given 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 product shipped to the site and received and signed for by the investigator
- Study Product Dispensing Log, which will list the lot number and total amount of study product used for each NLF for each subject
- ICF which must be available for each subject and be verified for proper documentation
- All correspondence

11.2.2 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 diagnosis/condition 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 sources of data.

11.3 Study Monitoring

Symbio 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.

11.4 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.

11.5 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/IEC prior to implementation. The only circumstance in which an amendment may be initiated without prior IRB/IEC 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/IEC within 5 working days after implementation.

11.6 Completion of the Study

The investigator is required to forward CRFs and all other relevant data and records to Symbio. 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.

12 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 product. 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).

13 LIST OF REFERENCES

Day DJ , Littler CM, Swift RW, Gottlieb S. The wrinkle severity rating scale: a validation study. Am J Clin Dermatol. 2004;5(1):49-52.

FDA. Draft guidance for industry: non-inferiority clinical trials. March 2010. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf

Restylane [package insert]. Scottsdale, AZ: Medicis Aesthetics Inc.; 2011.

14 INVESTIGATOR AGREEMENT

Protocol Number: **SYM 2014-02**

Protocol Title: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus Restylane® for the Correction of Nasolabial Folds

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 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 drugs under investigation in this study. 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 drug and conduct of the study. I agree to keep records on all subject information (case report forms, shipment and drug return forms, and all other information collected during the study) and drug 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

15 APPENDICES

15.1 Package Insert for Revanesse Ultra

Revanesse® Ultra
Cross Linked Hyaluronic Acid – High Viscosity

GB

COMPOSITION

Cross-linked hyaluronic acid (High Viscosity) 25mg/ml
In phosphate buffered saline
[Cross linked with Butandiol-diglycidylether (BDDE)]

DESCRIPTION

Revanesse® Ultra is a colorless, odorless, transparent and aqueous gel of synthetic origin. The gel is stored in a pre-filled disposable syringe. Each box contains two 1ml syringes of Revanesse® Ultra along with two sterilized needles.

APPLICATION RANGE / INDICATIONS

Revanesse® Ultra is a cross linked hyaluronic acid gel that is indicated for the filling of medium size and deep wrinkles of the face by injection into the middle part of the dermis layer. Implantation life is dependent on depth and location and averages 6-12 months.

ANTICIPATED SIDE EFFECTS

Physicians must inform patients that with every injection of Revanesse® Ultra there are potential adverse reactions that may be delayed or occur immediately after the injection. These include but are not limited to:

- Injection-related reactions might occur, such as transient erythema, swelling, pain, itching, discoloration or tenderness at the injection site. These reactions may last for one week.
- Nodules or induration are also possible at the injection site.
- Poor product performance due to improper injection technique.
- Glabellar necrosis, abscess formation, granulomas and hypersensitivity have all been reported with injections of hyaluronic acid products. It is important for physicians to take these reactions into account on a case by case basis.

Reactions thought to be of hypersensitivity in nature have been reported in less than one in every 1500 treatments. These have consisted of prolonged erythema, swelling and induration at the implant site.

These reactions have started either shortly after injection or after a delay of 2 – 4 weeks and have been described as mild or moderate, with an average duration of 2 weeks. Typically, this reaction is self-limiting and resolves spontaneously with time. However, it is imperative that patients with hypersensitivity type reactions contact their physician immediately for assessment. Patients with multiple allergic reactions should be excluded from the treatment.

CONTRAINDICATIONS

- Do not inject Revanesse® Ultra into eye contours (into the eye circle or eyelids).
- Pregnant women, or women during lactation should not be treated with Revanesse® Ultra.
- Revanesse® Ultra is only intended for intradermal use and must not be injected into blood vessels. This may occlude and could cause an embolism.
- Patients who develop hypertrophic scarring should not be treated with Revanesse® Ultra.
- Contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- Never use Revanesse® Ultra in conjuction with a laser, intense pulsed light, chemical peeling or dermabrasion treatments.
- People under the age of 18 should not be treated with Revanesse® Ultra.
- Patients with acne and / or other inflammatory diseases of the skin should not be treated with Revanesse® Ultra.
- Patients with unattainable expectations.
- Patients with auto-immune disorders or under immunotherapy.
- Patients with multiple severe allergies.
- Patients with acute or chronic skin disease in or near the injection sites.
- Coagulation defects or under anti-coagulation therapy.
- Patients with sensitivity to hyaluronic acid.

It is imperative that patients with adverse inflammatory reactions that persist for more than one week report this immediately to their physician. These conditions should be treated as appropriate (ie: corticosteroids or antibiotics). All other types of adverse reactions should be reported directly to the authorized distributor of the Revanesse® family of products and / or to Prollenium Medical Technologies Inc. directly.

ADMINISTRATION & DOSAGE

- Revanesse® Ultra should only be injected by or under the direct supervision of qualified physicians who have been trained on the proper injection technique for filling facial wrinkles.
- Before patients are treated they should be informed of the indications of the device as well as its contraindications and potential undesirable side effects.
- The area to be treated must be thoroughly disinfected. Be sure to inject only under sterile conditions.
- Revanesse® Ultra and needles packaged with it are for single use only. Do not re-use. If re-used, there is a risk of infection or transmission of blood born diseases.
- Keep the product at room temperature for 30 minutes prior to injection.
- The amount of Revanesse® Ultra that is injected will depend on the severity of the depression or the level of correction desired.
- If the skin turns a white color (blanching), the injection should be stopped immediately and the area should be massaged until the skin returns to its normal color.
- Before injecting, press on the plunger of the syringe until a small drop is visible at the tip of the needle.

PRECAUTIONS

- Revanesse® Ultra should not be injected into an area that already contains another filler product as there is no available clinical data on possible reactions.
- Revanesse® Ultra should not be injected into an area where there is a permanent filler or implant.
- Hyaluronic acid products have a known incompatibility with quaternary ammonium salts such as benzalkonium chloride. Please ensure that Revanesse® Ultra never comes into contact with this substance or medical instrumentation that has come into contact with this substance.
- Revanesse® Ultra should never be used for breast enlargement, or for implantation into bone, tendon, ligament or muscle.
- Avoid touching the treated area for 12 hours after injection and avoid prolonged exposure to sunlight, UV, as well as extreme cold and heat.
- Until the initial swelling and redness have resolved, do not expose the treated area to intense heat (e.g. solarium and sunbathing) or extreme cold.
- If you have previously suffered from facial cold sores, there is a risk that the needle punctures could contribute to another eruption of cold sores.
- If you are using aspirin, non-steroidal anti-inflammatory medications, St. John's Wort of High doses of Vitamin E supplements prior to treatment" or any similar medications be aware that these may increase bruising and bleeding at the injection site.

WARNINGS

Confirm that the seal on the box has not been broken and sterility has not been compromised. Confirm that the product has not expired. Product is for single use only; do not re-use. If re-used, there is a risk of infection or transmission of blood born diseases.

SHELF LIFE & STORAGE

Expiry is indicated on each individual package. Store between 2°-25° C, and protect from direct sun light and freezing.

NOTE: The correct injection technique is crucial to treatment success & patient satisfaction. Revanesse® Ultra should only be injected by a practitioner qualified according to local laws and standards.

The graduation on the syringe is not precise and should be used as a guide only. The amount of material to be injected is best determined by visual and tactile assessment by the user.

MANUFACTURER

Prollenium Medical Technologies, Inc.
138 Industrial Parkway North, Aurora, ON
L4G 4C3, Canada

EC REP	Authorized representative in Europe Emergo Europe Molenstraat 15 2513 BH, The Hague The Netherland Tel: (+31) 70 345 8570 FAX: (+31) 70 346 7299	STERILE	Syringe fluid path sterilized using moist heat
	Read instruction/product insert before use	LOT	Lot number/batch number
	Expiry date	2°C 25°C	Storage temperature (store between the temperatures of)
	Do not re-use		Manufacturing date
STERILE R	Sterilized Using Radiation (Needles)		Manufacturer
	Do not use if the package has been damaged		Keep package dry
	Protect from sunlight		

PN 13505 RV 04

15.2 Package Insert for Restylane

Restylane® **Printer-Friendly Version***

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

Description

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

Indication

Restylane is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Restylane is indicated for submucosal implantation for lip augmentation in patients over the age of 21.

Contraindications

- *Restylane* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane* contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *Restylane* is contraindicated for patients with bleeding disorders.
- *Restylane* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.

Warnings

- Defer use of *Restylane* 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., swelling, redness, tenderness, or pain) to *Restylane* have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 7 days duration in the nasolabial folds and less than 14 days duration in the lips. Rare post-market reports of immediate post-injection reactions included extreme swelling of lips, the whole face and symptoms of hypersensitivity such as anaphylactic shock.
- *Restylane* 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 greater than 1.5 mL per lip (upper or lower) per treatment session significantly increases the occurrence of the total of moderate and severe injection site reactions. If a volume of more than 3 mL is needed to achieve optimal correction, a follow-up treatment session is recommended.
- In a meta-analysis of all *Restylane* Premarket Approval Studies (that included 42 patients under the age of 36 and 820 patients over the age of 35), the incidence of swelling was higher in younger patients (28%) compared to older patients (18%) and incidence of contusion was higher in older patients (28%) compared to younger patients (14%). The majority of these events were mild in severity.

