Appendix 16.1.1 Protocol and Protocol Amendments

Protocol SYM 2016-02, Version 1.0 (08 July 2016)

1 TITLE PAGE

Title:	A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra + (with Lidocaine) versus Revanesse® Ultra for the Correction of Nasolabial Folds
Protocol No.:	SYM 2016-02
Sponsor:	Prollenium Medical Technologies Inc. 138 Industrial Parkway North Aurora Ontario L4G 4C3 Canada
Protocol Version:	1.0
Current Protocol Version Date:	08 July 2016

2 SPONSOR/CRO SIGNATURE PAGE

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PROTOCOL VERSION: 1.0

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

DocuSigned by:
2BB2317B7A5B4E7

7/8/2016

Mr. Ario Khoshbin
Managing Director
Prollenium Medical Technologies Inc.

Date

Debra A. Dow

11 July 2016

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 + (with Lidocaine) versus Revanesse® Ultra for the Correction of Nasolabial Folds
Name of Sponsor: Prollenium Medical Technologies Inc.
Name of Finished Products: Revanesse® Ultra +, Revanesse® Ultra
Device Composition: Hyaluronic acid gel with lidocaine (0.3% w/w); hyaluronic acid gel
Objectives: To compare the safety and efficacy profiles of Revanesse® Ultra + (with lidocaine, hereafter referred to as Revanesse Ultra +) to Revanesse Ultra 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 Revanesse Ultra 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 2 – interim visit, touch-up if the iGAI score = 3 or 4 Visit 3/Week 4 – interim visit Visit 4/Week 12 – interim visit Visit 5/ Week 24 –End of Study Evaluations include: Pain assessment using a visual analog scale (VAS) 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 Investigator Ease of Use Assessment.
Number of Study Centers: Approximately 5 sites in the United States
Duration of Participation: Subjects will participate in the study for approximately 24 weeks from the time they sign the informed consent form (ICF) through the final contact.
Duration of Study: The study will require approximately 12 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 100 subjects will be randomized.
Inclusion Criteria 1. Men or women 22 years of age or older seeking augmentation therapy for correction of bilateral nasolabial folds. 2. Two fully visible bilateral nasolabial folds each with a Wrinkle Severity Rating Scale Score (WSRS) of 3 or 4 that may be corrected with an injectable dermal filler. The NFLs should be symmetrical, i.e., WSRS scores at NLFs on both sides should be the same (both Moderate [3] or both Severe [4]). 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. Note: Where possible, subjects currently enrolled in the ongoing retreatment study SYM2014-02 entitled "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" (G140120) will be invited to participate in this 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, had undergone procedures based on active dermal response (e.g. laser or chemical peeling procedures) within 6 months (180 days) prior to study entry. 4. Use of any facial tissue augmenting therapy with non-permanent filler or aesthetic facial surgical therapy within 9 months prior to study entry. 5. Has ever received semi-permanent fillers or permanent facial implants anywhere in the face or neck, or is planning to be implanted with these products during the study. 6. Has a permanent implant placed in the NLF area. 7. Evidence of scar-related disease or delayed healing activity within the past 1 year. 8. Scars at the intended treatment sites. 9. History of keloid formation or hypertrophic scars. 10. Any infection or unhealed wound on the face. 11. Allergic history including anaphylaxis, multiple severe allergies, atopy, or allergies to natural rubber latex, lidocaine or any amide based anesthetic, hyaluronic acid products, or Streptococcal proteins or have plans to undergo desensitization therapy during the term of the study. 12. Aspirin or nonsteroidal anti-inflammatory drugs within 1 week (7 days) prior to treatment. 13. Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders, coagulation defects or connective tissue disorders. 14. Over-the-counter (OTC) wrinkle products or prescription wrinkle treatments within 4 weeks (28 days) prior to treatment and throughout the study.

15. Immunocompromised or immunosuppressed.
16. 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.
17. Received any investigational product within 30 days.
18. Facial tattoo that may interfere with diagnosis.
19. 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.
20. Acne and/or other inflammatory diseases of the skin
21. Acute or chronic skin disease, inflammation or related conditions, cancerous or pre-cancerous lesion on or near the injection sites

Products

Test product: Revanesse Ultra +: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 mg/mL of stabilized hyaluronic acid and lidocaine 0.3% w/w.

