SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: Revanesse® Ultra

Device Procode: LMH

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160042

Date of FDA Notice of Approval: 8/04/2017

Priority Review: No

Expedited Access Pathway (EAP): No

II. INDICATIONS FOR USE

Revanesse Ultra 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.

III. CONTRAINDICATIONS

Revanesse Ultra is only intended for intradermal use and must not be injected into blood vessels. Implantation of Revanesse Ultra into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

Revanesse Ultra contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.

Do not inject Revanesse® Ultra into eye contours. Serious adverse events have been reported related to the use of dermal fillers in the area of the eye.

This product has not been evaluated in pregnant women, or women during lactation, and these individuals should not be treated with Revanesse Ultra.

Patients who develop hypertrophic scarring or keloid formation should not be treated with Revanesse Ultra.

Patients with evidence of scars at the intended treatment sites should not be treated with Revanesse Ultra.

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.

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 treatment with Revanesse Ultra.

Revanesse Ultra 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.

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.

IV. WARNINGS AND PRECAUTIONS

Additional warnings and precautions can be found in the Revanesse Ultra labeling.

V. DEVICE DESCRIPTION

Revanesse Ultra is manufactured by Prollenium Medical Technologies, and is a biocompatible, biodegradable, non-pyrogenic, sterile, injectable viscoelastic clear colorless hydrogel based on bioresorbable cross-linked hyaluronan (HA) (22 – 28 mg / mL concentration). 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 Ultra contains two 1.0 mL syringes of Revanesse Ultra along with two 0.5-inch 27 gauge sterile needles in a molded rigid PVC tray. 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.

Revanesse Ultra is injected by qualified, trained physicians into the dermis of patients, using a variety of techniques. The injections place a small portion of the gel beneath a crease or wrinkle in the skin and the augmentation of the tissue produces a smoothing effect on the surface.

The Instructions for Use contains additional product details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Dermal fillers have been approved since 1981 in a variety of formulations (among them Collagen, Hyaluronic acid, Calcium hydroxylapatite, Polymethyl-methacrylate microspheres). Alternate treatments of mild wrinkling associated with aging and photo-damaged skin are most commonly accomplished by the use of over the counter and prescription topical creams, topical scrubs, chemical peeling procedures, or laser resurfacing. Other commercially available dermal filler devices are approved for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). Other options for moderate to severe wrinkles include surgery or implantation of tissue augmenting substances (e.g. injection of bovine collagen or autologous fat). In these cases, correction of the depression is the goal of therapy. Each of these alternatives has their own advantages and disadvantages. Each patient should discuss these alternatives with his / her physician to select the most appropriate method.

VII. MARKETING HISTORY

Since 2012, Prollenium has marketed Revanesse Ultra in Canada under Health Canada Device Licence (#69955) and in the European Union in accordance with CE certificate (# CE 634109). There have been no reported serious adverse events associated with Revanesse Ultra, and the product has not been withdrawn from the market for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

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.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Revanesse Ultra has been characterized by the following physical and chemical analysis (Table 1).

Table 1: Physical and Chemical Analysis

Test	Purpose	Results
HA Concentration (mg/mL)	Ensures that the HA concentration is within specification	Passed
pH	Ensures that the pH is within specification	Passed
Osmolality (mOsm)	Ensures that the osmolality is within specification	Passed
Viscosity (Pa.s)	Ensures that the viscosity is within specification	Passed
Extrusion Force (lbs)	Ensures extrusion force meets specification	Passed
Residual Crosslinker (ppm)	Ensures residual crosslinker levels are within specification	Passed
Endotoxin (EU/syringe)	Ensures endotoxin levels meet specification	Passed

Sterilization - Filled syringes are sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle is validated according to ISO 17665-1 sterilization standard. The validated sterilization cycle provides a minimum Sterility Assurance Level (SAL) of 10^{-6}.