Precautions

- *Restylane* is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Based on U.S. clinical studies, patients should be limited to 6.0 mL per patient per treatment in wrinkles and folds such as the nasolabial folds and to 1.5 mL per lip per treatment. The safety of injecting greater amounts has not been established.
- The safety or effectiveness of *Restylane* for the treatment of anatomic regions other than nasolabial folds or lips has not been established in controlled clinical studies.
- The safety and efficacy of *Restylane* for lip augmentation has not been established in patients under the age of 21 years.
- As with all transcutaneous procedures, *Restylane* implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of *Restylane* for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- Formation of keloids may occur after dermal filler injections including *Restylane*. Keloid formation was not observed in studies involving 430 patients (including 151 African-Americans and 37 other patients of Fitzpatrick Skin Types IV, V and VI). For additional information please refer to Studies MA-1400-02, MA-1400-01, and 31GE0003 in the Clinical Trials Section.
- *Restylane* injection may cause hyperpigmentation at the injection site. In a clinical study of 150 subjects with pigmented skin (of African-American heritage and Fitzpatrick Skin Types IV, V, and VI), the incidence of post-inflammatory hyperpigmentation was 9% (14/150). 50% of these events lasted up to six weeks after initial implantation.
- The safety profile for *Restylane* lip augmentation in persons of color is based upon information from 38 and 3 subjects with Fitzpatrick Skin Types IV and V, respectively. Within this population, the incidence of adverse events was similar to the overall study population, with the exception that swelling occurred more frequently in persons of color.
- *Restylane* should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *Restylane* injection sites. *Restylane* should be used with caution in patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the preceding 3 weeks.
- 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 *Restylane* with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least until any initial swelling and redness has resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Restylane*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane* is administered before the skin has healed completely after such a procedure.
- Injection of *Restylane* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *Restylane* is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe and notify Medicis Aesthetics Inc. at 1-800-555-5115. Glass is subject to breakage under a variety of unavoidable conditions. Care should be taken with the handling of the glass syringe and with disposing of broken glass to avoid laceration or other injury.
- *Restylane* should not be mixed with other products before implantation of the device.

Adverse Experiences

There were six U.S. studies that reported adverse experiences. Four of the six studies were conducted in support of the indication of mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and two of the six studies were conducted in support of the indication of submucosal implantation for lip augmentation.

Studies conducted in moderate to severe facial wrinkles and folds, such as nasolabial folds

Three U.S. studies (i.e., Study 31GE0003, MA-1400-01, and Study MA-1400-02) involved 430 patients at 33 centers. In study 31GE0003, 138 patients at 6 centers received *Restylane* injections in 1 side of the face and a bovine collagen dermal filler (Zyplast®) in the other side of the face. In Study MA-1400-01, 150 patients were injected with *Restylane* on one side of the face and *Perlane®* on the other side of the face. In study MA-1400-02, 283 patients were randomized to receive either *Restylane* or *Perlane* injection on both sides of the face. The adverse outcomes reported in patient diaries during 14 days after treatment in these studies are presented in Tables 1–6. The physician diagnosed adverse events identified in studies MA-1400-01 and MA-1400-02 at 72 hours after injection are presented in Table 7. Table 8 presents all investigator-identified adverse experiences recorded at study visits 2 weeks or more after injection in studies MA-1400-01, MA-1400-02, and 31GE0003.

In the fourth U.S. study (MA-004-03) involving 75 patients at 3 centers, adverse events reported by *Restylane* patients are presented in Table 9. Patients in the study received *Restylane* injections in both nasolabial folds at baseline, a second treatment in one nasolabial fold at 4.5 months and in the contralateral nasolabial fold at 9 months.

Table 7 shows the number of adverse experiences identified by investigators at 72 hours after injection for Studies MA-1400-01 and MA-1400-02. Some patients had multiple adverse experiences or had the same adverse experience at multiple injection sites. No adverse experiences were of severe intensity.

Table 8 presents the number of patients and per patient incidence of all adverse experiences identified by investigators at visits occurring two or more weeks after injection.

In a clinical study (31GE0003) in which safety was followed for 12 months with repeat administration of *Restylane* at six to nine months following the initial correction, the incidence and severity of adverse experiences were similar in nature and duration to those recorded during the initial treatment sessions.

In all three studies, investigators reported the following local and systemic events that were judged unrelated to treatment and occurred at an overall incidence of less than 2%, i.e., acne; arthralgia; tooth disorders (e.g., pain, infection, abscess, fracture); dermatitis (e.g., rosacea, unspecified, contact, impetigo, herpetic); unrelated injection site reactions (e.g., desquamation, rash, anesthesia); facial palsy with co-administration of botulinum toxin; headache/migraine; nausea (with or without vomiting); syncope; gastroenteritis; upper respiratory or influenza-like illness; bronchitis; sinusitis; pharyngitis; otitis; viral infection; cystitis; diverticulitis; injuries; lacerations; back pain; rheumatoid arthritis; and various medical conditions such as chest pain, depression, pneumonia, renal stones, urinary incontinence, and uterine fibroids.

Table 9 presents the number of patients and per patient incidence and severity of injection site adverse events identified by the investigator.

Two subjects had adverse events that were severe, one subject with bilateral facial bruising and one subject with infection at the injection site. These events were considered probably or possibly related and both subjects had their events resolve in approximately 3 weeks.

Studies conducted for submucosal implantation for lip augmentation

In the U.S. pivotal study (MA-1300-15) involving 180 subjects at 12 centers, the adverse outcomes reported in subject diaries are presented in Tables 10 and 11. Physician reported treatment emergent adverse events are presented in Table 12. At baseline, subjects were randomized to receive *Restylane* injections in the lips or no treatment (control group). At 6 months, all subjects were eligible to receive treatment or re-treatment in the lips with *Restylane*.

Of the 180 subjects enrolled in the study, 172 subjects received their first treatment with *Restylane* at either baseline/Day 0 or at 6 months, and 93 subjects received a second treatment at 6 months. There were 8 subjects enrolled in the study that were never treated. The number of events and subjects reporting TEAEs decreased between the first and second treatments. 87% of subjects receiving their first treatment reported a total of 795 TEAEs while 65% of subjects that received a second treatment reported a total of 267 TEAEs. Furthermore, an overwhelming majority of these TEAEs were mild in intensity (872/795, 85%; and 264/267, 99%; first and second treatment respectively), and were transient in nature, resolving in approximately 15 days or less.

The study results showed injection of greater than 1.5 mL per lip (upper or lower), per treatment session increased the occurrence of the total of moderate and severe injection site reactions. The incidence was 43% (33/76) for subjects receiving more than 3.0 mL of *Restylane* and 21% (20/96) for subjects receiving less than 3.0 mL of *Restylane* in a single treatment session. When optimal correction requires greater than 1.5 mL per upper or lower lip, subsequent treatment using additional product is recommended.

97% of the subjects reported at least one event of swelling, redness, tenderness, or pain in their diaries. These were mainly short-term events, which occurred immediately after treatment and resolved within 14 days. 15% of the subjects reported adverse events (typically swelling and tenderness) that lasted longer than 15 days in their diary. 46% of subjects reported at least one event as "affecting their daily activity" or "disabling."

Additional safety assessments in the study included lip texture, firmness, symmetry, movement, function, sensation, mass formation, and product palpability, which were evaluated as appropriate at the screening visits and at follow-up visits.

The majority of texture and firmness assessments showed mild abnormalities and lasted for less than 4 weeks. Sixteen subjects reported severe asymmetry (difference > 2mm) post-treatment, which all resolved within 4 weeks. GAIS assessments by these 16 subjects were rated as at least improved during those visits.

Assessments made by the trained health care provider showed 92% of subjects had product palpability at week 8, and 61% at week 24. The majority of palpations were rated as "expected feel." 3% of the subjects reported "unexpected feel" during the study, all of which were resolved with massaging.

One subject reported one mass formation (mucocele) during the study. The mucocele was drained and resolved by the next visit.

All other lip safety assessments showed no remarkable findings.

In the pilot study MA-1300-13K, 20 subjects were enrolled at 1 center and received *Restylane* for lip augmentation. Subjects were followed up through 24 weeks. Seven adverse events were reported. Two of the seven events, which were mild bruising, were related to injection procedure. The adverse outcomes reported in subject diaries are presented in Table 13.

Table 12 presents commonly reported (≥ 5%) treatment emergent adverse events (TEAEs) by treatment group.

For study MA-1300-13K, seven treatment emergent adverse events were experienced by four subjects. Two of these events, mild bruising, were considered related to treatment.

Post-Marketing Surveillance

The following adverse events were received from post-marketing surveillance for *Restylane* and *Perlane* in the U.S. and other countries: presumptive bacterial infections, inflammatory adverse events, necrosis, injection site numbness/tingling, and vasovagal reactions. Reported treatments have included systemic steroids, systemic antibiotics, and intravenous administrations of medications. Additionally, delayed inflammatory reaction to *Restylane* has been observed with swelling, redness, tenderness, induration and rarely acneiform papules at the injection site with onset as long as several weeks after the initial treatment. Average duration of these effects is two weeks.