Comparator product: Revanesse Ultra: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 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: To detect the difference between the null hypothesis proportion of responders of 50% and the alternative proportion of responders of 70% via a two-sided exact binomial test with a 0.05 significance level, 80 modified intent-to-treat (mITT) subjects will supply a power of 94.1%. For the alternative proportion of responders of 68%, 80 mITT subjects will supply a power of 87.8%. A responder is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra +) in VAS pain score of at least 10 mm immediately after injection.

A total of 100 subjects will be randomized to obtain 80 mITT subjects and 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 had VAS pain score immediately post injection from both sides of the face.

Per-protocol (PP): All randomized subjects who met all inclusion/exclusion criteria; received both study products; completed Visit 5/Week 24 within the specified window; had data on pain score from both sides of the face immediately post injection and at 15, 30, 45, and 60 minutes post injection at Visit 1/Day1; had data on pain score at 2 weeks post injection

(prior to touch-up); 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 the proportion of responders immediately after injection, where a responder is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra +) in VAS pain score of at least 10 mm on a 100-mm scale. Summary statistics include mean, standard deviation (SD), minimum, median, and maximum for VAS score for each treatment and for the within-subject difference. The proportion of responders will be summarized with frequency and percentage with a 95% confidence interval (CI) constructed using a one-sample binomial exact test. If the lower bound of this 95% CI is greater than 50%, the test product will be claimed to be superior to the comparator product. The primary endpoint will be summarized by site descriptively.

The secondary efficacy endpoints are the proportion of responders at 15, 30, 45, and 60 minutes post injection and at 2 weeks post injection (prior to touch-up). Upon the significance of the primary efficacy outcome, secondary endpoints will be analyzed using a hierarchical approach will be used. If success is achieved at 15 minutes, 30 minutes will be evaluated; if success is achieved at 30 minutes, 45 minutes will be evaluated; if success is achieved at 45 minutes, 60 minutes will be evaluated; and if success is achieved at 60 minutes, 2 weeks post-injection will be evaluated.

Other efficacy variables include change in WSRS score from baseline, pGAI, and iGAI at each scheduled post-baseline visit. Descriptive summaries will be provided for each treatment and for within-subject difference.

All efficacy analyses will be performed for both the PP and mITT populations. For the primary endpoint, the results from mITT are considered definitive and those from PP 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: One interim analysis is planned after all subjects have completed Visit 3 or discontinued prior to Visit 3. The purpose is to determine the safety and pain relief of Revanesse Ultra + to support regulatory submissions outside the US that are currently under review for products containing lidocaine. The sponsor does not plan to change the protocol or stop the study based on the results of the interim analysis.

3.2 Study Flow Chart

Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	
Scheduled Day (Week)	**Day 1 (Week 0)**	**Day 14 (Week 2)**	**Day 28 (Week 4)**	**Day 84 (Week 12)**	**Day 168 (Week 24)**	**Unsched Visit**
Scheduling Window	**none**	**± 2 days**	**± 2 days**	**± 4 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
Inclusion/exclusion criteria review	X					
Urine pregnancy test[a]	X					
Wrinkle Severity Rating Scale (WSRS)	X	X	X	X	X	X[b]
Randomization	X					
Treatment with study products	X	X[c]				
Pain score (VAS)	0, 15, 30, 45, 60 min[d]	X[e]	X[c]			
Investigator Ease of Use	X					
Evaluation for touch-up		X				
Patient GAI (pGAI)		X	X	X	X	X[b]
Investigator GAI (iGAI)		X	X	X	X	X[b]
Adverse event assessment	X	X	X	X	X	X
Subject Diary	Dispense	Review/ Dispense[b]	Collect	Collect[b]		
Schedule/confirm next visit	X	X	X	X	X	X[b]

a For women of childbearing potential, to be completed prior to enrollment.
b If applicable.
c For subjects who receive a touch-up treatment (iGAI = 3 or 4)
d To be administered to the subject immediately after injection and 15, 30, 45, and 60 minutes post injection.
e To be administered to subjects who will receive a touch-up treatment prior to touch-up, immediately after injection and 15, 30, 45, and 60 minutes post injection, and to be administered during the visit to subjects who do not receive a touch-up treatment.