Stability / Shelf life - Packaged product data has been collected through 12 months at 25 ^{0}C/60% relative humidity, and through 6 months at 45 ^{0}C/75% relative humidity. At each time point, product was evaluated for conformance with microbiological, physical and chemical properties. Conformance with all specifications was confirmed.

B. Biocompatibility Studies

The biocompatibility studies were performed in accordance with the Federal Good Laboratory Practices Regulations (21 CFR § 58), ISO 10993 and FDA's biocompatibility guidance "Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management". The results of the biocompatibility tests are summarized in Table 2 below.

Table 2: Biocompatibility Studies

Test	Method	ISO Standard	Results
Cytotoxicity	ISO Direct Contact Method - L-929 Mouse Fibroblast Cells	10993-5	Non-cytotoxic
Sensitization	ISO Guinea Pig Maximization Sensitization Test	10993-10	Non-sensitizing
Intracutaneous Reactivity (3 and 14 days)	In rabbits	10993-10	Irritant at 3 days Non-irritant at 14-days; showed a similar irritation profile to a FDA-approved dermal filler comparator
Intramuscular Implantation (4 and 12 Weeks)	In rabbits	10993-6	non-irritant
Acute Systemic Toxicity	Intraperitoneal injection in mice	10993-11	No mortality or evidence of systemic toxicity
Subchronic Systemic Toxicity (13 weeks)	Subcutaneous tissue implantation in rats	10993-6 10993-11	Not systemically toxic
Genotoxicity	Bacterial Reverse Mutation Assay, mouse lymphoma assay and mouse peripheral blood micronucleus assay	10993-3	Non-mutagenic Non-genotoxic
Pyrogenicity	Rabbit Pyrogen Study, Material Mediated	USP <151>	Non-pyrogenic

Carcinogenicity risks: The excess cancer risks for Revanesse Ultra are in the same range of acceptable cancer risks as other previously approved dermal filler products.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Prollenium Medical Technologies, Inc. performed a clinical study to establish a reasonable assurance of safety and effectiveness of correction of moderate to severe nasolabial folds with Revanesse Ultra in the US under IDE # G140120. In addition, the study includes an open label extension to evaluate the effect of repeat injections of Revanesse Ultra (SYM2014-02 Retreatment). Data from this clinical study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between 18 May 2015 and 04 April 2016. The database for the initial phase of the study reflected data collected through 03 March 2016 and included 163 patients. The database for the retreatment study reflected data collected through 07 September 2016 and included 71 patients. There were 4 investigational sites.

The study was a randomized, multicenter, double blind, split-face study in subjects seeking nasolabial fold (NLF) correction. Subjects were treated with Revanesse Ultra in the NLF on one side of the face and Comparator in the NLF on the other side of the face. The Comparator used was an FDA-approved crosslinked hyaluronic acid dermal filler which is legally marketed with similar indications for use. The side of the face for each product was randomly assigned. Randomization followed a 1:1 within-subject Comparator model of augmentation correction of NLFs. The investigator performing the evaluations and the subject were blinded to the treatment; injections of the study product were performed by an unblinded injecting investigator.

The primary efficacy variable was change from Baseline to Visit 6/Week 24 in Wrinkle Severity Rating Scale (WSRS) score (i.e., WSRS at Visit 1 – WSRS at Visit 6). Summary statistics and 95% confidence interval (CI) were presented for the change scores for each treatment and for the difference in change scores between the two treatments (Comparator minus Test product, i.e., Comparator minus Revanesse Ultra). The 95% CI for difference between treatments was constructed assuming a normal distribution of the change scores. If the upper bound of this 95% CI was less than the pre-specified non inferiority limit of 0.50, the Test product would be claimed to be non-inferior to the Comparator product.

Subjects meeting the inclusion and exclusion criteria were randomized to treatment with Revanesse Ultra in the NLF on one side of the face and Comparator in the NLF on the other side of the face.

SYM2014-02 Retreatment - Subjects could have open-label retreatment as needed with Revanesse Ultra at 6 months if their WSRS scores had returned to baseline, or as needed to achieve optimal correction if their WSRS scores had not returned to baseline, and were followed for a total of 12 months. The study design was appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation were used.