Implant and injection site reactions, mostly non-serious events, have also been reported. These include: discoloration, bruising, swelling, mass formation, erythema, pain, scarring and ischemia. Most instances of discoloration including hyperpigmentation, sometimes described as a blue or brown color and ranging from mild to severe, have occurred within the same day as treatment but have also occurred up to 6 months post-treatment. These events typically resolve within a few days but with some infrequent instances lasting up to 18 months. Implant and/or injection site bruising, swelling, erythema and pain generally occurred on the same day as treatment usually resolving within 1 to 4 weeks. Some occurrences have persisted for up to 6 months. Severity for these events is generally mild to moderate although some cases have been severe. Mild to moderate mass formations (typically described as lumps or bumps) have also been seen ranging in onset from 1 day to 6 months post-implantation. Rarely, events of this type have been observed for up to 13 months. These events usually resolved within 1 to 5 months. Mild to moderate scarring was rarely observed. Onset of symptoms ranged from immediate post-treatment to up to 1 year following implantation. Symptom resolution was approximately 3 weeks with 1 instance lasting up to 3 years. Most ischemic events have occurred immediately following implantation and ranged in severity from moderate to severe. Events were resolving as early as 2 days and up to 9 weeks post-treatment.

Symptoms associated with herpetic eruptions which included swelling, pain, whiteheads, vesicles and erythema have been reported and commonly occurred within 2 days to 1 month following implantation. Severity ranged from mild to moderate and resolution of symptoms ranged from 1 to 15 weeks.

Telangiectasias and capillary disorders, commonly characterized as broken capillaries, have been reported and occurred with an onset of 1 day to 7 weeks. Most events ranged in severity from mild to moderate with a few severe instances. Duration of events ranged from 2 weeks up to 13 months.

Very rarely, instances of moderate to severe biopsy confirmed granuloma were observed. Onset ranged from 3 weeks to 4 months with resolution between 6 weeks to 11 months.

Events of mild to moderate hypoaesthesia have occurred ranging in onset from 1 day to 1 week. Duration and resolution occurred between 1 day and 10 weeks.

Serious adverse events have been rarely reported. The most commonly reported serious adverse events (by MedDRA Preferred Term) were hypersensitivity, and implant and/or injection site swelling, ischemia and discoloration. Of these infrequently reported serious events, only the following occurred in a frequency of 5 or greater:

- Hypersensitivity reactions ranging from moderate to severe mostly occurred within 1 to 2 days of implantation and up to 3 weeks. Reported symptoms included swelling; itching on chest and back; puffy, burning, watery, and itchy eyes; and shortness of breath. Treatments included steroids, diphenhydramine, unspecified intravenous medication, oxygen and various creams. An evaluation of patients who reported potential hypersensitivity reactions did not demonstrate any evidence of IgE or cell mediated immunologic reactions specifically directed at hyaluronic acid. Most hypersensitivity events resolved within 1 to 14 days with or without treatment.
- *Allergic reaction and anaphylactic shock*: Eight patients experienced immediate post-injection reactions which included extreme swelling of lips and the whole face. Two of these patients had symptoms of hypersensitivity and one patient experienced anaphylactic shock and presented with shortness of breath, headache, nausea and vomiting. These patients had to be admitted to the emergency room or were hospitalized for immediate medical interventions. *Delayed hypersensitivity*: Two patients developed symptoms of hypersensitivity 7–10 days after injection. One patient experienced severe erythema and swelling in the lips and all over her face to the point that her eyes were shut and the other had swelling of the lips accompanied by dyspnea, lymphadenopathy, peripheral and laryngeal edema.
- *Vascular accidents and necrosis*: In 5 patients, skin discoloration, bruising, and blanching was seen immediately post-injection due to vascular accidents. The lesions later turned into necrosis and in some cases remained as scarring or dark spots. One example was a patient who had a "mustache-like" mark above her lips, even after receiving treatments. Later, one patient in this group developed hard bumps in her upper lips that looked like "granulomas."

- *Infection/Abscess:* Serious abscess formations ranging from moderate to severe occurred in eleven patients. Onset ranged from 3 days to one week with an average duration of approximately one month to resolution. Symptoms included swelling, redness, pain and hard nodules. Five patients required hospitalization for incision and drainage (I&D) and intravenous (IV) antibiotic therapy. Cultures for all patients ranged from gram positive staphylococcal, gram negative cellulitis, spathogen streptococci, gram positive cocci infection, polymorphonuclear neutrophils (PMN) with no bacteria and positive proprionibacterium malassezia. The remaining cultures were either negative or not reported. Treatment included various antibiotics and steroids in some cases.

The following non-serious events, extrusion of device, ischemia/necrosis, and device dislocation, were also reported in a frequency of 5 or more. These events were considered non-serious as they did not meet seriousness criteria.

Adverse reactions should be reported to Medicis Aesthetics Inc. at 1-866-222-1480.

Clinical Trials

The safety and effectiveness of *Restylane* in the treatment of facial folds and wrinkles (nasolabial folds and oral commissures) were evaluated in three prospective randomized controlled clinical studies involving 430 *Restylane*-treated subjects.

Restylane was shown to be effective when compared to crosslinked collagen and crosslinked hyaluronic acid dermal fillers with respect to the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

Table 1. Maximum Intensity of Symptoms after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study 31GE0003)[1]

	Restylane side	Zyplast side	*Restylane* side				Zyplast side			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Bruising	72 (52.2%)	67 (48.6%)	63 (45.6%)	32 (23.2%)	35 (25.4%)	5 (3.6%)	68 (49.3%)	43 (31.2%)	23 (16.7%)	1 (0.7%)
Redness	117 (84.8%)	117 (84.8%)	17 (12.3%)	56 (40.6%)	54 (39.1%)	7 (5.1%)	17 (12.3%)	72 (52.2%)	37 (26.8%)	8 (5.8%)
Swelling	120 (87.0%)	102 (73.9%)	14 (10.1%)	54 (39.1%)	61 (44.2%)	5 (3.6%)	32 (23.2%)	65 (47.1%)	35 (25.4%)	2 (1.4%)
Pain	79 (57.2%)	58 (42.0%)	55 (39.9%)	40 (29.0%)	34 (24.6%)	5 (3.6%)	76 (55.1%)	46 (33.3%)	10 (7.2%)	2 (1.4%)
Tenderness	107 (77.5%)	89 (64.5%)	27 (19.6%)	60 (43.5%)	43 (31.2%)	4 (2.9%)	45 (32.6%)	70 (50.7%)	17 (12.3%)	2 (1.4%)
Itching	42 (30.4%)	33 (23.9%)	91 (65.9%)	31 (22.5%)	11 (8.0%)	0 (0.0%)	101 (73.2%)	27 (19.6%)	6 (4.4%)	0 (0.0%)
Other	34 (24.6%)	33 (23.9%)	93 (67.4%)	14 (10.1%)	15 (10.9%)	5 (3.6%)	94 (68.1%)	20 (14.5%)	10 (7.2%)	3 (2.2%)

[1] Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.

Table 2. Duration of Adverse Events after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study 31GE0003)

	Restylane side	Zyplast side	*Restylane* side				Zyplast side			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	Number of days				Number of days			
			1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	72 (52.2%)	67 (48.6%)	7 (5.1%)	56 (40.6%)	6 (4.4%)	3 (2.2%)	7 (5.1%)	53 (38.4%)	5 (3.6%)	2 (1.4%)
Redness	117 (84.8%)	117 (84.8%)	19 (13.8%)	68 (49.3%)	18 (13.0%)	12 (8.7%)	19 (13.8%)	71 (51.4%)	15 (10.9%)	12 (8.7%)
Swelling	120 (87.0%)	102 (73.9%)	16 (11.6%)	84 (60.9%)	16 (11.6%)	4 (2.9%)	14 (10.1%)	70 (50.7%)	16 (11.6%)	2 (1.4%)
Pain	79 (57.2%)	58 (42.0%)	29 (21.0%)	48 (34.8%)	2 (1.4%)	0 (0.0%)	31 (22.5%)	25 (18.1%)	1 (0.7%)	1 (0.7%)
Tenderness	107 (77.5%)	89 (64.5%)	21 (15.2%)	78 (56.5%)	6 (4.4%)	2 (1.4%)	27 (19.6%)	54 (39.1%)	6 (4.4%)	2 (1.4%)
Itching	42 (30.4%)	33 (23.9%)	11 (8.0%)	25 (18.1%)	6 (4.4%)	0 (0.0%)	8 (5.8%)	22 (15.9%)	3 (2.2%)	0 (0.0%)
Other	34 (24.6%)	33 (23.9%)	7 (5.1%)	23 (16.7%)	3 (2.2%)	1 (0.7%)	10 (7.2%)	15 (10.9%)	6 (4.4%)	2 (1.4%)

Table 3. Maximum Intensity of Symptoms after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-02)[1]

