SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: Revanesse® Lips+

Device Procode: LMH

Applicant's Name and Address: Prollenium Medical Technologies Inc.
138 Industrial Parkway N.
Aurora, L4G 4C3, ON, Canada

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160042/S010

Date of FDA Notice of Approval: September 21, 2020

The original PMA for Revanesse® Versa PMA (PMA#P160042) was approved on August 4, 2017 and is indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, in adults 22 years of age or more. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. Revanesse® Versa+, which incorporates lidocaine into the formulation of Revanesse® Versa, was approved for the same indication on August 2, 2018 (P160042/S003). The current supplement was submitted to expand the indication for Revanesse® Lips+ (identical formulation to Revanesse® Versa+) for submucosal implantation for lip augmentation in patients 22 years of age or older.

II. INDICATIONS FOR USE

Revanesse® Lips+ is indicated for submucosal implantation for lip augmentation in patients 22 years of age or older.

III. CONTRAINDICATIONS

- Patients who develop hypertrophic scarring or keloid formation should not be treated with Revanesse® Lips+.
- Patients with evidence of scars at the intended treatment sites should not be treated with Revanesse® Lips+.
- Never use Revanesse® Lips+ 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.
- Patients with acne and / or other inflammatory diseases of the skin should not be treated with Revanesse® Lips+.
- Patients with unattainable expectations should not be treated with Revanesse® Lips+.
- Patients with multiple severe allergies or with allergic history including anaphylaxis, multiple severe allergies, and atopy should not be treated with Revanesse® Lips+.
- Patients with allergies to natural rubber latex should not be treated with Revanesse® Lips+.
- Patients with allergies to hyaluronic acid products, or Streptococcal proteins should not be treated with Revanesse® Lips+.
- Patients who have plans to undergo desensitization therapy should not be treated with Revanesse® Lips+.
- Revanesse® Lips+ should not be used in patients with acute or chronic skin disease in or near the injection sites, or with any infection or unhealed wound of the face.
- Patients who are under concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders, coagulation defects or connective tissue disorders should not use this product.
- Revanesse® Lips+ contains lidocaine, and is contraindicated for patients with a history of allergies or sensitivities to such material and should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- Revanesse® Lips+ is only intended for submucosal injection into the lips or intradermal injection into the nasolabial folds and must not be injected into blood vessels. Implantation of Revanesse® Lips+ into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Revanesse® Lips+ labeling.

V. DEVICE DESCRIPTION

Revanesse® Lips+ is a biocompatible, biodegradable, non-pyrogenic, sterile, injectable viscoelastic clear colorless hydrogel based on bioresorbable BDDE cross-linked hyaluronan (HA) (22 – 28 mg / mL concentration) containing 0.3% lidocaine. The HA is produced by the *Streptococcus* species of bacteria. The gel is delivered in a pre-filled disposable glass syringe. Each syringe is fitted with a Luer lock adaptor, a plunger rod, a rubber stopper tip cap, and a finger grip. Each box of Revanesse® Lips+ contains two 1.0 mL syringes of Revanesse® Lips+ along with two 0.5-inch 30- gauge sterile needles. The syringe is labeled with the product name, the manufacturer, lot number, and expiration date. There is a removable portion of the label, which can be affixed to the patient record.

The Instructions for Use contain additional product details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other commercially available products approved for lip augmentation. Other options include surgery or implantation of tissue augmenting substances (e.g., other dermal fillers or autologous fat). Each alternative has its own advantages and disadvantages. A patient should discuss these alternatives with his / her physician to select the most appropriate method that meets expectations and lifestyle.

VII. MARKETING HISTORY

Since 2012, Prollenium has marketed Revanesse® products in Canada. The lip augmentation product is marketed as Revanesse® Kiss+ under the Health Canada Device Licence (#69955) and is similar in composition, though not identical to Revanesse® Lips+. In addition, Revanesse® Kiss+ has been marketed in other countries outside of the United States including the following: Canada, Israel, Nigeria, Kuwait, Ukraine, United Arab Emirates, South Africa, Venezuela, Argentina, Costa Rica, Mexico, Singapore, Ecuador, Hong Kong, Iraq, Iran, Albania, Kazakhstan, and Azerbaijan. Revanesse® Kiss+ has not been withdrawn from the market for any reason.

Revanesse® Ultra (now known as Revanesse® Versa) has been on the market in the United States since 2017 for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. In 2018, the product containing lidocaine (Revanesse® Versa+) was approved for US marketing for the same indications. Revanesse® Versa+ is identical in formulation to Revanesse® Lips+. Please see Postmarket Surveillance Data for Revanesse® Kiss+, Revanesse® Versa, and Versa+ below.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of the device, as well as for other devices in the same category include: tenderness, swelling, firmness (induration), lumps/bumps (mass), bruising, pain, redness, discoloration, and itching.

Rare, but serious, adverse events associated with the intravascular injection of soft-tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

For the specific adverse events that occurred in the clinical study, please see Section X below.

Postmarket Surveillance Data

Revanesse® Lips+ is identical in formulation to Revanesse® Versa+. Postmarket surveillance for Revanesse® Versa and Revanesse® Versa+ reported the following adverse events (AEs) with 5 or greater instances: swelling, bruising, and lumps for the United States. Revanesse® Kiss+ is the lips product marketed in the rest of the world markets, and is similar in composition, though not identical. There were no incidences of more than 5 of any adverse event type for Revanesse® Kiss+ reported to the company, nor were there any contained in the literature.

IX. SUMMARY OF NONCLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for submucosal implantation for lip augmentation in patients 22 years of age or older. There was no change in the product manufacturing or specifications or shelf life (24 months). Therefore, please refer to the nonclinical data previously presented in support of PMA P160042 and P160042/S003.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Prollenium Medical Technologies, Inc. performed two clinical studies to establish a reasonable assurance of safety and effectiveness of Revanesse® Lips+ for injection into the lips for lip augmentation in adults 22 years of age or older in the US under IDE # G180071. PRO 2018-02 *A Multicenter, Double-blind, Randomized, Controlled Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation* was the treatment study which enrolled 158 subjects and lasted for a duration of 10 months. PRO 2018-03 *A Multicenter, Open-Label Retreatment Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation* was the retreatment study, which enrolled 84 subjects that were initially treated in PRO 2018-02 and lasted 8 months. Data from these clinical studies

were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

A. Study Design

Subjects in PRO 2018-02 *A Multicenter, Double-blind, Randomized, Controlled Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation* were treated between July 13, 2018 and May 3, 2019. The purpose of the study was to compare the safety and effectiveness profiles of Revanesse® Lips+ to an approved dermal filler Comparator, for subjects seeking lip augmentation. This study included 158 patients. There were 6 investigational sites.

This was a double-blind, randomized, controlled, multicenter clinical study of subjects seeking lip augmentation. Subjects were treated with Revanesse® Lips+ or with the Comparator. Subjects were randomized to treatment with the subject product or Comparator control in a 1:1 ratio. The evaluating investigator (EI) assessing the effectiveness endpoint and the subject were blinded to the treatment; however, the treating investigator (TI) was unblinded. The maximum volume allowed per treatment was 1.5 mL per lip (1.5 for upper, 1.5 for lower) and 1.0 mL for perioral rhytid correction. Thus, the maximum amount that could be used at one treatment session was 4.0 ml. The TI determined the amount product injected into the treatment area (did not exceed 4.0 mL per treatment session).

The subjects were men or non-pregnant, non-breastfeeding women over 22 years of age with an overall score of very thin (0) or thin (1) lips on the 5 point Lip Fullness Grading Scale (LFGS) The scale ratings were 0 for very thin, 1 for thin, 2 for moderately thick, 3 for thick, and 4 for full (A Validated Lip Fullness Grading; Scale; Carruthers, A. et al, Dermatol Surg 2008; 34: S161-S166) , or had a Fitzpatrick Skin Type (FST) of IV, V, or VI and an LFGS score of thick (3) or full (4) and desired treatment to the vermilion body of one or both lips.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the clinical studies PRO 2018-02 treatment and PRO 2018-03 retreatment was limited to subjects who met the following inclusion criteria:

   Inclusion Criteria:

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

the Treating and Evaluating Investigators, and desired at least a 1-point improvement in overall LFGS score; OR Had a Fitzpatrick skin phototype IV, V or VI and an LFGS score of thick or full, as agreed upon by the Treating and Evaluating Investigators, and desired treatment to the vermilion body of 1 or both lips

4. Willing to give written informed consent

Subjects were not permitted to enroll in the PRO 2018-02 treatment and PRO 2018-03 retreatment studies if they met any of the following exclusion criteria:

Exclusion Criteria

1. Women who were pregnant, lactating, or planning a pregnancy
2. History of allergy, anaphylaxis or hypersensitivity to injectable hyaluronic acid products, local anesthetics of the amide type such as lidocaine, or to latex, or planning to undergo desensitization therapy during the study
3. Had lip tattoos, piercings, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments
4. Had abnormal lip function, with inability to effectively sip water through a straw
5. Had abnormal lip sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip
6. Had moderate or severe abnormal lip asymmetry
7. Had any mass formation on the lip
8. Had dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities as judged by the Treating Investigator. Subjects planning to undergo extensive dental procedures such as dental implants, multiple tooth extractions, or oral surgery could not participate. Minor dental procedures such as teeth cleaning and repair of caries were not exclusionary
9. Had undergone facial plastic surgery or received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene, polyacrylamide, lifting threads) anywhere in the face or neck, or planning to be implanted with any of these products during the study
10. Had undergone semi-permanent dermal filler treatment (e.g., calcium hydroxylapatite, poly-L lactic acid) in the lower face (below the orbital rim) within 12 months before enrollment or planning to undergo such treatment during the study
11. Had undergone facial tissue augmentation with fat injections, botulinum toxin injections in the lower face (below the orbital rim), mesotherapy, or cosmetic procedures in the face or neck (e.g., face-lift, laser, photo-

modulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, microneedling, or other ablative procedures) within 9 months before enrollment or planning to undergo any of these procedures during the study

12. Had used ANY lip filling agents within 12 months of study enrollment (hyaluronic acid products, collagen-based products, etc.)
13. Had used any lip plumping products or devices within 10 days before enrollment or planning to use such products during the study
14. Had begun using any over-the-counter (OTC) or prescription oral or topical anti-wrinkle products for the lips or around the mouth within 90 days before enrollment or planning to begin using such products during the study (Subjects who had been on a stable regimen of such products for at least 90 days were eligible for the study and had to continue their regimen throughout the study.)
15. On an ongoing regimen of anticoagulation therapy (e.g., warfarin), thrombolytics, or inhibitors of platelet aggregation or nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., aspirin, ibuprofen) or other substances known to increase coagulation time (e.g., herbal supplements with garlic or gingko) within 10 days of undergoing study device injections. Subjects who withheld such therapy for 10 days before AND after any injection session could participate
16. Had a history or presence of bleeding disorders
17. Had used systemic corticosteroids or immunosuppressive medications within 30 days prior to treatment
18. On a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine)
19. Had an active inflammation (skin eruptions such as cysts, pimples, rashes, or hives), infection, cancerous or precancerous lesion, or unhealed wound on the face
20. Had a history of known susceptibility to keloid formation or hypertrophic scars
21. Had porphyria
22. Had active herpes labialis lesions at the time of injections. Subjects with a history of herpes labialis who had four (4) or more outbreaks in the 12 months prior to enrollment were also excluded even in the absence of lesions at the baseline visit
23. Had impaired cardiac conduction, severely impaired hepatic function, or severe renal dysfunction that, in the opinion of the investigator, would place them at risk of associated complications from these illnesses during the course of the study
24. Had any uncontrolled disease, i.e., a condition that has not been appropriately diagnosed, evaluated, and received medically appropriate

treatment or care

25. Had severe cardiovascular disease; examples include but are not limited to New York Heart Association heart failure classification III or IV, unstable angina, and internal pacemakers.

2. Follow-up Schedule

Subjects meeting inclusion/exclusion criteria were randomized 1:1 to treatment with either Revanesse® Lips+ or the Comparator (an FDA-approved dermal filler containing lidocaine). Up to 2 treatments approximately 1 month apart (initial treatment and up to 1 touch-up treatment) were allowed. All subjects returned for routine safety and effectiveness follow-up visits at 1, 2, 3, and 6 months after the initial treatment during the primary safety and effectiveness phase. Comparator control subjects followed a similar effectiveness evaluation schedule through Month 6. Subjects were treated at Visit 1/baseline with an optional touch up at Visit 2/Month 1. Subjects were then evaluated at Visit 3/Month 2, Visit 4/Month 3 and Visit 5/Month 6. At Visit 5/Month 6, subjects were invited to participate in an optional repeat treatment (retreatment) study (discussed below). 84 subjects participated after completion of the treatment study, with follow-up for 6 months after retreatment. Subjects were seen at the retreatment visit, and again at Visit 2/Month 1 and Visit 3/Month 2 with a follow-up phone calls at Day 3, Day 14, and Day 168 (Month 6).

Safety was assessed by monitoring adverse events (AEs) at all study visits. Safety was also assessed with vision evaluations by a trained evaluator: Snellen visual acuity, confrontational visual fields, and ocular motility. These assessments were performed prior to any treatment. These assessments were also repeated 30 minutes following any treatment and at all follow-up visits. In addition, safety was assessed with the following functional evaluations: Lip Function, Lip Sensation, Lip Texture, Lip Firmness, Lip Symmetry, Lip Movement/Function.

Adverse Events of Special Interest (AESI) were monitored for safety, defined as events that required more detailed and timely reporting, including:

- any changes in vision
- any events attributable to an embolic or ischemic cause (i.e., skin infarction)
- Any incidence of an event due to an embolic or ischemic cause or visual disturbances (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye, blind spot or shadow in the visual field, trouble moving eyes, etc.)

3. Clinical Endpoints

With respect to safety, preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments. Subjects were instructed to record the quadrant of the face the sign/symptom was located and rate each treatment site response listed on the diary as "Mild (easily tolerated)," "Moderate (affecting daily activity)," or "Severe (unable to do daily activity)". Adverse Events were reported by the TI at all follow-up visits where applicable.

With regards to effectiveness, the primary effectiveness measure was the blinded EI's assessment of the subject's lip fullness using the validated 5-point photonumeric LFGS (Table 1). The LFGS is a 5-point photonumeric rating scale that was developed to objectively quantify the 3-dimensional fullness of the lip (Carruthers et al, 2008).

Table 1. Lip Fullness Grading Scale (LFGS)

Rating	Scale Description of lips
0	Very Thin
1	Thin
2	Moderately Thick
3	Thick
4	Full

The primary effectiveness endpoint was change from baseline to Visit 3/Month 2 in overall LFGS of both lips together. A 95% confidence interval (CI) for the difference between the two treatment groups (Revanesse® Lips+ minus Comparator product) with respect to the primary endpoint was constructed.

The secondary effectiveness endpoints were the following:

- Percent of subjects with treatment success (responder on overall LFGS) at Visit 3/Month 2, where responder was defined as a subject with at least a 1 grade increase from baseline on the overall LFGS of both lips together
- Change from baseline to Visit 4/Month 3 in overall LFGS of both lips together
- Change from baseline to Visit 5/Month 6 in overall LFGS of both lips together

The Global Aesthetic Improvement Score was assessed by the investigator (iGAI) and patient (pGAI). The GAI 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.

All effectiveness analyses were performed for both the mITT and PP populations.

Other effectiveness analyses included:

- Patient Global Aesthetic Improvement (pGAI), Investigator Global Aesthetic Improvement (iGAI), and Swelling Assessment at each scheduled visit,
- Percent of subjects with treatment success (responder: upper lips, lower lips LFGS) at Visit 3/Month 2 where responder was defined as a subject with at least a 1-grade increase from baseline on the LFGS post augmentation,
- Satisfaction with lips Visual Analog Scale (VAS) at each scheduledvisit,
- Change from baseline to Visit 4/Month 3 and Visit 5/Month 6 in upper lips, lower lips LFGS.

Safety analysis included:

- Lip Sensation Test (Cotton Wisp and 0.4G Monofilament) by Visit
- Lip Texture, Firmness, Symmetry, and Movement/Function Evaluation by Visit
- Vision evaluations by a trained evaluator: Snellen visual acuity, confrontational visual fields, and ocular motility
- Adverse Events: Related to and Excluding Vascular Injections/Visual Events, Related to and Excluding Vascular Injections/Visual Events Leading to Study Treatment Interrupted/Discontinued, Serious Adverse Events Related to and Excluding Vascular Injections/Visual Events, Related to Vascular Injections/Visual Events lasting more than 30 Days

B. Accountability of PMA Cohort

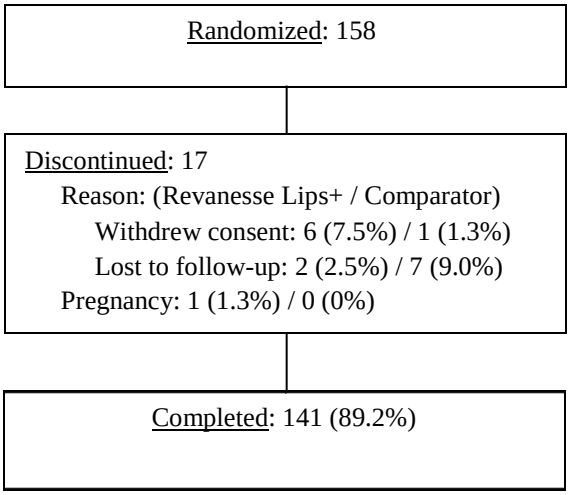
The clinical study PRO 2018-02 *A Multicenter, Double-blind, Randomized, Controlled Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation* included 158 randomized subjects, 141 subjects (89.2% N=158) completed the study. The most frequent reason for discontinuation was withdrawal of consent in the Revanesse® Lips+ group, 6 subjects (7.5% N=80) and lost to follow-up in the Comparator group, 7 subjects (9.0% N=78). One subject (1.3% N=78) withdrew consent in the Comparator group, 1 subject (1.3% N=80) discontinued due to pregnancy in the Revanesse® Lips+ group and 2 subjects (2.5% N=80) were lost to follow-up in the Revanesse® Lips+ group.