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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
MI	multiple imputation
min	minimum
mITT	modified intent-to-treat
NI	non-inferiority
NLF	nasolabial fold
OTC	over-the-counter
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
VAS	visual analog scale
WHO	World Health Organization
WSRS	Wrinkle Severity Rating Scale
w/w	weight/weight

6 INTRODUCTION

6.1 Background

Revanesse Ultra + (with lidocaine, hereafter referred to as Revanesse Ultra +) is a stabilized hyaluronic acid (HA) dermal filler with lidocaine 0.3% w/w and Revanesse Ultra is a stabilized HA dermal filler. Both products are commercially available in Canada and several European countries. The purpose of this study is to compare the efficacy and safety of these two products.

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 Revanesse Ultra 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.

7 STUDY OBJECTIVES

The objectives of this study are to compare the safety and efficacy profiles of Revanesse Ultra + to Revanesse Ultra 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 + (test product) in the NLF on one side of the face and Revanesse Ultra (comparator product) 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 100 subjects will be randomized at approximately 5 study sites in the United States (US). Where possible, subjects currently enrolled in the ongoing retreatment study SYM2014-02 entitled “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” (G140120) will be invited to participate in this study. Those subjects will receive a third treatment with Revanesse Ultra.

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

Visit 3/Week 4 (± 2 days) – interim visit

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

Visit 5/ Week 24 (± 7 days) – End of Study

Evaluations include pain assessment by a visual analog scale (VAS) , 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 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 the occurrence and extent of symptoms 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 is considered to have completed the study after he/she has completed Visit 5/Week 24.

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 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 Revanesse Ultra.

It is anticipated that the duration of this study will be 12 months.

8.3 Study Population

Approximately 100 healthy males and females at least 22 years of age and with NLFs will be selected to participate in the study.

Where possible, subjects currently enrolled in the ongoing retreatment study SYM2014-02 entitled "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" (G140120) will be invited to participate in this 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 seeking augmentation therapy for correction of bilateral nasolabial folds.
2. Two fully visible bilateral nasolabial folds each with a Wrinkle Severity Rating Scale Score (WSRS) of 3 or 4 that may be corrected with an injectable dermal filler. The NFLs should be symmetrical, i.e., WSRS scores at NLFs on both sides should be the same (both Moderate [3] or both Severe [4]).
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, or had undergone procedures based on active dermal response (e.g., laser or chemical peeling procedures) within 6 months (180 days) prior to study entry.
4. Use of any facial tissue augmenting therapy with non-permanent filler or aesthetic facial surgical therapy within 9 months prior to study entry.

5. Has ever received semi-permanent fillers anywhere in the face or neck, or is planning to be implanted with these products during the study.
6. Has a permanent implant placed in the NLF area.
7. Evidence of scar-related disease or delayed healing activity within the past 1 year.
8. Scars at the intended treatment sites.
9. History of keloid formation or hypertrophic scars.
10. Any infection or unhealed wound on the face.
11. Allergic history including anaphylaxis, multiple severe allergies, atopy, or allergies to natural rubber latex, lidocaine or any amide-based anesthetic, hyaluronic acid products, or Streptococcal proteins or have plans to undergo desensitization therapy during the term of the study.
12. Aspirin or nonsteroidal anti-inflammatory drugs within 1 week (7 days) prior to treatment.
13. Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders, coagulation defects or connective tissue disorders.
14. Over-the-counter (OTC) wrinkle products or prescription wrinkle treatments within 4 weeks (28 days) prior to treatment and throughout the study.
15. Immunocompromised or immunosuppressed.
16. 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.
17. Received any investigational product within 30 days of signing the Informed Consent Form.
18. Facial tattoo that may interfere with diagnosis.
19. 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.
20. Acne and/or other inflammatory diseases of the skin.
21. Acute or chronic skin disease, inflammation or related conditions, cancerous or precancerous lesions on or near the injection sites.

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 5/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 and lidocaine 0.3% w/w.

Comparator product: Revanesse Ultra: a clear, colorless gel in 1.0 mL pre-filled syringes with 25 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 Revanesse Ultra 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 subjects 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 2.

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.

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.

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 Ultra + and Revanesse Ultra study products. Investigators will be instructed to follow instructions regarding storage in accordance with the products' Instructions for Use.

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

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

8.4.6 Study Product Accountability

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

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, pain VAS, 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, pain VAS, 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.