	Restylane	*Perlane*	*Restylane* Patients				*Perlane* Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Tolerable[2] n (%)	Affected Daily Activity[2] n (%)	Disabling[2] n (%)	None n (%)	Tolerable[2] n (%)	Affected Daily Activity[2] n (%)	Disabling[2] n (%)
Bruising	111 (78.2%)	122 (86.5%)	28 (20.1%)	82 (59%)	28 (20.1%)	1 (0.7%)	17 (12.2%)	97 (69.8%)	24 (17.3%)	1 (0.7%)
Redness	114 (80.3%)	118 (83.7%)	25 (18%)	96 (69.1%)	17 (12.2%)	1 (0.7%)	21 (15.1%)	105 (75.5%)	12 (8.6%)	1 (0.7%)
Swelling	127 (89.4%)	128 (90.8%)	12 (8.6%)	102 (73.4%)	23 (16.5%)	2 (1.4%)	11 (7.9%)	107 (77%)	19 (13.7%)	2 (1.4%)
Pain	108 (76.1%)	114 (80.9%)	31 (22.3%)	93 (66.9%)	14 (10.1%)	1 (0.7%)	25 (18%)	96 (69.1%)	18 (12.9%)	0 (0%)
Tenderness	123 (86.6%)	130 (92.2%)	16 (11.5%)	109 (78.4%)	12 (8.6%)	2 (1.4%)	9 (6.5%)	112 (80.6%)	18 (12.9%)	0 (0%)
Itching	67 (47.2%)	45 (31.9%)	72 (51.8%)	66 (47.5%)	1 (0.7%)	0 (0%)	94 (67.6%)	40 (28.8%)	3 (2.2%)	2 (1.4%)
Other[3]	3 (2.1%)	1 (0.7%)	NA	NA	NA	NA	NA	NA	NA	NA

[1] Missing values are not reported.
[2] Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[3] Two patients reported pimples (one *Perlane*/one *Restylane*); one *Restylane* patient reported a sore throat; one *Restylane* patient reported a runny nose; degree of disability was not reported for any of the four events.

Table 4. Duration of Adverse Events after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-02)[1]

	Restylane Patients	*Perlane* Patients	*Restylane* Patients				*Perlane* Patients			
			Number of days[2]				Number of days[2]			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	111 (78.2%)	122 (86.5%)	9 (8.1%)	69 (62.2%)	30 (27%)	3 (2.7%)	6 (4.9%)	81 (66.4%)	28 (23%)	7 (5.7%)
Redness	114 (80.3%)	118 (83.7%)	31 (27.2%)	71 (62.3%)	9 (7.9%)	3 (2.6%)	19 (16.1%)	87 (73.7%)	8 (6.8%)	4 (3.4%)
Swelling	127 (89.4%)	128 (90.8%)	12 (9.4%)	93 (73.2%)	19 (15.0%)	3 (2.4%)	6 (4.7%)	100 (78.1%)	17 (13.3%)	5 (3.9%)
Pain	108 (76.1%)	114 (80.9%)	37 (34.3%)	69 (63.9%)	2 (1.9%)	0 (0%)	46 (40.4%)	66 (57.9%)	2 (1.8%)	0 (0%)
Tenderness	123 (86.6%)	130 (92.2%)	21 (17.1%)	92 (74.8%)	9 (7.3%)	1 (0.8%)	24 (18.5%)	89 (68.5%)	16 (12.3%)	1 (0.8%)
Itching	67 (47.2%)	45 (31.9%)	22 (32.8%)	38 (56.7%)	6 (9.0%)	1 (1.5%)	19 (42.2%)	23 (51.1%)	3 (6.7%)	0 (0%)
Other[3]	3 (2.1%)	1 (0.7%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)

[1] Missing values are not reported.
[2] Data are cumulated from up to four injection sites per patient with earliest and latest time point for any reaction provided.
[3] Two patients reported pimples (one Perlane/one Restylane); one Restylane patient reported a sore throat; one Restylane patient reported a runny nose; degree of disability was not reported for any of the four events.

Table 5. Maximum Intensity of Symptoms after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-01)[1,2]

	Restylane	*Perlane*	*Restylane* Patients				*Perlane* Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Tolerable[3] n (%)	Affected Daily Activity[3] n (%)	Disabling[3] n (%)	None n (%)	Tolerable[3] n (%)	Affected Daily Activity[3] n (%)	Disabling[3] n (%)
Bruising	70 (46.7%)	74 (49.3%)	79 (53%)	66 (44.3%)	4 (2.7%)	0 (0%)	75 (50.3%)	67 (45%)	7 (4.7%)	0 (0%)
Redness	87 (58%)	92 (61.3%)	62 (41.6%)	81 (54.4%)	6 (4%)	0 (0%)	57 (38.3%)	85 (57%)	7 (4.7%)	0 (0%)
Swelling	125 (83.3%)	121 (80.7%)	24 (16.1%)	109 (73.2%)	14 (9.4%)	2 (1.3%)	28 (18.8%)	108 (72.5%)	11 (7.4%)	2 (1.3%)
Pain	96 (64%)	103 (68.7%)	53 (35.6%)	84 (56.4%)	11 (7.4%)	1 (0.7%)	46 (30.9%)	90 (60.4%)	12 (8.1%)	1 (0.7%)
Tenderness	122 (81.3%)	130 (86.7%)	27 (18.1%)	110 (73.8%)	11 (7.4%)	1 (0.7%)	19 (12.8%)	116 (77.9%)	13 (8.7%)	1 (0.7%)
Itching	53 (35.3%)	58 (38.7%)	96 (64.4%)	49 (32.9%)	4 (2.7%)	0 (0%)	91 (61.1%)	54 (36.2%)	4 (2.7%)	0 (0%)
Other[4]	3 (2%)	3 (2%)	NA	3 (100%)	0 (%)	0 (%)	NA	3 (100%)	0 (%)	0 (%)

[1] Missing values are not reported.
[2] Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.
[3] Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[4] Two patients reported mild transient headache and one patient reported mild "twitching"; neither could be associated with a particular product.

Table 6. Duration of Adverse Events after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-01)[1,2]

	Restylane Patients	*Perlane* Patients	*Restylane* Patients				*Perlane* Patients			
			Number of days[3]				Number of days[3]			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	70 (46.7%)	74 (49.3%)	13 (18.6%)	51 (72.9%)	6 (8.6%)	0 (0%)	23 (31.1%)	44 (59.5%)	6 (8.1%)	1 (1.4%)
Redness	87 (58%)	92 (61.3%)	33 (37.9%)	52 (59.8%)	2 (2.3%)	0 (0%)	38 (41.3%)	52 (56.5%)	2 (2.2%)	0 (0%)
Swelling	125 (83.3%)	121 (80.7%)	23 (18.4%)	89 (71.2%)	12 (9.6%)	1 (0.8%)	22 (18.2%)	85 (70.2%)	11 (9.1%)	3 (2.5%)
Pain	96 (64%)	103 (68.7%)	27 (28.1%)	67 (69.8%)	2 (2.1%)	0 (0%)	32 (31.1%)	67 (65%)	2 (1.9%)	2 (1.9%)
Tenderness	122 (81.3%)	130 (86.7%)	26 (23%)	87 (71.3%)	7 (5.7%)	0 (0%)	26 (20%)	94 (72.3%)	6 (4.6%)	4 (3.1%)
Itching	53 (35.3%)	58 (38.7%)	22 (41.5%)	27 (50.9%)	4 (7.5%)	0 (0%)	29 (50%)	26 (44.8%)	2 (3.4%)	1 (1.7%)
Other[4]	3 (2%)	3 (2%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)

[1] Missing values are not reported.
[2] Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.
[3] Data are cumulated from up to two injection sites per patient with earliest and latest time point for any reaction provided.
[4] Two patients reported mild transient headache and one patient reported mild "twitching"; neither could be associated with a particular product.