Of the subjects that were randomized, there were 158 as treated (AT), 149 modified intent-to-treat (mITT), 141 completed, 109 per-protocol (PP) subjects (Figure 2, Table 2). Of the

141 who completed the initial study, 84 were enrolled in the retreatment study PRO 2018-03 *A Multicenter, Open-Label Retreatment Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation.* Details of the retreatment study are shown in the section 4, Retreatment study - PRO 2018-03 A Multicenter, Open-Label Retreatment Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation.

1. Subject Disposition Flow Chart

Figure 2. Subject Accountability



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

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

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

Effectiveness analyses was performed on the mITT and PP populations, with PP as the primary population and mITT supportive. Safety analyses was performed on the ITT population.

Table 2. Analysis Populations / Reason for Discontinuation

Population	Revanesse® Lips+	Comparator	Total
Subjects Randomized	80	78	158
Subjects Included in the As-Treated (AT) Population	80 (100%)	78 (100%)	158 (100%)
Subjects Included in the Modified Intent-to-Treat (mITT) Population	76 (95.0%)	73 (93.6%)	149 (94.3%)
Subjects completed study	71 (88.8%)	70 (89.7%)	141 (89.2%)
Subjects discontinued prematurely	9 (11.3%)	8 (10.3%)	17 (10.8%)
Subjects Included in the Per-Protocol (PP) Population	54 (67.5%)	55 (70.5%)	109 (69.0%)
Reason subjects discontinued			
Subject or legal representative withdrew consent	5 (6.3%)	0	5 (3.2%)
Subject withdrew consent after hyaluronidase treatment for a TEAE	1 (1.3%)	1 (1.3%)	2 (1.3%)
Subject became pregnant	1 (1.3%)	0	1 (0.6%)
Lost to follow-up	2 (2.5%)	7 (9.0%)	9 (5.7%)

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the Revanesse® Lips+ and Comparator groups are presented in Table 3.

Table 3. Demographic and Baseline Characteristics (ITT Population)

Parameter	Category	Revanesse® Lips+ (N = 80)	Comparator (N = 78)	Total (N = 158)	p-value
Gender	Female	80 (100%)	76 (97.4%)	156 (98.7%)	0.142
	Male	0 (0%)	2 (2.6%)	2 (1.3%)	
Ethnicity	Hispanic or Latino	26 (32.5%)	18 (23.1%)	44 (27.8%)	0.044
	Not Hispanic or Latino	54 (67.5%)	60 (76.9%)	114 (72.2%)	
Race	White	65 (81.3%)	61 (78.2%)	126 (79.7%)	N/A
	Asian	1 (1.3%)	0 (0%)	1 (0.6%)	
	Black or African American	12 (15.0%)	15 (19.2%)	27 (17.1%)	
	Other	2 (2.5%)	0 (0%)	2 (1.3%)	

Parameter	Category	Revanesse® Lips+ (N = 80)	Comparator (N = 78)	Total (N = 158)	p-value
	Mixed	0 (0%)	2 (2.6%)	2 (1.3%)	
Age (years)	N	80	78	158	0.048
	Mean ± SD	45.6 ± 11.85	49.2 ± 11.85	47.4 ± 11.94	
	Median	47.5	52.0	49.0	
	Min, Max	22, 71	22, 74	22, 74	
Age Groups	18 to < 40	26 (32.5%)	15 (19.2%)	41 (25.9%)	N/A
	40 to < 64	51 (63.8%)	55 (70.5%)	106 (67.1%)	
	64 to < 75	3 (3.8%)	8 (10.3%)	11 (7.0%)	
Body Mass Index (BMI)	N	80	78	158	0.094
	Mean ± SD	25.87 ± 4.360	27.64 ± 5.696	26.75 ± 5.125	
	Median	25.10	26.70	26.00	
	Min, Max	18.1, 35.3	18.3, 46.1	18.1, 46.1	
Fitzpatrick Skin Type	N	80	78	158	
	I	3 (3.8%)	7 (9.0%)	10 (6.3%)	0.195
	II	25 (31.3%)	19 (24.4%)	44 (27.8%)	
	III	24 (30.0%)	27 (34.6%)	51 (32.3%)	
	IV	17 (21.3%)	10 (12.8%)	27 (17.1%)	
	V	5 (6.3%)	4 (5.1%)	9 (5.7%)	
	VI	6 (7.5%)	11 (14.1%)	17 (10.8%)	

D. Safety and Effectiveness Results

The safety and effectiveness of Revanesse® Lips+ for lip augmentation was not evaluated in men in the initial PRO 2018-02 study. Two men were initially treated with the Comparator device, but received retreatment with Revanesse® Lips+ in the retreatment study, PRO 2018-03. To further support the safe use of Revanesse® Lips+ in males, a comparison of six clinical studies for safety and effectiveness by gender was performed. The clinical studies included in the comparison are SYM 2014-02 and SYM 2014-02 Retreatment *A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra versus the Comparator for the Correction of Nasolabial Folds* where 7 male subjects were treated and retreated, SYM 2016-02 *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* where 7 male subjects were treated, PRO 2018-02 *A Multicenter, Double-blind, Randomized, Controlled Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation* where 0 male subjects were treated and PRO 2018-03 *A Multicenter, Open-Label Retreatment Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation* where 2 male subjects were

treated. Note that Revanesse® Ultra+ and Revanesse® Versa+ are identical in formulation to Revanesse® Lips+. Revanesse® Ultra has the same formulation, without added lidocaine (the name was changed to Revanesse® Versa).

The demographics of the male subjects in each study are included in the Table 4 below. In addition, the TEAEs that were reported are broken down by Fitzpatrick skin type. The TEAEs reported for male subjects in the six studies were similar to those reported for female subjects.

Table 4. Number of Male Subjects Treated by Fitzpatrick Skin Type (FST) in Revanesse® Versa/Revanesse® Versa+ Studies

Protocol	FST I	FST II	FST III	FST IV	FST V	FST VI
SYM 2014-02	0	1	4	2	0	0
SYM 2016-02	0	0	5	0	2	0
PRO 2018-02	0	0	0	0	0	0
PRO 2018-03	0	1	1	0	0	0

Note that Revanesse® Versa+ is identical in formulation to Revanesse® Lips+

Table 5. Number of Male Subjects With Reported Treatment Emergent Adverse Events by Fitzpatrick Skin Type (FST) in Revanesse® Versa/Revanesse® Versa+ Studies

TEAE Description	FST I N=0	FST II N=2	FST III N=10	FST IV N=2	FST V N=2	FST VI N=0
Injection Site Swelling	N/A	1	3	1	0	N/A
Injection Site Haematoma	N/A	0	2	2	0	N/A
Injection Site Pain	N/A	1	2	0	0	N/A
Headache	N/A	0	2	0	0	N/A
Erythema	N/A	0	2	0	0	N/A
Papule	N/A	0	1	0	0	N/A
Pruritus	N/A	0	2	0	0	N/A

Note that Revanesse® Versa+ is identical in formulation to Revanesse® Lips+

The retrospective complaint data for the Revanesse® dermal fillers since the first PMA approval in the United States and Worldwide complaint data from 2016 did not identify safety concerns for men treated with Revanesse® dermal fillers.

1. Safety Results

The studies did not demonstrate any device related serious adverse effects (SAEs) associated with the use of Revanesse® Lips+. Subjects were treated in the upper and lower lips, and some subjects were injected in perioral areas (34 injections with Revanesse® Lips+ and 38 injections with Comparator).

Table 6. Number of Injections by Lip Location

Lip Location	Revanesse® Lips+	Comparator
Upper Lip	117	104
Lower Lip	108	103
Total	259	245

The treatment-emergent adverse events (TEAEs) are included in Tables 7, 8, and 9. There were 4 adverse events of special interest (AESI), which are described as any changes in vision, and any events attributable to an embolic or ischemic cause. These events were considered unlikely related to investigational product. Two subjects experienced blurred vision, one subject experienced retinal detachment and one subject experienced Bell's palsy. An additional SAE was reported during the study: a subject was diagnosed with breast cancer.

TEAEs, SAEs, and AESI were monitored. Other safety evaluations included lip function, lip sensation, lip texture, lip firmness, lip symmetry, and lip movement/function. Tables 7, 8, 9 and 10 include detailed information related to the AEs that occurred in the clinical study.

TEAEs, excluding vascular injections/visual events, were reported for 75 subjects in each treatment group (93.8% Revanesse® Lips+, 96.2% Comparator). The most frequently reported TEAEs (with Revanesse® Lips+ and Comparator, respectively) were injection site swelling (87.5%, 89.7%), injection site bruising (71.3%, 56.4%), injection site pain (21.3%, 30.8%), and facial asymmetry (15.0%, 10.3%). Except for 1 event of facial asymmetry, these TEAEs were considered treatment-related. Most TEAEs were reported as mild or moderate in intensity.