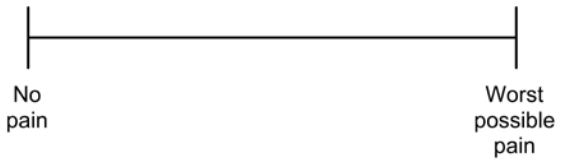
8.6.6 Urine Pregnancy Test and Acceptable Contraceptive Methods

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 Visual Analog Scale for Pain (VAS)

Pain from the injection will be assessed at each NLF by the subject using a 100-mm VAS scale from 0 = no pain to 100 = worst possible pain (Figure 1) at Visit 1/Day 1 immediately after the injection and 15, 30, 45, and 60 minutes post injection. At Visit 2/Day 14, this assessment will be performed for subjects who do not have a touch-up treatment and prior to touch-up, immediately after the injection and 15, 30, 45, and 60 minutes post injection for subjects who do have a touch-up treatment. Subjects will be asked the question "How would you rate your pain from the injection of study material?" and will respond by placing a mark on the VAS.

Figure 1 Visual Analog Scale for Subject Assessment of Pain Following Injection



8.6.8 Wrinkle Severity Rating Scale (WSRS)

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 5/Week 24 (Visit 1/Day 1, Visit 2/Week 2, Visit 3/Week 4, Visit 4/Week 12, and Visit 5/Week 24 [End of Study/Early Termination]) by an evaluator blinded to the treatment assignment of each NLF.

8.6.9 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.

8.6.10 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.

8.6.11 Evaluation for Touch-up

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

8.6.12 Patient Global Aesthetic Improvement (pGAI) Score

The pGAI score is a 5-point scale used to assess the subject's satisfaction with the visual appearance of their NLF correction after treatment by assessment of wrinkle improvement using 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 GAIS score will be assessed for each NLF at Visit 2/Week 2, Visit 3/Week 4, Visit 4/Week 12, and Visit 5/Week 24 (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?" Treatment success is defined as at least a 1-grade improvement from pre-treatment.

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 2, Visit 3/Week 4, Visit 4/Week 12, and Visit 5/Week 24 (End of Study/Early Termination) by a blinded evaluator (blinded to the treatment assignment of each NLF).

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 4. A diary card will be dispensed at Visit 2/ Week 2 if a touch-up treatment is administered. The diary card will be collected at Visit 4/Week 12.

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 8.6.4)
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 8.6.8)
7. Evaluate inclusion/exclusion criteria (Section 8.3)
8. Randomization (Section 8.4.2)
9. Treatment administration (Section 8.4.3)
10. Pain assessment immediately following injection and 15, 30, and 60 minutes post injection (Section 8.6.7)
11. Investigator Ease of Use 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 14 (± 2 days), Visit 3/Day 28 (± 2 days), and Visit 4/Day 84 (± 4 days): Interim Visits

1. WSRS assessment (Section 8.6.8)
2. At Visit 2/Day 14 only, evaluation for touch-up (Section 8.6.11) and administration of touch-up if iGAI score = 3 or 4
3. At Visit 2/Day 14, pain assessment if a touch-up treatment is not administered and pain assessment prior to touch-up, immediately following injection and 15, 30, and 60 minutes post injection if a touch-up treatment is administered. Pain assessment at Visit 3/Day 28 only for subjects who had a touch-up treatment administered at Visit 2/Day 14 (Section 8.6.7)
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 28; dispense subject diary card at Visit 2/Day 14, if applicable and collect subject diary card at Visit 4/ Week 12 if applicable (Section 8.6.14)
9. Schedule next visit
10. Complete CRFs (Section 11.2.1)

8.7.3 Visit 5/Day 168 (Week 24) (± 7 days): Final Visit/Early Termination

1. WSRS assessment (Section 8.6.8)
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)

8.7.4 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 8.6.8)
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 the proportion of responders immediately after injection, where a responder is defined as a subject who had a within-subject difference (Revanesse Ultra – Revanesse Ultra +) in VAS pain score of at least 10 mm.

8.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are the proportion of responders at 15, 30, 45, and 60 minutes post injection and at 2 weeks post injection (prior to touch-up).

8.8.3 Other Efficacy Endpoints

Other efficacy endpoints include change in WSRS score from baseline, pGAI, and iGAI at each scheduled post-baseline visit.

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 Revanesse Plus Instructions for Use and the Revanesse Ultra Instructions for Use.