**Table 7. All Investigator-Identified Adverse Experiences (72 Hours)
Number of Events per Patient per Study for the Nasolabial Fold Indication**

Study Term	MA-1400-01		MA-1400-02	
	Number of Events *Restylane* (N=150)	Number of Events *Perlane* (N=150)	Number of Events *Restylane* (N=142)	Number of Events *Perlane* (N=141)
Ecchymosis	9	10	48	44
Edema	4	4	6	10
Erythema	13	13	3	5
Tenderness	4	4	7	5
Pain	2	2	2	2
Hyperpigmentation	2	3	0	1
Pruritus	2	1	1	0
Papule	1	0	2	2
Burning	1	0	0	0
Hypopigmentation	1	0	0	0
Injection site scab	3	0	0	0

Table 8. Investigator-Identified Adverse Experiences (2 Weeks or More After Implantation) (Number of Patients) (*Restylane* v. Specified Active Controls—All Studies for the Nasolabial Fold Indication)

Study Term	MA-1400-01 *Restylane* (n=150) (%)	MA-1400-01 *Perlane* (n=150) (%)	MA-1400-02 *Restylane* (n=142) (%)	MA-1400-02 *Perlane* (n=141) (%)	31GE0003 *Restylane* (n=138) (%)	31GE0003 Zyplast (n=138) (%)
Ecchymosis	4 (2.7%)	7 (4.8%)	14 (9.9%)	15 (10.6%)	8 (5.8%)	6 (4.3%)
Edema	0 (0%)	0 (0%)	2 (1.4%)	3 (2.1%)	11 (8.0%)	14 (10.1%)
Erythema	2 (1.3%)	2 (1.3%)	1 (0.7%)	2 (1.4%)	30 (21.7%)	37 (26.8 %)
Tenderness	0 (0%)	1 (0.7%)	0 (0%)	1 (0.7%)	8 (5.8%)	10 (7.2%)
Pain	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	4 (2.9%)	3 (2.2%)
Papule	1 (0.7%)	0 (0%)	2 (1.4%)	1 (0.7%)	5 (3.6%)	13 (9.4%)
Pruritus	1 (0.7%)	0 (0%)	1 (0.7%)	0 (0%)	4 (2.9%)	8 (5.8%)
Rash	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.7%)
Hyperpigmentation	8 (5.3%)	7 (4.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injection site scab	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin exfoliation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 9. MA-004-03 Adverse Events Reported by *Restylane* Patients Treated in the Nasolabial Folds

Adverse Event	Number of Subjects with Events(%) N=75	Total Number of Events[1]	Severity Mild	Moderate	Severe
Swelling	18 (24%)	46	37	9	0
Bruising	14 (19%)	33	19	12	2
Pain/Soreness	4 (5%)	14	12	2	0
Discoloration	3 (4%)	5	5	0	0
Infection	1 (1%)	1	0	0	1
Hardness/Nodule	2 (3%)	3	2	1	0

[1]Most subjects had bilateral events at either the initial injection or touch-up. Bilateral events are counted as two events.

Table 10. MA-1300-15 Intensity of Adverse Event, Subject Diary for the Lip Augmentation Indication Study

	No Treatment (N=45)	1st Treatment (N=172)	2nd treatment (N=93)	No Treatment (N=45)				1st Treatment with *Restylane* (N=172)				2nd Treatment with *Restylane* (N=93)			
	Subjects Reporting Symptoms	Subjects Reporting Symptoms	Subjects Reporting Symptoms	None	Tolerable	Affects Daily Activity	Disabling	None	Tolerable	Affects Daily Activity	Disabling	None	Tolerable	Affects Daily Activity	Disabling
Maximum Severity Reported for any Diary AE															
Upper and Lower Lips Combined	2	167	89	37 (95%)	2 (5%)	0	0	2 (1%)	88 (52%)	62 (37%)	17 (10%)	1 (1%)	60 (67%)	25 (28%)	4 (4%)
Bruising															
Upper and Lower Lips Combined	2	147	58	37 (95%)	2 (5%)	0	0	22 (13%)	109 (65%)	33 (20%)	5 (3%)	31 (35%)	48 (53%)	10 (11%)	1 (1%)
Redness															
Upper and Lower Lips Combined	1	130	60	38 (97%)	1 (3%)	0	0	39 (23%)	118 (70%)	12 (7%)	0	30 (33%)	55 (62%)	2 (2%)	3 (3%)
Swelling															
Upper and Lower Lips Combined	0	166	89	39 (100%)	0	0	0	3 (2%)	90 (53%)	65 (38%)	11 (7%)	1 (1%)	64 (71%)	22 (25%)	3 (3%)
Pain (Includes burning)															
Upper and Lower Lips Combined	1	146	72	38 (97%)	1 (3%)	0	0	23 (14%)	111 (66%)	27 (16%)	8 (5%)	18 (20%)	55 (61%)	14 (16%)	3 (3%)
Tenderness															
Upper and Lower Lips Combined	1	164	81	38 (97%)	1 (3%)	0	0	5 (3%)	120 (71%)	40 (24%)	4 (2%)	9 (10%)	63 (70%)	15 (17%)	3 (3%)
Itching															
Upper and Lower Lips Combined	0	56	23	39 (100%)	0	0	0	114 (67%)	51 (30%)	5 (3%)	0	67 (74%)	22 (25%)	1 (1%)	0

Table 11. MA-1300-15 Duration of Adverse Event, Subject Diary for the Lip Augmentation Indication Study

Location/Adverse Event	Any n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
No Treatment at Baseline (N=45) — Number of Days					
Upper and Lower Lip Combined					
Bruising	2 (4%)	2 (100%)	0	0	0
Redness	1 (2%)	1 (100%)	0	0	0
Swelling	0	0	0	0	0
Pain (Includes Burning)	1 (2%)	1 (100%)	0	0	0
Tenderness	1 (2%)	1 (100%)	0	0	0
Itching	0	0	0	0	0
First Treatment with *Restylane* (N=172) — Number of Days					
Upper and Lower Lip Combined					
Bruising	147 (85%)	7 (5%)	93 (63%)	43 (29%)	4 (3%)
Redness	130 (76%)	20 (15%)	86 (66%)	23 (18%)	1 (<1%)
Swelling	166 (97%)	3 (2%)	88 (53%)	50 (30%)	25 (15%)
Pain (Includes Burning)	146 (85%)	35 (24%)	95 (65%)	14 (10%)	2 (1%)
Tenderness	164 (95%)	11 (7%)	81 (49%)	49 (30%)	23 (14%)
Itching	55 (32%)	16 (29%)	32 (58%)	7 (13%)	0
Second Treatment with *Restylane* (N=93) — Number of Days					
Upper and Lower Lip Combined					
Bruising	59 (63%)	3 (5%)	40 (68%)	16 (28%)	0
Redness	60 (65%)	16 (27%)	38 (63%)	5 (8%)	1 (2%)
Swelling	89 (96%)	10 (11%)	54 (61%)	21 (24%)	4 (5%)
Pain (Includes Burning)	72 (77%)	21 (30%)	43 (60%)	5 (7%)	3 (4%)
Tenderness	81 (87%)	5 (6%)	52 (65%)	16 (20%)	8 (10%)
Itching	23 (25%)	10 (43%)	13 (57%)	0	0

[1] Duration of "other" diary symptoms could not be calculated.

Table 12. MA-1300-15 Summary of Treatment Emergent Adverse Events for the Lip Augmentation Indication Study

Adverse Event	No Treatment at Baseline (N=45)		First Treatment with *Restylane* (N=172)		Second Treatment with *Restylane* (N=93)	
	Events	Subjects	Events	Subjects	Events	Subjects
Pain	1	1 (2%)	97	36 (21%)	51	19 (20%)
Swelling	0	0	224	100 (58%)	103	52 (56%)
Tenderness	0	0	69	38 (22%)	29	16 (17%)
Nasopharyngitis	3	2 (4%)	9	9 (5%)	2	2 (2%)
Contusion (bruising/ ecchymosis)	0	0	131	76 (44%)	41	26 (28%)
Headache	3	2 (4%)	17	12 (7%)	3	3 (3%)
Erythema	0	0	57	29 (17%)	19	10 (11%)
Skin Exfoliation**	0	0	21	14 (8%)	2	2 (2%)

**Includes sloughing of the skin, peeling, desquamation, and superficial desquamation.

Table 13. MA-1300-13K Maximum Intensity of Symptoms after Initial Treatment, Subject Diary for the Lip Augmentation Indication Pilot Study

Reaction (N=20)	Total subjects reporting symptoms n (%)	None n (%)	Tolerable n (%)	Affected Daily Activity n (%)	Disabling n (%)
Bruising	17 (85%)	3 (15%)	13 (65%)	4 (20%)	0 (0%)
Redness	14 (70%)	6 (30%)	12 (60%)	2 (10%)	0 (0%)
Swelling	19 (95%)	1 (5%)	12 (60%)	7 (35%)	0 (0%)
Pain	17 (85%)	3 (15%)	17 (85%)	0 (0%)	0 (0%)
Tenderness	19 (95%)	1 (5%)	18 (90%)	1 (5%)	0 (0%)
Itching	2 (10%)	18 (90%)	2 (10%)	0 (0%)	0 (0%)
Mass Formation[1]	18 (90%)	2 (10%)	17 (85%)	1 (5%)	0 (0%)

[1] Documentation of mass formation was the result of a miscommunication with the subjects. Subjects were specifically instructed to record any product palpability as mass formation in their diary, whether or not the palpability was the intended feel of the product.

U.S. Clinical Studies

31GE0003: Prospective, Randomized, Blinded, Controlled, Clinical Study

Design

1:1 randomized, prospective study at 6 U.S. centers, which compared the safety and effectiveness of *Restylane* and Zyplast in a "within-patient" control model of augmentation correction of bilateral nasal folds, using *Restylane* on the randomized nasal labial fold and the control treatment on the opposite nasal labial fold. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were unmasked.

Effectiveness was studied with 6-month follow-up. Safety was studied with 12-month follow-up.

Endpoints

Effectiveness

Primary:

The difference in effect of *Restylane* and Zyplast on the visual severity of the nasolabial folds, as assessed by an Evaluating Investigator at 6 months after baseline.

Secondary:

Wrinkle Severity Rating Scale (WSRS) score assessed at other follow-up points by the evaluating investigator and by the subject.