Table 7. Overall Summary of TEAEs for As-Treated Population

Duration	Revanesse® Lips+ Number of Events N=257	Comparator Number of Events N=261
0-7 days	171 (66.5%)	203 (77.8%)
8-14 days	40 (15.6%)	30 (11.5%)
15-30 days	22 (8.6%)	12 (4.6%)
>31 days	24 (9.3%)	16 (6.1%)

Table 8. Duration of TEAEs for as-treated population

	Revanesse® Lips+ N=257 events				Comparator N=261 events			
System Organ Class Preferred Term	0-7 days	8-14 days	15-30 days	>31 days	0-7 days	8-14 days	15-30 days	>31 days
	N=171 (66.5%)	N=40 (15.6%)	N=22 (8.6%)	N=24 (9.3%)	N=203 (77.8%)	N=30 (11.5%)	N=12 (4.6%)	N=16 (6.1%)
Injection site bruising	59/171 (78.1%)	14/40 (35.0%)	4/22 (18.2%)	0 (0.0%)	47/203 (23.2%)	12/30 (40.0%)	1/12 (8.3%)	0 (0.0%)
Injection site erythema	7/171 (4.1%)	0 (0.0%)	1/22 (4.5%)	0 (0.0%)	6/203 (3.0%)	2/30 (6.7%)	0 (0.0%)	0 (0.0%)
Injection site mass	1/171 (0.6%)	0 (0.0%)	1/22 (4.5%)	4/24 (16.7%)	7/203 (3.0%)	0 (0.0%)	1/12 (8.3%)	1/16 (6.3%)
Injection site movement impairment	2/171 (1.2%)	1/40 (2.5%)	0 (0.0%)	0 (0.0%)	6/203 (3.0%)	1/30 (3.3%)	2/12 (16.7%)	0 (0.0%)
Injection site pain	14/171 (8.2%)	5/40 (12.5%)	4/22 (18.2%)	0 (0.0%)	29/203 (14.3%)	1/30 (3.3%)	0 (0.0%)	0 (0.0%)
Injection site pruritus	3/171 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2/203 (1.0%)	0 (0.0%)	1/12 (8.3%)	0 (0.0%)
Injection site swelling	73/171 (42.7%)	15/40 (37.5%)	2/22 (9.1%)	4/24 (16.7%)	82/203 (40.4%)	10/30 (33.3%)	5/12 (41.7)	2/16 (12.5%)
Facial asymmetry	6/171 (3.5%)	1/40 (2.5%)	4/22 (18.2%)	5/24 (20.8%)	4/203 (2.0%)	0 (0.0%)	0 (0.0%)	2/16 (12.5%)
Haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1/203 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection site dryness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1/12 (8.3%)	0 (0.0%)

Eighteen subjects treated with Revanesse® Lips+ experienced 24 adverse events that lasted longer than 30 days with the longest duration of TEAEs being 4 instances of injection site mass lasting between 47 and 56 days, swelling lasting between 53 days and ongoing at the end of the study, and facial asymmetry lasting between 45 days and ongoing at the end of the study. Events related to the injection procedure included, swelling, lip asymmetry, injection site mass or lump and mucocele. The remaining AEs were not treatment related and included endometriosis, insulin resistance, chapped lips, high platelet count, insomnia, herpes, breast cancer, allergic rhinitis and influenza.

Thirteen subjects treated with the Comparator experienced 16 AEs that lasted longer than 30 days with the longest duration of TEAEs being 2 instances of swelling, one instance lasting 35 days, the other ongoing at the end of the study, and 2 instances of facial asymmetry ongoing at the end of the study. There was 1 instance of injection site mass lasting 83 days. Events related to the injection procedure were the same as subjects

treated with Revanesse® Lips+ with the exception of 1 instance of haemorrhage and 1 instance of injection site dryness. The remaining AEs were not treatment related and included headache, tingling in lips, muscles and joint locked, fever, back pain, vomiting, cold sore, swollen gums, lesion on lip, ear infection, fever blister, canker sore, upper respiratory infection, chapped lips, torn ligaments in ankle, shoulder torn rotator cuff, herniated disc, rib fracture, strep throat, perleche, neck pain thermal burn on arm and intermittent drooling.

Table 9. Number of Subjects Experiencing TEAEs by Severity after Initial Treatment Occurring in > 5% of Treated Subjects

System Organ Class Preferred Term	Revanesse® Lips+ N=80			Comparator N=78		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Injection site bruising	44 (55.0%)	12 (15.0%)	1 (1.3%)	34 (43.6%)	10 (12.8%)	0 (0.0%)
Injection site erythema	7 (8.8%)	1 (1.3%)	0 (0.0%)	7 (9.0%)	1 (1.3%)	0 (0.0%)
Injection site mass	6 (7.5%)	0 (0.0%)	0 (0.0%)	9 (11.5%)	0 (0.0%)	0 (0.0%)
Injection site Movement impairment	2 (2.5%)	0 (0.0%)	1 (1.3%)	4 (5.1%)	2 (2.6%)	0 (0.0%)
Injection site pain	12 (15.0%)	4 (5.0%)	1 (1.3%)	17 (21.8%)	7 (9.0%)	0 (0.0%)
Injection site pruritus	4 (5.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)	0 (0.0%)	0 (0.0%)
Injection site swelling	58 (72.5%)	11 (13.8%)	1 (1.3%)	51 (65.4%)	16 (20.5%)	3 (3.8%)

Counts reflect numbers of subjects reporting one or more TEAE Excluding Vascular Injections/Visual Events that map to the MedDRA (version 20.0) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one TEAE Excluding Vascular Injections/Visual Events are counted only once

Table 10. Number of Subjects Experiencing TEAEs Excluding Vascular Injection/Visual Events Reported for More Than 1 Subject in Either Treatment Group

System Organ Class Preferred Term	Revanesse® Lips + (N= 80) n (%)	Comparator (N=78) n (%)
General disorders and administration site conditions		
Injection site bruising	57 (71.3)	44 (56.4)
Injection site erythema	8 (10.0)	8 (10.3)
Injection site mass	6 (7.5)	9 (11.5)
Injection site movement impairment	3 (3.8)	6 (7.7)
Injection site pain	17 (21.3)	24 (30.8)
Injection site pruritus	4 (5.0)	3 (3.8)
Injection site swelling	70 (87.5)	70 (89.7)

System Organ Class Preferred Term	Revanesse® Lips + (N= 80) n (%)	Comparator (N=78) n (%)
Infections and infestations		
Influenza	2 (2.5)	0 (0%)
Oral herpes	1 (1.3)	2 (2.6)
Sinusitis	2 (2.5)	0 (0%)
Upper respiratory tract infection	1 (1.3)	3 (3.8)
Musculoskeletal and connective tissue disorders		
Facial asymmetry	12 (15.0)	8 (10.3)
Nervous system disorders		
Headache	1 (1.3)	8 (10.3)

Counts reflect numbers of subjects reporting one or more TEAE Excluding Vascular Injections/Visual Events that map to the MedDRA (version 20.0) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one TEAE Excluding Vascular Injections/Visual Events are counted only once

Adverse Events of Special Interest

Four subjects (2 Revanesse® Lips +, 2 Comparator) reported AESIs, which is defined as TEAEs related to vascular injections or visual events. The events were mild to moderate and unlikely related to investigational product. One subject experienced myopia (Comparator) and another subject experienced blurry vision (Revanesse® Lips+). Two of the AESIs, retinal detachment (Revanesse® Lips+) and facial paralysis (Comparator), were initially reported as AEs and were subsequently elevated to SAEs.

Three subjects reported SAEs (Right invasive mammary carcinoma grade 2 (Revanesse® Lips+), right eye retinal detachment (Revanesse® Lips+), and Bell's Palsy (facial paralysis) (Comparator) which were determined to be unlikely related to investigational product.

There were no AESIs that were reported by 5% or more of subjects in either treatment group. The AESIs are summarized in Table 11.

Table 11. Adverse Events of Special Interest by MedDRA System Organ Class and Preferred Term for As-Treated Population

System Organ Class Preferred Term	Revanesse® Lips +	Comparator
Subjects with at Least One TEAE Related to Vascular Injections/Visual Events	2 (2.5%)	2 (2.6%)
Eye disorders	2 (2.5%)	1 (1.3%)
Myopia	0 (0.0%)	1 (1.3%)
Retinal detachment	1 (1.3%)	0 (0.0%)
Vision blurred	1 (1.3%)	0 (0.0%)
Nervous system disorders	0 (0.0%)	1 (1.3%)
Facial paralysis	0 (0.0%)	1 (1.3%)

Three subjects had AEs and had treatment with hyaluronidase after initial treatment in the PRO 2018-02 treatment study.