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 device-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	Colin Eric Hall, Ph.D. Director of Quality Assurance & Regulatory Affairs Prollenium Medical Technologies Inc. 138 Industrial Parkway North Aurora Ontario L4G 4C3 CANADA Tel: 905/508-1469 ext 225 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: Injection-related reactions might occur, such as transient erythema, swelling, pain, itching, discoloration, or tenderness at the injection site. These reactions may last for 1 week. Nodules or induration are also possible at the injection site. Glabellar necrosis, abscess formation, granulomas, and hypersensitivity have all been reported with injections of HA products. Reactions thought to be of hypersensitivity in nature have been reported in less than 1 in every 1,500 treatments. These have consisted of prolonged erythema, swelling, and induration at the implant site.

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, and 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 pain score immediately post injection from both sides of the face.
- Per-protocol (PP): All randomized subjects who met all inclusion/exclusion criteria; received both study products; completed Visit 5/Week 24 within the specified window; had data on pain score from both sides of the face immediately post injection and at 15, 30, 45, and 60 minutes post injection at Visit 1/Day1; had data on pain score at 2 weeks post injection (prior to touch-up); 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 the proportion of responders immediately after injection, where a responder is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra +) in VAS pain score of at least 10 mm on a 100-mm scale. The VAS score will be summarized for each treatment and for the within-subject difference with mean, standard deviation (SD), minimum, median, and maximum. The proportion of responders will be summarized with frequency and percentage. A 95% CI for proportion of responders will be constructed using a one-sample binomial exact test. If the lower bound of this 95% CI is greater than 50%, the test product will be claimed to be superior to the comparator product. The primary endpoint will be summarized by site descriptively.

The secondary efficacy endpoints are the proportion of responders at 15, 30, 45, and 60 minutes post injection and at 2 weeks post injection (prior to touch-up). Upon the significance of the primary efficacy outcome, secondary endpoints will be analyzed using a hierarchical approach will be used. If success is achieved at 15 minutes, 30 minutes will be evaluated; if success is achieved at 30 minutes, 45 minutes will be evaluated; if success is achieved at 45 minutes, 60 minutes will be evaluated; and if success is achieved at 60 minutes, 2 weeks post-injection will be evaluated.

Other efficacy variables include change in WSRS score from baseline, pGAI, and iGAI at each scheduled post-baseline visit. Descriptive summaries will be provided for each treatment and for within-subject difference.

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

9.4.1 Handling of Missing Data

There will not be missing data for the primary efficacy endpoint for the mITT and PP based on the definitions of these analysis populations (Section 9.1).

For the mITT analysis of the secondary efficacy endpoints, missing VAS scores will be replaced using the multiple imputation (MI) method. To evaluate the robustness of MI method, subjects with missing VAS scores will be considered in two different ways: (1) as non-responders to the test product (worse case scenario), and (2) as responders to the test product (best case scenario).

Other efficacy endpoints will be tabulated using the observed data; no missing values will be replaced in the analyses.

9.4.2 Interim Analysis

One interim analysis is planned after all subjects have completed Visit 3 or discontinued prior to Visit 3. The purpose is to determine the safety and pain relief of Revanesse Ultra + to support regulatory submissions outside the US that are currently under review for products containing lidocaine. The sponsor does not plan to change the protocol or stop the study based on the results of the interim analysis.

To maintain the integrity of the study, there will be a separate Statistical Analysis Plan for the interim analysis. The interim analysis will be performed by an independent group that is not involved in the day-to-day trial activities. Access to the interim analysis results will be strictly limited to people who are not directly involved in the study conduct.

Because no change in the study conduct is planned based on the results of the interim analysis, the Haybittle-Peto method will be used to guard the overall Type 1 error rate, with a 0.001 level of significance for the interim analysis and a 0.05 level of significance for the final analysis.

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

Restylane-L Injectable Gel was approved in supplement P040024/S039 on January 29, 2010 for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds such as NLFs. For the supplement study (MA-1100-001), the primary endpoint was the proportion of subjects who had a within-subject difference in VAS (Restylane minus Restylane-L) pain assessment of at least 10 mm at injection. The objective was to show that the 95% confidence interval for the within-subject difference lay above 50%. The key study results are shown in Table 2 (Source: Summary of Safety and Effectiveness Data (SSED), for Restylane-L Injectable Gel).