Global Aesthetic Improvement (GAI): Very much improved / much improved / improved / no change / worse, assessed at 2, 4, and 6 months by the evaluating investigator and by the subject.

Number of treatment sessions to achieve optimal cosmesis.

The primary evaluation parameter was the 5-point WSRS Score. A change in WSRS=1 was considered to be clinically significant during follow-up. Baseline was defined to begin at the follow-up demonstrating that optimal correction had been sustained for 2 weeks.

Optimal correction was defined to be the best cosmetic result obtainable, as determined by the evaluating physician. A specific, objective score or goal for correction was not defined; 2 injectable implant sessions were expected.

Outcomes

Demographics:

The study enrolled a population of predominately healthy, female, Caucasian non-smokers with history of prior facial aesthetic procedures and minimal sun exposure. There were few men or other racial/ethnic groups; few smokers or patients with extensive sun exposure.

• Gender			• Tobacco use		
Male:	9	(6.6%)	Non-smokers	118	(86.1%)
Female:	128	(93.4%)	Smokers:	19	(13.9%)
• Ethnicity			• Sun Exposure		
Caucasian:	122	(89.0%)	None:	83	(60.6%)
Black:	2	(1.5%)	Natural Sun:	52	(38.0%)
Asian:	2	(1.5%)	Artificial:	2	(1.5%)
Hispanic:	11	(8.0%)			

Effectiveness

Primary:

Based on the per patient evaluation, the WSRS scores at 6 months by the evaluating investigator demonstrated that WSRS for

Restylane was lower (better) than Control:	in 78 patients
Restylane was equal to Control:	in 46 patients
Restylane was higher (worse) than Control:	in 13 patients

For the entire cohort, however, the Mean of the WSRS Score by evaluating investigator demonstrated that while there was essentially no difference between *Restylane* and Control-treated cohort sides at pre-treatment (0.02 units WSRS) and baseline (0.01 units WSRS), for the cohort of 134 patients, there was a difference of 0.58 units of WSRS at 6 months.

Table 14. Blinded Evaluator Mean Wrinkle Severity Scores

	N	*Restylane*	Control	Absolute Difference
Pre-treatment	138	3.29	3.31	0.02
Baseline	138	1.80	1.79	0.01
6 months	134	2.36	2.94	0.58

MA-1400-02: Prospective, Randomized, Blinded, Controlled Clinical Study

Design

1:1 randomized, prospective study at 17 U.S. centers, which compared the safety and effectiveness of *Restylane* and *Perlane* following treatment to baseline condition. Patients were randomized to either *Restylane* or *Perlane* treatment. A touch-up was allowed 2 weeks after initial treatment. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were unmasked.

Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.

Endpoints

Effectiveness

Primary:

The difference in effect of *Restylane* at week 12 versus baseline condition on the visual severity of the nasolabial folds, as assessed by the Blinded Evaluator.

The primary study endpoint was wrinkle severity 12 weeks after optimal correction was achieved. Wrinkle severity was evaluated on a five-step validated Wrinkle Severity Rating Scale (WSRS) (i.e., none, mild, moderate, severe, extreme) by a live evaluator blinded to treatment. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes were calculated for each treatment group. Each group was compared to its own baseline, with no comparison of *Restylane* to *Perlane*.

Secondary:

Wrinkle Severity Rating Scale (WSRS) assessed at other follow-up points (2, 6, and 24 weeks after optimal correction) by the Blinded Evaluator, the investigator and the patient and compared to baseline score by the same evaluator. Duration of effect was defined as 6 months or time point, if earlier, at which less than 50% of patients had at least a 1-grade response remaining in both nasolabial folds (NLFs).

Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse experiences to injection technique.

Outcomes

Demographics:

The study enrolled 283 (i.e., 142 *Restylane* and 141 *Perlane*) patients with moderate to severe NLF wrinkles. The patients were predominantly healthy ethnically diverse females. Bilateral NLFs and oral commissures were corrected with 2.1 mL to 5.2 mL of *Restylane*. The greatest amount used in any patient was 8.8 mL.

Gender – Female: 266 (94%); Male: 17 (6%)

Ethnicity – White: 226 (80%); Hispanic or Latino: 31 (11%); African American: 23 (8%); Asian: 3 (1%)

Efficacy:

The results of the blinded evaluator assessment of NLF wrinkle severity for *Restylane* and control (*Perlane*) are presented in Table 15. In the primary effectiveness assessment at 12 weeks, 77% of the *Restylane* and 87% of the control patients had maintained at least a 1-point improvement over baseline.

Table 15. Blinded Evaluator Wrinkle Severity Response Scores

Time point	No. of *Restylane* Patients	No. of *Restylane* Pts. maintaining ≥ 1 Unit Improvement of NLF on WSRS	No. of *Perlane* Patients	No. of *Perlane* Pts. maintaining ≥1 Unit Improvement of NLF on WSRS
6 weeks	136	113 (83%)[1]	136	121 (89%)[1]
12 weeks	140	108 (77%)[1]	141	122 (87%)[1]
24 weeks	140	103 (74%)[1]	138	87 (63%)[1]

[1] All p-values <0.0001 based on t-test compared to baseline condition

Antibody Testing:

15/142 (10.6%) subjects displayed a pre-treatment antibody response against *Restylane* (which was believed to be related to co-purifying *Streptococcus* capsule antigens). One subject also developed measurable increase in antibody titer after *Restylane* injection. 7/21 (33.3%) patients with antibodies against *Restylane* had adverse experiences at the injection site, which was similar to the local adverse event rate observed in the entire *Restylane* population (i.e., 53/142 (37%)). No severe events were noted and the subject who developed an antibody response after *Restylane* injection did not experience any adverse event at the injection site. Immediate type skin testing demonstrated that no patient developed IgE to *Restylane*. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Restylane*.

MA-1400-01: Prospective, Randomized, Blinded, Controlled Clinical Study

Design

1:1 randomized, prospective study at 10 U.S. centers, which compared the safety and effectiveness of *Restylane* and *Perlane* following treatment to baseline condition in 150 patients with pigmented skin and predominantly African-American ethnicity. Patients were randomized to *Restylane* or *Perlane* treatment in a "within-patient" model of augmentation correction of bilateral nasolabial folds (NLFs) and oral commissures with one treatment assigned to one side and the other treatment to the other side. A touch-up was allowed 2 weeks after initial treatment. Patients and treating physicians were partially masked. Evaluations were performed by live investigator assessment for the primary analysis.

Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.

Endpoints

Effectiveness

Primary:
The difference in effect of *Restylane* at week 12 versus baseline condition on the visual severity of the NLFs.

The primary study endpoint was wrinkle severity 12 weeks after optimal correction was achieved. Wrinkle severity was evaluated with a five-step validated Wrinkle Severity Rating Scale (WSRS) (i.e., none, mild, moderate, severe, extreme) by an on-site blinded evaluator. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes was calculated for each group. Each treatment group was compared to its own baseline, with no comparison of *Restylane* to *Perlane*.

Secondary:
Wrinkle Severity Rating Scale (WSRS) was assessed at other follow-up points (2, 6, and 24 weeks after optimal correction) by the investigator and the patient and compared to baseline score by the same evaluator. A photographic assessment of patient outcomes was also performed. Duration of effect was defined as 6 months or time point, if earlier, at which less than 50% of patients had at least a 1-grade response at both nasolabial folds.

Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse experiences to injection technique.

Outcomes

Demographics:

The study enrolled 150 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy African-American females.

Gender – Female: 140/150 (93%); Male 10/150 (7%)

Ethnicity – White: 2 (1.3%); Hispanic or Latino: 9 (6%); African-American: 137 (91%); American Indian: 2 (1.3%)

Fitzpatrick Skin Type – I to III: 0 (0%); IV: 44 (29%); V: 68 (45%); VI: 38 (25%)

Efficacy:

The results of the live blinded evaluator assessment of wrinkle severity for *Restylane* and control (*Perlane*) are presented in Table 16 and are based on the Intent-to-Treat analysis. In the primary effectiveness assessment at 12 weeks, 93% of the *Restylane*-treated and 92% of the *Perlane*-treated NLF maintained at least a 1-point improvement over baseline.

Table 16. Live Evaluator Wrinkle Severity Response Scores

Time point	No. of patients	No. of *Restylane* Pts. maintaining 1 Unit Improvement on WSRS	95% *Restylane* Confidence Interval	No. of *Perlane* Pts. maintaining [1] 1 Unit Improvement on WSRS	95% *Perlane* Confidence Interval
6 weeks	148	142 (96%)[1]	92–99%	140 (95%)[1]	90–99%
12 weeks	149	139 (93%)[1]	89–98%	137 (92%)[1]	87–97%
24 weeks	147	108 (73%)[1]	66–81%	104 (71%)[1]	63–77%

[1] All p-values <0.0001 based on t-test compared to baseline condition

Antibody Testing:

9/150 (6%) subjects displayed a pre-treatment antibody response against *Restylane* (which was believed to be related to co-purifying *Streptococcus* capsule antigens). No subjects developed a measurable increase in antibody titer after *Restylane* injection. 1/6 (17%) patients with antibodies against *Restylane* had adverse experiences at the injection site as compared to the local adverse event rate observed in the entire *Restylane* population (i.e., 28/150 (18.7%)). All the adverse experiences in the patients with a humoral response against *Restylane* were mild in severity. Immediate type skin testing demonstrated that no patient developed IgE to *Restylane*. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Restylane*.