- A 49-year-old white female (FST II) randomized to Revanesse® Lips +, did not like the results but completed the study. This subject experienced TEAEs of severe injection site swelling, bruising, pain, and movement impairment from Days 1 to 10 post-treatment that were considered probably related to study device and resolved. She also had mild injection site mass from Days 1 to 56 (probably related) and mild facial (lip) asymmetry from Days 35 to 56 (unlikely related), both of which resolved. She was treated with hyaluronidase on Day 6.
- A 53-year-old white female (FST IV) randomized to Revanesse® Lips+, had TEAEs of mild injection site swelling and bruising starting on Day 1 or 2 that were considered probably related to study device. She was treated with hyaluronidase by another provider within 18 days of initial treatment. The subject was discontinued due to withdrawal of consent and the outcome of these events was not known.
- A 22-year old black or African American female (FST V) randomized to the Comparator, had 2 TEAEs of severe injection site swelling, from Days 1 to 3 and Days 119 to 127, that were considered possibly or probably related to study device and resolved. She was treated with hyaluronidase on Day 127. The blinding as to whether the subject was treated with the study device or Comparator was broken and the subject discontinued due to withdrawal of consent.

Two subjects were hospitalized for three AEs in the PRO 2018-02 treatment and PRO 2018-03 retreatment studies. One subject was diagnosed with breast cancer. This event was deemed serious, severe in intensity, unlikely related to study device. A second subject was hospitalized for abdominal pain and was diagnosed with stenosis of the sigmoid colon. This event was deemed unlikely related to the study device or study procedure and the outcome is unknown.

Lip Assessments:
All subjects were able to sip liquid through a straw at all visits, feel sensation of a cotton wisp at all visits, feel sensation of a 0.4G monofilament at all visits, and evaluated as normal the ability to pucker lips, blow with lips, and pronounce words that began with "w". All except 2 subjects (1 treated with Revanesse® Lips+, 1 treated with the Comparator) evaluated lip texture as normal at all visits and all except 1 subject (Revanesse® Lips+) evaluated lip firmness as normal at all visits.

Lip symmetry was evaluated as abnormal - mild by 5.4% (2/37) of subjects in the Revanesse® Lips+ group and 3.2% (1/31) in the Comparator prior to injection at Visit 1/Day 1. At subsequent visits, the proportion who evaluated lip symmetry as abnormal ranged from 4.1% (3/73) to 11.1% (7/63) in the Revanesse® Lips+ group and 0% (0/67) to 8.6% (6/70) in the Comparator group.

2. Effectiveness Results:

Primary Effectiveness:
The primary effectiveness endpoint was the change from baseline to Visit 3/Month 2 in overall LFGS of both lips together. The study was undertaken to disprove the null hypothesis, which was that Revanesse® Lips+ was inferior to the Comparator by more than 0.50.

The mean change from baseline to Visit 3/Month 2 in overall LFGS of both lips together in the PP population, the primary endpoint, was 1.52 (49/54 (90.7%)) in the Revanesse® Lips+ group and 1.53 (51/55 (92.7%)) in the Comparator group. The difference between the groups was not statistically significant and the 95% CI for Revanesse® Lips+ minus Comparator was (-0.33, 0.31) using t-test, demonstrating that Revanesse® Lips+ was non-inferior to the Comparator (Table 12).

Table 12. Primary Endpoint: Change from Baseline to Visit 3/ Month 2 in Overall Lip Fullness Grading Scale (LFGS) of Both Lips Together (Per-protocol and mITT Populations)

	Revanesse® Lips + CI	Comparator	p-value	95%
Per-protocol, N	54	55		
Mean ± SD	1.52 ± 0.885	1.53 ± 0.790	0.9566	(-0.33, 0.31)
95% confidence interval of mean	(1.28, 1.76)	(1.31, 1.74)		
Median (minimum, maximum)	1.00 (0.0, 4.0)	1.00 (0.0, 3.0)		
Modified intent-to-treat combined analysis, N	76	73		
Mean (SE)	1.55 (0.099)	1.53 (0.102)	0.8831	(-0.26, 0.31)

LFGS: 0=Very Thin Lips, 1=Thin Lips, 2=Moderately Thick Lips, 3=Thick Lips, 4=Full Lips.
[1]P-value and 95% confidence interval for the difference in means between treatments are derived using t-test.
[2]P-value is derived from Wilcoxon Mann-Whitney test. The 95% CI for the difference in medians between treatment groups is constructed using the distribution-free bootstrap method. Among the 10000 bootstrap samples, the differences in medians between treatments are -1 for 28.8%, -0.5 for 4.2%, 0 for 48.1%, 0.5 for 5.1%, 1 for 13.8%.
[3]The 95% CI for the difference in means between treatment groups is constructed using the same bootstrap method.

Secondary Effectiveness:

The percent of subjects with treatment success at Visit 3/Month 2 in the PP population, where success was defined as achieving a ≥ 1-grade increase from baseline on the overall LFGS of both lips together, was 90.7% with Revanesse® Lips+ (49/54) and 92.7% with the Comparator (51/55) (95% CI for Revanesse® Lips + minus Comparator: -12.3%, 8.35%).

Results for the secondary effectiveness endpoints are summarized in Table 13.
All statistical comparisons for the secondary endpoints were considered non-inferential.

Table 13. Secondary Effectiveness Endpoints

Endpoint Analysis Population Result	Revanesse ® Lips+	Comparator	p-value	95% CI for Revanesse® Lips+ minus Comparator
Percent of subjects with treatment success on overall LFGS of both lips together at Visit 3/Month 2				
Per-protocol, N	54	55		
Treatment success, n/N (%)	49/54 (90.7%)	51/55 (92.7%)	N/A	(-12.3%, 8.35%)
Modified intent-to-treat, N	76	73		
Combined analysis: % Treatment success	92.89%	92.88%	N/A	(-9.18%, 9.21%)
Change from baseline to Visit 4/Month 3 in LFGS of both lips together				
Per-protocol, N	54	55		
Mean ± SD	1.37 ± 0.917	1.42 ± 0.712	0.7615	(-0.36, 0.26)
95% CI of mean	(1.12, 1.62)	(1.23, 1.61)		
Median (minimum, maximum)	1.00 (0.0, 4.0)	1.00 (0.0, 3.0)		
Modified intent-to-treat, N	76	73		
Combined analysis: Mean (SE)	1.39 (0.105)	1.40 (0.091)	0.9702	(-0.28, 0.27)
Change from baseline to Visit 5/Month 6 in LFGS of both lips together				
Per-protocol, N	54	55		
Mean ± SD	1.00 ± 0.727	0.93 ± 0.634	0.5787	(-0.19, 0.33)
95% CI of mean	(0.80, 1.20)	(0.76, 1.10)		
Median (minimum, maximum)	1.00 (0.0, 3.0)	1.00 (01.0, 2.0)		
Modified intent-to-treat, N	76	73		
Combined analysis: Mean (SE)	1.05 (0.090)	0.90 (0.084)	0.2302	(-0.10, 0.40)

Note: The number of injections by lip location is in Table 4.

Based on the pGAI for the PP population, the proportion of subjects who were much improved or very much improved was greatest at Visit 3/Month 2 for both groups (81% (44/54) Revanesse® Lips+, 76% (42/55) Comparator) and least at Visit 5/Month 6 (65% (35/54) Revanesse® Lips+, 44% (24/55) Comparator) as shown in Table 14.

Table 14. Other Effectiveness: Patient Global Aesthetic Improvement (pGAI) by Visit Based on Observed Data (Per protocol population)

Study Visit	Category	Revanesse® Lips +	Comparator
Visit 3 / Month 2	N	54	55
	1 = Worse	1 (1.9%)	0 (0.0%)
	2 = No Change	0 (0.0%)	2 (3.6%)
	3 = Improved	9 (16.7%)	11 (20.0%)
	4 = Much Improved	16 (29.6%)	18 (32.7%)
	5 = Very Much Improved	28 (51.9%)	24 (43.6%)
Visit 5 / Month 6	N	54	55
	1 = Worse	1 (1.9%)	1 (1.8%)
	2 = No Change	1 (1.9%)	8 (14.5%)
	3 = Improved	17 (31.5%)	22 (40.0%)
	4 = Much Improved	15 (27.8%)	13 (23.6%)
	5 = Very Much Improved	20 (37.0%)	11 (20.0%)

Based on the iGAI for the PP population, the proportion of subjects who were much improved or very much improved was greatest at Visit 3/Month 2 for both groups (78% (42/54) Revanesse® Lips +, 78% (43/55) Comparator) and least at Visit 5/Month 6 (46% (25/54) Revanesse® Lips +, 40% (22/55) Comparator) as shown in Table 15.

Table 15. Other Effectiveness: Investigator Global Aesthetic Improvement (iGAI) by Visit based on Observed Data (Per protocol population)

Study Visit	Category	Revanesse® Lips+	Comparator
Visit 3 / Month 2	N	54	55
	1 = Worse	0 (0.0%)	0 (0.0%)
	2 = No Change	0 (0.0%)	1 (1.8%)
	3 = Improved	12 (22.2%)	11 (20.0%)
	4 = Much Improved	17 (31.5%)	12 (21.8%)
	5 = Very Much Improved	25 (46.3%)	31 (56.4%)
Visit 5 / Month 6	N	54	55
	1 = Worse	0 (0.0%)	1 (1.8%)
	2 = No Change	0 (0.0%)	12 (21.8%)
	3 = Improved	29 (53.7%)	20 (36.4%)
	4 = Much Improved	16 (29.6%)	11 (20.0%)
	5 = Very Much Improved	9 (16.7%)	11 (20.0%)

3. Subgroup Analyses

The following characteristics were evaluated for potential association with outcomes: Age (Table 16) and FST (Table 17). Table 18 below presents the summary of the primary and secondary effectiveness data, as well as the TEAEs for subgroups age and FST.