Table 2 Subjects with at Least a 10 mm Difference in VAS (*Restylane – Restylane-L*)

Table 11. Subjects with at least a 10 mm difference in VAS (*Restylane - Restylane-L*)

Timepoint	No. of subjects with assessments**	Number of subjects with Δ ≥ 10 mm			
		n	%	95% LCL	95% UCL
Treatment*	60	43	71.7	58.6	82.5
15 Minutes	60	28	46.7	33.7	60.0
30 Minutes	60	17	28.3	17.5	41.4
45 Minutes	60	10	16.7	8.3	28.5
60 Minutes	60	4	6.7	1.8	16.2

Source: Statistical Report: Appendix 16.1.9, Table 1.23, Appendix 16.2.6.1
*Primary endpoint
**Denominator (N), % = 100*n/N
UCL=upper confidence limit; LCL=lower confidence limit

The following sample size is calculated based on the data from the above Restylane-L study, assuming that similar statistics and the same criterion will be applicable for Revanesse Ultra + vs Revanesse Ultra.

Table 3 Sample Size Calculations

Proportion of Responders	Power by N (Number of mITT subjects)	
	N=90	N=80
70%	97.2%	94.1%
68%	93.3%	87.8%

To detect the difference between the null hypothesis proportion of responders of 50% and the alternative proportion of responders of 70% via a two-sided exact binomial test with a 0.05 significance level, 80 mITT subjects will supply a power of 94.1%. For the alternative proportion of responders of 68%, 80 mITT subjects will supply a power of 87.8%.

A total of 100 subjects will be randomized to obtain 80 mITT subjects and to provide adequate data for monitoring 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 medical device 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 - NONE

14 INVESTIGATOR AGREEMENT

Protocol Number: SYM 2016-02

Protocol Title: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra + versus Revanesse® Ultra 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 devices 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 device and conduct of the study. I agree to keep records on all subject information (case report forms, shipment and device return forms, and all other information collected during the study) and device disposition in accordance with FDA regulations. I will not enroll any subjects into this protocol until IRB approval and sponsor approval are obtained.

_____

Investigator Name (Print)

_____ _____

Investigator Signature Date

15 APPENDICES

15.1 Revanesse Ultra + (with Lidocaine) Instructions for Use

COMPOSITION

Cross-linked hyaluronic acid (High Viscosity) 25 mg/mL

Lidocaine 0.3% w/w

In phosphate buffered saline

[Cross-linked with Butanediol-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. The product is being evaluated to compare the safety and efficacy profiles of Revanesse® Ultra + (with lidocaine, hereafter referred to as Revanesse Ultra +) to Revanesse Ultra for subjects undergoing correction of nasolabial folds (NLFs). The product is not currently approved by US FDA.

APPLICATION RANGE / INDICATIONS

Revanesse® Ultra + is intended for nasolabial fold correction. The product is intended for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

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

• Contains lidocaine and is contraindicated for patients with a history of allergies to such material.

• 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 or keloid formation should not be treated with Revanesse® Ultra +, or has evidence of scars at the intended treatment sites.

• Contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material, or patients who are Immunocompromised or immunosuppressed.

• Never use Revanesse® Ultra + in conjunction with a laser, intense pulsed light, chemical peeling or dermabrasion treatments, or with Over-the-counter (OTC) wrinkle products or prescription wrinkle treatments within 4 weeks (28 days) prior to treatment and throughout the study.

• Use of any facial tissue augmenting therapy with non-permanent filler or aesthetic facial surgical therapy within 9 months, or a permanent implant placed in the NLF area, or has ever received semi-permanent fillers anywhere in the face or neck, or is planning to be implanted with these products during the study, or a facial tattoo that would interfere with the NLF correction.

• 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.

- People under the age of 22 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 multiple severe allergies, or with allergic history including anaphylaxis, multiple severe allergies, atopy, or allergies to natural rubber latex, lidocaine or any amide-based anaesthetic, hyaluronic acid products, or Streptococcal proteins or have plans to undergo desensitization therapy during the term of the study

• Patients with acute or chronic skin disease in or near the injection sites, or with any infection or unhealed wound of the face.

• Coagulation defects or under anti-coagulation therapy, or Aspirin or nonsteroidal anti- inflammatory drugs within 1 week (7 days) prior to treatment. Individuals who are under Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders, coagulation defects or connective tissue disorders should not use this product.