MA-04-003

The duration of effectiveness of *Restylane* for correction of nasolabial folds (NLF) was evaluated in a randomized, evaluator-blinded, multi-center study. *Restylane* was shown to have an overall duration of effectiveness of 18 months from baseline following re-treatment at 4.5 or 9 months.

MA-04-003: Randomized Clinical Study

Design

Randomized, evaluator-blinded study at 3 U.S. centers, which compared the safety and effectiveness of *Restylane* using two re-treatment schedules. Initially *Restylane* was injected in both nasolabial folds (NLF). Subsequently, one NLF was re-treated at 4.5 months after the initial treatment. The contralateral NLF was treated with *Restylane* and re-treated at 9 months (± 1 week). The Blinded Evaluators were blinded to the re-treatment schedule while patients and treating physicians were not.

Effectiveness was studied at 18 months after the initial injection (i.e., either 9 or 13.5 months after the second treatment).

Endpoints

Effectiveness

Primary:

The difference in effect of *Restylane* injected 4.5 or 9 months after the initial treatment on the visual severity of the nasolabial folds was assessed by an Evaluating Investigator at 18 months after the baseline treatment. The primary study endpoint was the proportion of subjects with at least one grade improvement in the Wrinkle Severity Rating Scale (WSRS) from baseline as assessed by the Blinded Evaluator at the 18 month visit.

Secondary:

The Wrinkle Severity Rating Scale (WSRS) score was assessed by the evaluating investigator at all follow-up visits prior to the 18 month visit and at all visits by subjects and independent photographic reviewers.

Global Aesthetic Improvement Scale (GAIS) comparing the pre-treatment appearance at all follow-up visits up to 18 months, was determined by the treating investigator and patient. The GAIS is a 5-point scale for assessing global aesthetic improvement: "very much improved / much improved / improved / no change / worse."

Safety

Severity and duration of injection site reactions and adverse events were recorded.

Outcomes

Demographics:

The study enrolled an adult population of predominately Caucasian, healthy, non-smoking females.

Number of Subjects	Age		Gender		Race	
75	Mean ± SD	53.8 ± 8.4	Male	5 (6.7%)	White	50 (66.7%)
	Median	54	Female	70 (93.3%)	Black	3 (4.0%)
	Minimum	26			Hispanic	22 (29.3%)
	Maximum	73				

Prior Augmentation to NLF		History of Tobacco Use		History of Sun Exposure	
Yes	6 (8.0%)	No	55 (73.3%)	No	63 (84.0%)
No	69 (92.0%)	Yes	20 (26.7%)	Yes	12 (16.0%)

Number of Subjects enrolled and observed at 4.5, 9, 12, 15 and 18 months

	SCR/ TRT	Touch-up	Wk2	M 4.5	M9	M12	M15	M18
Enrolled	75	-	75	75	75	75	75	75
Withdrew Consent (total)	0	-	1	5	6	6	6	7
Lost to Follow-up	0	-	0	2	4	4	4	4
Missed Visit	0	-	2	1	0	1	1	1
Actual	75	44	72	67	65	64	64	64

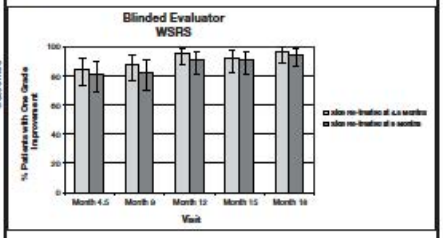
Volume (mL) of *Restylane* Treatment Used by Visit

Visit	Side Assigned to Re-treatment at 4.5 Months	Side Assigned to Re-treatment at 9 Months
Baseline		
N	75	75
Mean ± SD	1.1 ± 0.61	1.1 ± 0.56
Median	1.0	1.0
Minimum	0.1	0.2
Maximum	2.5	2.5
Touch-up Visit		
N	44	44
Mean ± SD	0.5 ± 0.22	0.5 ± 0.21
Median	0.5	0.5
Minimum	0.2	0.2
Maximum	1.0	1.0
Re-treatment Visit (4.5 Months/9 months)		
N	67	63
Mean ± SD	0.7 ± 0.33	0.7 ± 0.36
Median	0.8	0.6
Minimum	0.2	0.1
Maximum	1.8	2.0

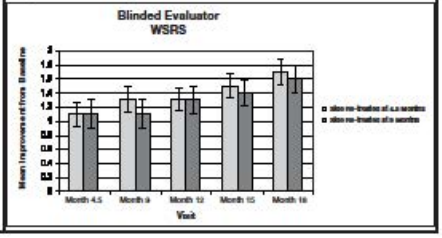
Outcomes

Effectiveness

The results of the blinded evaluator assessment of NLF wrinkle severity for subjects treated at baseline, 4.5 or 9 months is presented in the Figure below for subject outcomes at 4.5, 9, 12, 15 and 18 months after initial treatment.



At 18 months after the initial treatment, the blinded evaluator determined that 97% of the NLFs re-treated at 4.5 months displayed at least 1 WSRS grade improvement over baseline, with a mean change in wrinkle severity score of 1.7 units. At 18 months after the initial treatment, the blinded evaluator determined that 95% of the NLFs re-treated at 9 months displayed at least 1 WSRS grade improvement over baseline, with a mean change in wrinkle severity score of 1.6 units.



MA-1300-15

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

MA-1300-15: Randomized Clinical Study

Design

This was a randomized, evaluator blinded, no treatment as a control study of 180 subjects who were seeking lip fullness augmentation at 12 investigational centers. At entry of the study, subjects were randomized in a 3:1 ratio to (1) Restylane treatment or (2) no treatment. The study recruited a minimum of 30 subjects with darker skin types based on classification of Fitzpatrick skin types IV, V, or VI. Each lip qualified by MLFS score was analyzed for effectiveness and all lips were analyzed for safety. Subjects randomized to treatment at baseline were re-treated at 6 months and subjects randomized to no treatment at baseline received their first treatment at 6 months. The safety of all subjects was then monitored for one month after the 6 month treatment.

Endpoints

Effectiveness

Primary:

The primary effectiveness objective was to identify whether *Restylane* was more effective in lip augmentation than no treatment. This was determined by the blinded evaluator assessment of lip fullness at 8 weeks after the first treatment as compared to the baseline assessment by the treating investigator, separately in the upper and lower lips (co-primary endpoints), using separate 5-grade Medicis Lip Fullness Scales (MLFS) with photoguides for each (one scale for upper lip and one scale for lower lip). Treatment success was defined as at least a one grade improvement in the MLFS for the blinded evaluator assessments at Week 8 (as compared to the treating investigator's baseline assessment of the MLFS) for both the upper and lower lips.

The primary safety objective was to define the incidence of all adverse events; including subject complaints reported during the first fourteen days after treatment as recorded in the subject diary; safety assessments at the 72 hour visits; treating investigator assessments at 2, 4, 8, 12, 16, 20, 24 weeks as well as 2 and 4 weeks after the 6 month treatment; and any reported or observed adverse events.

Secondary:

Secondary effectiveness objectives included:

- Assessment of lip fullness augmentation after treatment with *Restylane* as compared to no treatment, as measured by the blinded evaluator, treating investigator, and IPR at post-baseline time points as compared to the baseline assessment. Response was determined by at least one grade improvement from baseline in the upper and lower lips using the MLFS.
- Identification of lip improvement at each time point after treatment with *Restylane* as compared to no treatment using the GAIS by the treating investigator and the subject. Response is defined as a GAIS rating of "improved" or better in the upper or lower lips.

The secondary safety objectives included assessment of lip texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation.

Outcomes

Demographics:

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

Characteristics	Total (N=180)
Age (years)	
n	180
Mean (S.D.)	47.6 (10.6)
Median	50.0
Minimum	18
Maximum	65
Gender	
Male	1 (<1%)
Female	179 (99%)

Characteristics	Total (N=180)
Race	
American Indian/Alaskan Native	2 (1%)
Black/African American	2 (1%)
Native Hawaiian/Pacific Islander	1 (<1%)
Asian	0
White	169 (94%)
Other	6 (3%)
Ethnicity	
Not Hispanic or Latino	161 (89%)
Hispanic or Latino	19 (11%)
Fitzpatrick Skin	
I, II, and III	139 (77%)
IV and V	41 (23%)

Outcomes

Volume (mL) of *Restylane* used:

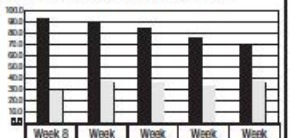
Assessment (upper and lower lips)	Initial Treatment: No Treatment (N=45)	Initial Treatment: *Restylane* (1st Treatment) (N=135)	6 Month Treatment: No Treatment (1st Treatment) (N=45)	6 Month Treatment: *Restylane* (2nd Treatment) (N=135)
Volume of Injection (mL) (includes treatment and touch up)				
n	–	135	37	93
Mean (S.D.)	–	2.853 (0.984)	2.387 (1.380)	1.783 (0.921)
Median	–	3.000	2.250	1.700
Minimum	–	0.60	0.60	0.03
Maximum	–	5.60	8.00	5.00

Effectiveness

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

The results of the blinded evaluator MLFS assessments of lip fullness are presented in the figure below for subject outcomes 8, 12, 16, 20, and 24 weeks.