The following table provides the safety data based on Age.

Table 16. - TEAEs by MedDRA System Organ Class, Preferred Term and Age Group

System Organ Class Preferred Term	Treatment Group	22-40 Years of Age	>=41 Years of Age
Subjects with at Least One TEAE	Revanesse® Lips+	26/27 (96.3%)	49/53 (92.5%)
	Comparator	17/17 (100%)	58/61 (95.1%)
Injection site bruising	Revanesse® Lips+	19/27 (70.4%)	38/53 (71.7%)
	Comparator	6/17 (35.3%)	38/61 (62.3%)
Injection site erythema	Revanesse® Lips+	5/27 (18.5%)	3/53 (5.7%)
	Comparator	0/17 (0.0%)	8/61 (13.1%)
Injection site mass	Revanesse® Lips+	3/27 (11.1%)	3/53 (5.7%)
	Comparator	1/17 (5.9%)	8/61 (13.1%)
Injection site movement impairment	Revanesse® Lips+	0/27 (0.0%)	3/53 (5.7%)
	Comparator	0/17 (0.0%)	6/61 (9.8%)
Injection site pain	Revanesse® Lips+	5/27 (18.5%)	12/53 (22.6%)
	Comparator	3/17 (17.6%)	21/61 (34.4%)
Injection site pruritus	Revanesse® Lips+	2/27 (7.4%)	2/53 (3.8%)
	Comparator	2/17 (11.8%)	1/61 (1.6%)
Injection site swelling	Revanesse® Lips+	24/27 (88.9%)	46/53 (86.8%)
	Comparator	16/17 (94.1%)	54/61 (88.5%)
Facial asymmetry	Revanesse® Lips+	2/27 (7.4%)	10/53 (18.9%)
	Comparator	1/17 (5.9%)	7/61 (11.5%)

Counts reflect numbers of subjects with one or more TEAE that map to the MedDRA (version 20.0) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects with more than one TEAE are counted only once.

The following tables provide the safety data based on FST.

Table 17. Summary of TEAEs by FST for As-Treated Population

System Organ Class Preferred Term	Treatment Group	FST I	FST II	FST III	Pooled FST I-III	FST IV	FST V	FST VI	Pooled FST IV-VI	Overall Total
Subjects with at Least One Injection Site TEAE	Revanesse® Lips+	3/3 (100%)	24/25 (96.0%)	22/24 (91.7%)	49/52 (94.2%)	15/17 (88.2%)	5/5 (100%)	5/6 (83.3%)	25/28 (89.3%)	74/80 (92.5%)
	Comparator	7/7 (100%)	18/19 (94.7%)	24/27 (88.9%)	49/53 (92.5%)	10/10 (100%)	4/4 (100%)	11/11 (100%)	25/25 (100%)	74/78 (94.9%)
Injection site bruising	Revanesse® Lips+	3/3 (100%)	20/25 (80.0%)	19/24 (79.2%)	42/52 (80.8%)	13/17 (76.5%)	2/5 (40.0%)	0/6 (0.0%)	15/28 (53.6%)	57/80 (71.3%)
	Comparator	6/7 (85.7%)	12/19 (63.2%)	15/27 (55.6%)	33/53 (62.3%)	7/10 (70.0%)	0/4 (0.0%)	4/11 (36.4%)	11/25 (44.0%)	44/78 (56.4%)
Injection site erythema	Revanesse® Lips+	0/3 (0.0%)	3/25 (12.0%)	1/24 (4.2%)	4/52 (7.7%)	3/17 (17.6%)	1/5 (20.0%)	0/6 (0.0%)	4/28 (14.3%)	8/80 (10.0%)
	Comparator	1/7 (14.3%)	2/19 (10.5%)	4/27 (14.8%)	7/53 (13.2%)	1/10 (10.0%)	0/4 (0.0%)	0/11 (0.0%)	1/25 (4.0%)	8/78 (10.3%)
Injection site mass	Revanesse® Lips+	0/3 (0.0%)	2/25 (8.0%)	0/24 (0.0%)	2/52 (3.8%)	1/17 (5.9%)	0/5 (0.0%)	3/6 (50.0%)	4/28 (14.3%)	6/80 (7.5%)
	Comparator	1/7 (14.3%)	1/19 (5.3%)	3/27 (11.1%)	5/53 (9.4%)	1/10 (10.0%)	0/4 (0.0%)	3/11 (27.3%)	4/25 (16.0%)	9/78 (11.5%)
Injection site movement impairment	Revanesse® Lips+	0/3 (0.0%)	1/25 (4.0%)	1/24 (4.2%)	2/52 (3.8%)	1/17 (5.9%)	0/5 (0.0%)	0/6 (0.0%)	1/28 (3.6%)	3/80 (3.8%)
	Comparator	1/7 (14.3%)	2/19 (10.5%)	2/27 (7.4%)	5/53 (9.4%)	1/10 (10.0%)	0/4 (0.0%)	0/11 (0.0%)	1/25 (4.0%)	6/78 (7.7%)
Injection site pain	Revanesse® Lips+	0/3 (0.0%)	6/25 (24.0%)	5/24 (20.8%)	11/52 (21.2%)	6/17 (35.3%)	0/5 (0.0%)	0/6 (0.0%)	6/28 (21.4%)	17/80 (21.3%)
	Comparator	3/7 (42.9%)	7/19 (36.8%)	8/27 (29.6%)	18/53 (34.0%)	4/10 (40.0%)	0/4 (0.0%)	2/11 (18.2%)	6/25 (24.0%)	24/78 (30.8%)
Injection site pruritus	Revanesse® Lips+	1/3 (33.3%)	1/25 (4.0%)	1/24 (4.2%)	3/52 (5.8%)	1/17 (5.9%)	0/5 (0.0%)	0/6 (0.0%)	1/28 (3.6%)	4/80 (5.0%)
	Comparator	0/7 (0.0%)	0/19 (0.0%)	1/27 (3.7%)	1/53 (1.9%)	0/10 (0.0%)	0/4 (0.0%)	2/11 (18.2%)	2/25 (8.0%)	3/78 (3.8%)
Injection site swelling	Revanesse® Lips+	3/3 (100%)	23/25 (92.0%)	20/24 (83.3%)	46/52 (88.5%)	14/17 (82.4%)	5/5 (100%)	5/6 (83.3%)	24/28 (85.7%)	70/80 (87.5%)
	Comparator	7/7 (100%)	16/19 (84.2%)	24/27 (88.9%)	47/53 (88.7%)	8/10 (80.0%)	4/4 (100%)	11/11 (100%)	23/25 (92.0%)	70/78 (89.7%)

Counts reflect numbers of subjects with one or more injection site TEAE that map to the MedDRA (version 20.0) system organ class/preferred term.
At each level of summarization (system organ class or preferred term), subjects with more than one injection site TEAE are counted only once.
Note: For each cell, n/N (x.x%), n = number of subjects of the FST within the treatment arm who reported incidence, N = total number of subjects of the FST within the treatment arm.

Table 18. Overall Summaries of Subgroups, Age and FST for Lip Fullness Grading Score, iGAI, pGAI, and TEAEs

		Age subgroup 22-40	Age subgroup >= 41
LFGS at Visit 3/Month 2 (PP pop.)*	Revanesse® Lips+	N=13	N=41
	Mean ± SD	1.77 ± 0.927	1.44 ± 0.867
	Median	2.00	1.00
	Min, Max	0.0, 3.0	0.0, 4.0
	Comparator	N=13	N=42
	Mean ± SD	1.46 ± 0.776	1.55 ± 0.803
	Median	1.00	1.50
	Min, Max	0.0, 3.0	0.0, 3.0
iGAI Visit 3/Month 2 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=13	N=41
		11 (84.6%)	31 (75.6%)
	Comparator	N=13	N=42
		12 (92.3%)	31 (73.8%)
iGAI Visit 5/Month 6 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=13	N=41
		8 (61.5%)	17 (41.5%)
	Comparator	N=13	N=42
		6 (46.2%)	16 (38.1%)
pGAI Visit 3/Month 2 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=13	N=41
		11 (84.6%)	33 (80.5%)
	Comparator	N=13	N=42
		13 (100%)	29 (69.0%)
pGAI Visit 5/Month 6 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=13	N=41
		9 (69.2%)	26 (63.4%)
	Comparator	N=13	N=42
		9 (69.2%)	15 (35.7%)
TEAEs (AT pop.)	Revanesse® Lips+ n/N (%)**	26/27 (96.3%)	49/53 (92.5%)
	Comparator n/N (%)**	17/17 (100%)	58/61 (95.1%)
		FST Subgroup I-III	FST Subgroup IV-VI
LFGS at Visit 3/Month 2 (PP pop.)*	Revanesse® Lips+	N=41	N=13
	Mean ± SD	1.56 ± 0.838	1.38 ± 1.044
	Median	2.00	1.00
	Min, Max	0.0, 4.0	0.0, 3.0
	Comparator	N=41	N=14
	Mean ± SD	1.61 ± 0.737	1.29 ± 0.914
	Median	2.00	1.00
	Min, Max	0.0, 3.0	0.0, 3.0
iGAI Visit 3/Month 2 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=41	N=13
		21 (51.2%)	11 (84.6%)
	Comparator	N=41	N=14
		30 (73.2%)	13 (93.0%)
iGAI Visit 5/Month 6 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=41	N=13
		18 (43.9%)	7 (53.8)
	Comparator	N=41	N=14
		14 (34.1%)	8 (61.5%)
pGAI Visit 3/Month 2 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=41	N=13
		34 (82.9%)	10 (76.9%)
	Comparator	N=41	N=14
		29 (70.7%)	13 (92.9%)