- 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 investigational site of the Revanesse Ultra + clinical study 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 depth of injection is at the discretion of the practitioner/physician and is dependent on the severity of the wrinkle/depression and 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.

• Individuals using aspirin, non-steroidal anti-inflammatory medications, St. John's Wort or high doses of Vitamin E supplements prior to treatment or any similar medications be aware that these may increase bruising and bl eeding at the injection site.

• Based on a toxicological risk assessment for lidocaine, patients should be limited to 20 mL per 60 kg (130 lbs) body mass per annum. The safety of injecting greater amounts has not been established.

• The safety for use in patients under 22 y ears has not been established, and treatment must not be used.

• Patients who are visibly ill, with bacterial or viral infections, influenza, or active fever should not be treated until a resolution of their symptoms.

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 borne diseases.

The Revanesse family of products should not be used in areas that have high vascularity. Use in these areas such as the glabella and nose region has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion (i.e.: blindness).

Physicians should take extra precautions when treating patients with auto immune disorder, HIV, AIDS or who are under immuno-therapy as these patients are at higher risk of adverse events.

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 FDA 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

CLINICAL RESEARCH ORGANIZATION

Symbio LLC 21 Perry Street

Port Jefferson, NY 11777 Tel: (631) 474-8531

Fax: (631) 474-8534

15.2 Revanesse Ultra Instructions for Use

Revanesse Ultra

COMPOSITION

Cross-linked hyaluronic acid (High Viscosity) 25 mg/mL

In phosphate buffered saline

[Cross-linked with Butanediol-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. The product is being evaluated to compare the safety and efficacy profiles of Revanesse Ultra + (with lidocaine, hereafter referred to as Revanesse Ultra +) to Revanesse Ultra for subjects undergoing correction of nasolabial folds (NLFs). The product is not currently approved by US FDA.

APPLICATION RANGE / INDICATIONS

Revanesse Ultra is intended for nasolabial fold correction. The product is intended for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

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 or keloid formation should not be treated with Revanesse Ultra, or has evidence of scars at the intended treatment sites.

• Contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material, or patients who are Immunocompromised or immunosuppressed.

• Never use Revanesse Ultra in conjunction with a laser, intense pulsed light, chemical peeling or dermabrasion treatments, or with Over-the-counter (OTC) wrinkle products or prescription wrinkle treatments within 4 weeks (28 days) prior to treatment and throughout the study.

• Use of any facial tissue augmenting therapy with non-permanent filler or aesthetic facial surgical therapy within 9 months, or a permanent implant placed in the NLF area, or has ever received semi-permanent fillers anywhere in the face or neck, or is planning to be implanted with these products during the study, or a facial tattoo that would interfere with the NLF correction.

• 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.

• People under the age of 22 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 multiple severe allergies, or with allergic history including anaphylaxis, multiple severe allergies, atopy, or allergies to natural rubber latex, hyaluronic acid products, or Streptococcal proteins or have plans to undergo desensitization therapy during the term of the study

• Patients with acute or chronic skin disease in or near the injection sites, or with any infection or unhealed wound of the face.

• Coagulation defects or under anti-coagulation therapy, or Aspirin or nonsteroidal anti-inflammatory drugs within 1 week (7 days) prior to treatment. Individuals who are under Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders, coagulation defects or connective tissue disorders should not use this product.

• 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 investigational site of the Revanesse Ultra clinical study 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 borne diseases.

• Keep the product at room temperature for 30 minutes prior to injection.

• The depth of injection is at the discretion of the practitioner/physician and is dependent on the severity of the wrinkle/depression and 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.

• Individuals using aspirin, non-steroidal anti-inflammatory medications, St. John's Wort or 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.

• The safety for use in patients under 22 years has not been established, and treatment must not be used.

• Patients who are visibly ill, with bacterial or viral infections, influenza, or active fever should not be treated until a resolution of their symptoms.

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 borne diseases.

The Revanesse family of products should not be used in areas that have high vascularity. Use in these areas such as the glabella and nose region has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion (i.e.: blindness).

Physicians should take extra precautions when treating patients with auto immune disorder, HIV, AIDS or who are under immuno-therapy as these patients are at higher risk of adverse events.

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 FDA 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

CLINICAL RESEARCH ORGANIZATION

Symbio LLC

21 Perry Street

Port Jefferson, NY 11777

Tel: (631) 474-8531

Fax: (631) 474-8534