Proportion (%) of MLFS Responders Measured by the Blinded Evaluator



	Week 8	Week 12	Week 16	Week 20	Week 24
■ *Restylane* Treatment (%)	92.6	90.1	84.2	75.0	69.6
No Treatment (%)	28.9	36.8	35.9	33.3	36.8

p-value < 0.001 for all time points

Subjects assessed lip improvement at each time point after treatment with a 7-point non-validated GAIS. When upper and lower lip outcomes were combined, the following percentage of *Restylane* subjects assessed themselves as improved or better from Baseline: 97.7% (Week 2), 99.2% (Week 4), 96.7% (Week 8), 91.7% (Week 12), 85.0% (Week 16), 76.1% (Week 20), and 74.1% (Week 24). No patients in the No Treatment group assessed themselves as improved from Baseline at any visit.

80% of the eligible subjects elected to receive re-treatment at Week 24 which suggests that subjects believed that the safety concerns associated with *Restylane* lip injections were less than the aesthetic value provided by the device.

MA-1300-13K

Design

A prospective, open label, single center, blinded evaluator study in 20 subjects

Endpoints

The effectiveness evaluation parameter was the Global Aesthetic Improvement Scale (GAIS)

To assess the incidence and severity of adverse experiences from *Resilylane* when used in the lips

Outcomes

A total of 20 subjects (2 male, 18 female) were enrolled and 19 subjects completed the study. One 80 year old subject died during the study due to cardio-respiratory arrest. Mean age was 52.8 years old. Seventeen subjects were white.

At 12 weeks, 7/19 (37%) subjects were rated as improved on their GAIS assessment by the Blinded Evaluator. At 12 weeks, all (100%) subjects rated themselves as improved on their GAIS assessment.

Parameter	N	n	Subjects with Lip Improvement	Percent	90% CI	p-Value[1]
Lip Improvement Using the Blinded Evaluator's Assessment[1]	20	19	7	37%	(0.19, 0.58)	0.820
Lip Improvement Using the Treating Investigator's Assessment	20	19	19	100%	(0.85, 1.00)	<0.001
Lip Improvement Using the Subject's Assessment	20	17	17	100%	(0.84, 1.00)	<0.001

[1] Due to the protocol deviation, the live blinded evaluator's assessment was a photo assessment.

Mean Volume Used		
Lip	Statistic	Volume of Injection (mL)
Upper	N	20
	Mean (S.D.)	0.82 (0.30)
	Median	0.73
	Min, Max	0.08, 1.40
Lower	N	20
	Mean (S.D.)	0.88 (0.37)
	Median	0.80
	Min, Max	0.05, 1.80
Total	N	20
	Mean (S.D.)	1.69 (0.62)
	Median	1.60
	Min, Max	0.13, 3.20

HOW SUPPLIED

Restylane is supplied in a disposable glass syringe with a Luer-Lok® fitting. *Restylane* is co-packed with sterilized needle(s) as indicated on the carton, either 30 G x ½" or 29 G x ½".

A patient record label is a part of the syringe label. Remove it by pulling the flap marked with three small arrows. This label is to be attached to patient records to ensure traceability of the product.

The contents of the syringe are sterile.

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

SHELF LIFE AND STORAGE

Restylane must be used prior to the expiration date printed on the package.

Store at a temperature of up to 25° C (77° F). Do not freeze. Protect from sunlight. Refrigeration is not required.

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

Do not use if the package is damaged. Immediately return the damaged product to Medicis Aesthetics Inc.

℞ only

U.S. PATENT 5,827,937

Manufactured for
Medicis Aesthetics Inc.
7720 N. Dobson Road
Scottsdale, AZ 85256
U.S.A.
Phone: 1-866-222-1480

Manufactured by
Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala
Sweden

Made in Sweden

Restylane and *Perlane* are registered trademarks of HA North American Sales AB.

All other trademarks are the property of their respective owners.

* NOTE: This printer-friendly version has been modified to print on letter paper. The formatting, size, and location of text, diagrams, and tables may be different from the package insert.

Revised: October 2011
13130225

DIRECTIONS FOR ASSEMBLY

ASSEMBLY OF 30 G NEEDLE TO SYRINGE

For safe use of *Restylane*, it is important that the needle is properly assembled. Improper assembly may result in separation of the needle and syringe during implantation.

See pictures A through E.

1. Unscrew the tip cap (B) of the syringe carefully.
2. Grasp the narrow part of the needle shield loosely; mount the needle on the Luer-Lok (C) by turning it clockwise until you feel counterpressure.
3. Grasp the wider part of the needle shield firmly (D).
4. Press and turn the needle shield 90° (a quarter turn).

4a. The quarter turn is necessary to lock the needle onto the syringe.

5. Remove the patient record label marked with three small arrows (E) and attach to patient chart.
6. Pull off the needle shield.

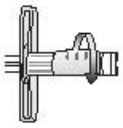
A.

B.

C.

D.

E.



ASSEMBLY OF 29 G NEEDLE TO SYRINGE

Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the Luer-Lok adapter. Grasp the needle shield with the other hand. To facilitate proper assembly, both push and rotate firmly.

PRE-TREATMENT GUIDELINES

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

TREATMENT PROCEDURE

1. It is necessary to counsel the patient and discuss the appropriate indication, risks, benefits and expected responses to the *Restylane* treatment.

   Advise the patient of the necessary precautions before commencing the procedure.
2. Assess the patient's need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
3. The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
4. Sterile gloves are recommended while injecting *Restylane*.
5. Before injecting, press rod carefully until a small droplet is visible at the tip of the needle.
6. *Restylane* is administered using a thin gauge needle (30 G x ½" or 29 G x ½"). The needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle, fold, or lip. For the nasolabial folds, *Restylane* should be injected into the mid-to-deep dermis. For lip augmentation, *Restylane* should be injected into the submucosal layer; care should be taken to avoid intramuscular injection. If *Restylane* is injected too superficially this may result in visible lumps and/or bluish discoloration.
7. Inject *Restylane* applying even pressure on the plunger rod. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
8. Only correct to 100% of the desired volume effect. Do not overcorrect. With cutaneous deformities the best results are obtained if the defect can be manually stretched to the point where it is eliminated. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique.
9. Typical usage for each treatment session is specific to the site as well as wrinkle severity. In a prospective study of midface wrinkle correction, the median total dose was 3.0 mL. Based on U.S. clinical studies, the maximum recommended dose per treatment is 6.0 mL for the nasolabial folds and 1.5 mL per lip per treatment.

INJECTION TECHNIQUES

1. *Restylane* can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
2. **Serial puncture** (F) involves multiple, closely spaced injections along wrinkles or folds. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
3. **Linear threading** (includes retrograde and antegrade) (G) is accomplished by fully inserting the needle into the middle of the wrinkle or fold and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle has been fully inserted and is being withdrawn, it can also be performed while advancing the needle ("push-ahead" technique). To enhance the vermillion of the lip, the retrograde linear threading technique is the most advisable.
4. Serial threading is a technique that utilizes elements of both approaches.
5. **Cross-hatching** (H) consists of a series of parallel linear threads injected at intervals of five to ten mm followed by a new series of threads injected at right angles to the first set to form a grid. This technique is particularly useful in facial contouring when coverage of the treatment region needs to be maximized.

F. Serial Puncture

G. Linear Threading (includes retrograde and antegrade)

H. Cross-hatching

6. **Note! The correct injection technique is crucial for the final result of the treatment.**
   Dissection of the sub-epidermal plane with lateral movement of the needle, rapid flows (>0.3 mL/min), rapid injection or high volumes may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.
7. When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers, or against the underlying area to obtain optimal results.
8. If so called "blanching" is observed, i.e., the overlying skin turns a whitish color, the injection should be stopped immediately and the area massaged until it returns to a normal color.
9. If the wrinkle or lips need further treatment, the same procedure should be repeated until a satisfactory result is obtained. Additional treatment with *Restylane* may be necessary to achieve the desired correction.
10. 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.
11. Patients may have mild to moderate injection site reactions, which typically resolve in less than 7 days in the nasolabial folds and less than 14 days in the lip.

STERILE NEEDLE(S)

- Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.
- *Restylane* is provided with a needle that does not contain engineered injury protection. Administration of *Restylane* requires direct visualization and complete and gradual insertion of the needle making engineered protections infeasible. Care should be taken to avoid sharps exposure by proper environmental controls.

Ordering Information

Medicis Aesthetics Inc. and its distributor, McKesson Specialty, are your only sources for FDA-approved *Restylane*. Purchasing from any other agent is illegal.

To order call 877-520-0500.