		FST Subgroup I-III	FST Subgroup IV-VI
pGAI Visit 5/Month 6 (PP pop.) Much Improved + Very Much Improved	Revanesse® Lips+	N=41	N=13
		23 (56.1%)	12 (92.3%)
	Comparator	N=41	N=14
		15 (36.6%)	9 ^4.3%)
TEAEs (AT pop.)	Revanesse® Lips+ n/N (%)**	50/52 (96.2%)	25/28 (89.3%)
	Comparator n/N (%)**	50/53 (94.3%)	25/25 (100%)

Abbreviation: PP = Per-protocol, AT = As-treated, LFGS = Lip Fullness Grading Scale, iGAI = Investigator Global Aesthetic Improvement, pGAI = Patient Global Aesthetic Improvement, FST = Fitzpatrick Skin Type
*Primary effectiveness endpoint: Change from Baseline to Visit 3/Month 2 in Overall LFGS of Both Lips Together
**For each cell, n/N (x.x%), n = number of subjects of the site within the treatment arm who reported incidence, N = total number of subjects of the site within the treatment arm.

4. **Retreatment study - PRO 2018-03** ***A Multicenter, Open-Label Retreatment Study of the Safety and Effectiveness of Revanesse® Lips+ for Lip Augmentation***

This was a multicenter, open-label clinical study of retreatment of subjects seeking lip augmentation who received treatment with either Revanesse® Lips+ or the Comparator in prior Protocol PRO 2018-02. Subjects meeting the inclusion/exclusion criteria received a single additional treatment with Revanesse® Lips+.

Subjects eligible for the retreatment study were in the per-protocol population (i.e., met all inclusion/exclusion criteria); received study device, completed PRO 2018-02 Visit 5/Month 6 within the specified window; had LFGS score by the Blinded Evaluating Investigator at PRO 2018-02 Visit 3/Month 2, and had no significant protocol violations that would affect the treatment evaluation.

Subjects who elected to enroll in the retreatment study received retreatment at Visit 5 (Day 168) of Protocol PRO 2018-02 / Visit 1 (Day 1) of PRO 2018-03. There was an interim follow-up visit at Visit 2/Month 1 following repeat treatment and an End of Study (EOS) Visit (Visit 3) at Month 2 following repeat treatment. Telephone contacts for safety follow-up occurred at Day 3, Day 14, and Day 168 after retreatment. Subjects were seen at the retreatment visit, and again at Visit 2/Month 1 and Visit 3/Month 2 with follow-up phone calls at Day 3, Day 14, and Day 168 (Month 6).

Of the 158 patients in the initial treatment study, 84 continued in the retreatment study, 73 subjects did not continue into the retreatment study (Table 19).

Table 19. Subjects who did not Roll-over into the Retreatment Study PRO 2018-03

Reason subject did not roll-over into the retreatment study	Number of subjects (N=73)
Did not meet criteria for the study	21/73 (28.8%)
Discontinued from the previous study	17/73 (23.3%)
Satisfied with results and did not want additional treatment	12/73 (16.4%)
Injection related events	10/73 (13.7%)
Other reasons	13/73 (17.8%)

Other reasons included: 6 subjects were not happy with the results, 3 subjects' husbands were not happy with the results, 2 subjects declined to participate with no reason given, 2 subjects did not want more product

Of the 84 retreated subjects, 94.0% completed the study. Three subjects withdrew consent, 1 subject was discontinued due to a significant protocol violation (use of a prohibited medication, cortisol), and 1 subject was lost to follow-up (Table 20).

Table 20. Subject Accountability - Retreatment

Subject Accountability - Retreatment	
Subjects Randomized	84
Subjects Included in the As-Treated (AT) Population	84
Subjects completed study	79/84 (94.0%)
Subjects withdrew consent	3/84 (3.6%)
Significant protocol violation	1/84 (1.2%)
Subject lost to follow up	1/84 (1.2%)

Overall, 97.6% of subjects were female, 79.8% were not Hispanic or Latino, and the mean age was 50 years (range 24 to 70). The most common races were white (83.3%) and black or African American (14.3%). The majority of subjects, 72.6%, were FST I, II, or III and 27.4% were FST IV, V, or VI.

Table 21. Demographics for PRO 2018-03 Retreatment with Revanesse® Lips+

Parameter	Category	Initial Treatment in PRO 2018-02		Total (N = 84)
		Revanesse® Lips+ (N = 38)	Comparator (N = 46)	
Gender	Female	38 (100%)	44 (95.7%)	82 (97.6%)
	Male	0 (0.0%)	2 (4.3%)	2 (2.4%)
Ethnicity	Hispanic or Latino	11 (28.9%)	6 (13.0%)	17 (20.2%)
	Not Hispanic or Latino	27 (71.1%)	40 (87.0%)	67 (79.8%)
Race	White	32 (84.2%)	38 (82.6%)	70 (83.3%)
	Asian	0	0	0
	Black or African American	5 (13.2%)	7 (15.2%)	12 (14.3%)
	Other	1 (2.6%)	0 (0.0%)	1 (1.2%)
	Mixed[a]	0 (0.0%)	1 (2.2%)	1 (1.2%)
Age (years)	N	38	46	84
	Mean ± SD	47.9 ± 11.00	51.1 ± 10.31	49.7 ± 10.68
	Median	50.0	52.5	52.0
	Min, Max	25, 69	24, 70	24, 70
Age Groups	18 to < 40	10 (26.3%)	5 (10.9%)	15 (17.9%)
	40 to < 64	25 (65.8%)	36 (78.3%)	61 (72.6%)
	64 to < 75	3 (7.9%)	5 (10.9%)	8 (9.5%)
Body Mass Index (BMI)[b]	N	38	46	84
	Mean ± SD	26.29 ± 4.822	29.02 ± 6.184	27.78 ± 5.741
	Median	25.65	28.05	26.85
	Min, Max	18.6, 35.5	18.3, 44.6	18.3, 44.6
Fitzpatrick Skin Type	I	1 (2.6%)	3 (6.5%)	4 (4.8%)
	II	10 (26.3%)	14 (30.4%)	24 (28.6%)
	III	18 (47.4%)	15 (32.6%)	33 (39.3%)
	IV	4 (10.5%)	6 (13.0%)	10 (11.9%)
	V	1 (2.6%)	2 (4.3%)	3 (3.6%)
	VI	4 (10.5%)	6 (13.0%)	10 (11.9%)

Retreatment Study Results:

Retreatment with Revanesse® Lips+ resulted in improvement in lip augmentation as evaluated by LFGS, pGAI, and iGAI.

The mean LFGS rating, for treatment and control groups together, was 1.93 at retreatment Visit 1/Day 1. Following retreatment, the mean rating increased to 2.73 at Visit 3/Month 2 (Table 22).

Table 22. PRO 2018-03 Effectiveness: Change from Baseline Prior to Retreatment in Overall Lip Fullness Grading Scale (LFGS)* at Visit 3/Month 2 After Retreatment with Revanesse® Lips+

Study Visit	Category	Statistics	Retreated Subjects
Visit 1/Day 1 Retreatment	Number of Subjects	N	84
LFGS Score		Mean ± SD	1.93 ± 1.050
		Median	2.00
		Min, Max	0.0, 4.0
Visit 3/Month 2	Number of Subjects	N	79
LFGS Score		Mean ± SD	2.73 ± 0.916
		Median	3.00
		Min, Max	1.0, 4.0
	Change from Visit 1/Day 1 Retreatment	N	79
LFGS Score		Mean ± SD	0.82 ± 0.747
		Median	1.00
		Min, Max	-1.0, 3.0

*LFGS was evaluated prior to treatment at any study visits where a treatment was administered.

Based on the pGAI (Table 23), the proportion of subjects who were much improved or very much improved increased from 45.2% at retreatment Visit 1/Day 1 to 85.4% at Visit 2/Month 1 and 75.9% at Visit 3/Month 2.

Table 23. Pro 2018-03 Effectiveness: Patient Global Aesthetic Improvement (pGAI) by Visit in PRO 2018-02

Study Visit	Category	Total
Visit 1/Day 1 Retreatment	N	84
	1 = Worse	0 (0.0%)
	2 = No Change	6 (7.1%)
	3 = Improved	40 (47.6%)
	4 = Much Improved	17 (20.2%)
	5 = Very Much Improved	21 (25.0%)
Visit 3/Month 2	N	79
	1 = Worse	0 (0.0%)
	2 = No Change	2 (2.5%)
	3 = Improved	17 (21.5%)
	4 = Much Improved	19 (24.1%)
	5 = Very Much Improved	41 (51.9%)

Based on the iGAI, the proportion of subjects who were much improved or very much improved increased from 46.4% at retreatment Visit 1/Day 1 to 76.8% at Visit 2/Month 1 and 73.4% at Visit 3/Month 2 (Table 24).

Table 24. PRO 2018-03 Effectiveness: Investigator Global Aesthetic Improvement (iGAI) by Visit in PRO 2018-02

Study Visit	Category	Total
Visit 1/Day 1 Retreatment	N	84
	1 = Worse	1 (1.2%)
	2 = No Change	10 (11.9%)
	3 = Improved	34 (40.5%)
	4 = Much Improved	24 (28.6%)
	5 = Very Much Improved	15 (17.9%)
Visit 3/Month 2	N	79
	1 = Worse	0 (0.0%)
	2 = No Change	1 (1.3%)
	3 = Improved	20 (25.3%)
	4 = Much Improved	30 (38.0%)
	5 = Very Much Improved	28 (35.4%)

Safety results for retreatment with Revanesse® Lips+: One subject had an AESI (TEAE related to vascular injections/visual events), which was blurred vision that was not treatment-related.

- Most subjects, 73.8% (62/84), had TEAEs excluding vascular injections/visual events with the most frequent being injection site swelling (57.1% (48/84)), injection site bruising (47.6% (40/84)), and injection site pain (11.9% (10/84)). These events were generally treatment-related (Table 25).
- Of the TEAE reported, 105/114 (92.1%) were reported as mild, and 9/114 (7.9%) were reported as moderate in intensity (Table 26).
- One subject, who was lost to follow-up, experienced SAEs of beta-hemolytic streptococcal infection and large intestinal stenosis. Both events were deemed unlikely related to study drug or study procedures and the outcome unknown.
- No subject discontinued the study due to a TEAE.

Table 25. PRO 2018-03 TEAEs Reported for More Than 1 Subject

System Organ Class Preferred Term	Based on treatment in initial study PRO 2018-02 Revanesse® Lips+ (N=38) n (%)	 Comparator (N = 46) n (%)	Total (N = 84) n (%)
Subjects with at least 1 TEAE excluding vascular injections/visual events	25 (65.8)	37 (80.4)	62 (73.8)
Injection site bruising	16 (42.1)	24 (52.2)	40 (47.6)
Injection site erythema	2 (5.3)	4 (8.7)	6 (7.1)
Injection site mass	0	6 (13.0)	6 (7.1)
Injection site pain	4 (10.5)	6 (13.0)	10 (11.9)
Injection site swelling	16 (42.1)	32 (69.6)	48 (57.1)
Influenza	1 (2.6)	1 (2.2)	2 (2.4)
Sinusitis	1 (2.6)	1 (2.2)	2 (2.4)
Facial asymmetry	1 (2.6)	4 (8.7)	5 (6.0)

Counts reflect numbers of subjects with one or more TEAE Excluding Vascular Injections/Visual Events that map to the MedDRA (version 20.0) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects with more than one TEAE Excluding Vascular Injections/Visual Events are counted only once.

Table 26. PRO 2018-03 TEAEs by MedDRA System Organ Class, Preferred Term and Severity

System Organ Class Preferred Term	Severity	PRO 2018-02 Revanesse Lips+ (N=41 events)	PRO 2018-02 Comparator (N=73 events)	Total (N=114 events)
Subjects with at Least One TEAE Excluding Vascular Injections/Visual Events	Mild	35 (85.4%)	70 (95.9%)	105 (92.1%)
	Moderate	6 (14.6%)	3 (4.1%)	9 (7.9%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection site bruising	Mild	15 (36.6%)	23 (31.5%)	38 (33.3%)
	Moderate	1 (2.4%)	1 (1.4%)	2 (1.8%)
Injection site erythema	Mild	2 (4.9%)	4 (5.5%)	6 (5.3%)
Injection site exfoliation	Moderate	1 (2.4%)	0 (0.0%)	1 (0.9%)
Injection site haemorrhage	Mild	0 (0.0%)	1 (1.4%)	1 (0.9%)
Injection site induration	Mild	1 (2.4%)	0 (0.0%)	1 (0.9%)
Injection site mass	Mild	0 (0.0%)	6 (8.2%)	6 (5.3%)
Injection site pain	Mild	2 (4.9%)	6 (8.2%)	8 (7.0%)
	Moderate	2 (4.9%)	0 (0.0%)	2 (1.8%)
Injection site pruritus	Mild	1 (2.4%)	0 (0.0%)	1 (0.9%)
Injection site swelling	Mild	14 (34.1%)	30 (41.1%)	44 (38.6%)
	Moderate	2 (4.9%)	2 (2.7%)	4 (3.5%)

Counts reflect numbers of TEAEs Excluding Vascular Injections/Visual Events that map to the MedDRA (version 20.0) system organ class/preferred term. At each level of summarization (system organ class or preferred term), TEAEs Excluding Vascular Injections/Visual Events are counted only once (under the greatest reported severity).

Retreatment with Revanesse® Lips+ showed safety similar to the results in the prior controlled study PRO 2018-02 with either Revanesse® Lips+ or Comparator treatment.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 6 investigators. None of the clinical investigators had disclosable financial interests/arrangements. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

This multicenter, double-blind, randomized, controlled study compared the safety and effectiveness profile of Revanesse® Lips+ versus Comparator for lip augmentation. The primary effectiveness endpoint was change from baseline to Visit 3/Month 2 in overall LFGS of both lips together. Non-inferiority was achieved with a 95% CI of (-0.33, 0.31) for the definitive analysis in the PP population and was supported by the results for the mITT population and by sensitivity analysis for the PP population. Both treatments demonstrated similarly high rates of treatment success across the secondary and other effectiveness endpoints, and also high rates of subject satisfaction with their lips.

The percent of subjects with treatment success at Visit 3/Month 2 in the PP population, where success was defined as achieving a ≥ 1-grade increase from baseline on the overall

LFGS of both lips together, was 90.7% with Revanesse® Lips + and 92.7% with the Comparator (95% CI for Revanesse® Lips + minus Comparator: -12.3%, 8.35%).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies, as well as data collected in clinical studies conducted to support PMA approval as described above.

The treatment study under protocol PRO 2018-02 included 117 injections of Revanesse® Lips+ and 104 injections of Comparator in the upper lip, 108 injections of Revanesse® Lips+ and 103 injections of Comparator in the lower lip, and 34 injections of Revanesse® Lips+ and 38 injections of Comparator in the perioral areas. In each treatment group, a TEAE excluding vascular injections/visual events was reported for 75 subjects in each treatment group (93.8% Revanesse® Lips+, 96.2% Comparator). The TEAEs reported for more than 1 subject in either treatment group are summarized in Table 11.

As expected, the most common TEAEs were at the injection site. The most frequently reported TEAEs were injection site swelling, injection site bruising, injection site pain, and facial asymmetry. The only TEAE reported more frequently (difference of more than 5%) with Revanesse® Lips+ was injection site bruising. TEAEs reported more frequently with Comparator were injection site pain and headache.

Most TEAEs were reported as mild or moderate in intensity. Three subjects in each treatment group had TEAEs that were reported as severe. Severe events were ovarian cyst ruptured, endometriosis, breast cancer stage II, injection site swelling, injection site bruising, injection site pain, and injection site movement impairment in the Revanesse® Lips+ group and 4 events of injection site swelling in 3 subjects in the Comparator group.

Following retreatment, there were no unexpected AEs related to retreatment with Revanesse® Lips+.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the clinical study conducted to support PMA supplement approval as described above.

In conclusion, given the available information above, the data support the use of Revanesse® Lips+ for submucosal implantation for lip augmentation in patients 22 years of age or older, and the probable benefits outweigh the probable risks.

1. Patient Perspective

   Patient perspectives considered during the review included the pGAI assessments. The results of the pGAI are noted in Table 14.

   Patient perspectives were also considered in the safety assessment. Diaries were completed by subjects after each treatment.

   Table 2 shows the disposition of subjects and why subjects discontinued from the study.

D. Overall Conclusions

The device related adverse events are generally mild in nature, anticipated, expected, and are included in the current Summary of Safety and Effectiveness Data (SSED) for P160042 (original and S003). The study did not demonstrate any device related serious adverse effects associated with the use of Revanesse® Lips+.

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on September 21, 2020.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.