1. Clinical Inclusion and Exclusion Criteria

   Key Inclusion and Exclusion Criteria for Main Study SYM2014-02: Men or women at least 22 years of age with two fully visible bilateral nasolabial folds each with a WSRS score of 3 or 4 (moderate or severe) that may have been corrected with an injectable dermal filler.

   Subjects must have met all of the following inclusion criteria to be eligible for the study:

   - Men or women 22 years of age or older.

- Two fully visible bilateral nasolabial folds each with a Wrinkle Severity Rating Scale Score of 3 or 4 that may have been corrected with an injectable dermal filler.
- If female and of childbearing potential, a negative urine pregnancy test and agreed to use adequate contraception. Female subjects of childbearing potential (excluding women who were surgically sterilized or postmenopausal for at least 2 years) must have had a negative urine pregnancy test and must have been willing to use a medically accepted method of contraception during the study. The following were considered acceptable methods of birth Comparator 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 Comparator if the subject became sexually active. Subjects entering the study who were 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.
- Ability to understand and comply with the requirements of the study.
- Willingness and ability to provide written informed consent.
- Agreed to refrain from seeking other treatment for this condition during the study.

Patients were <u>not</u> permitted to enroll in the SYM2014-02 study if they met any of the following exclusion criteria:

- Wrinkle Severity Rating Scale Score of ≤ 2 on the right or left nasolabial fold.
- Women who were pregnant or lactating.
- Received prior dermabrasion, facelift, or Botox below the orbital rim within 6 months (180 days) prior to entry into the study.
- Previous tissue augmentation (bulking agents) for facial wrinkles and scars within 6 months (180 days) at the proposed injection sites.
- Previous tissue augmentation with permanent implants.
- Evidence of scar-related disease or delayed healing activity within the past 1 year.
- Scars at the intended treatment sites.
- History of keloid formation or hypertrophic scars.
- Any infection or wound on the face.
- Allergic history including anaphylaxis or multiple severe allergies to natural rubber latex or lidocaine.
- Aspirin or nonsteroidal anti-inflammatory drugs within 1 week (7 days) prior to treatment.
- Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders or connective tissue disorders.

- Over-the-counter (OTC) wrinkle products or prescription wrinkle treatments within 4 weeks (28 days) prior to treatment and throughout the study.
- Immunocompromised or immunosuppressed.
- 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, precluded participation in the trial.

2. Follow-up Schedule

Every subject received Revanesse Ultra on one side of the face and Comparator on the other side of the face. Subjects who satisfied all of the inclusion and none of the exclusion criteria were randomized at Visit 1/Day 1 with respect to which side of the face received which treatment. Randomization was performed according to a computer-generated randomization scheme. The randomization scheme was generated and maintained by an independent third party. A copy of the randomization scheme was retained at each site and is available to regulatory authorities at the time of site inspection to allow for verification of the treatment identity for each subject. All subjects received treatment at Visit 1/Day 1. A touch-up treatment was administered for subjects whose Investigator Global Aesthetic Improvement (iGAI) score was 3 or 4 at Visit 2/Week 1. Follow-up visits occurred at day 14 (Visit 3 / week 2), day 28 (Visit 4 / week 4), day 84 (Visit 5 / week 12) and day 168 (Visit 6 / week 24).

Optional Retreatment at Week 24 / SYM2014-02 Retreatment: At Visit 6/Week 24, a subject could be retreated with Revanesse Ultra, and retreatment was open-label. Subjects were eligible for retreatment when WSRS scores had returned to baseline for either or both NLFs. If scores had not returned to baseline, subjects were also eligible to be injected for either one or both NLFs as needed to achieve optimal correction. The retreatment group and the optimal correction group were separated for data analysis. These subjects continued to day 196 (Visit 7 / week 28), received a phone contact at day 280 (week 40), and completed at day 364 (Visit 8 / week 52).

Adverse events and complications assessments were recorded at all visits. Subjects were encouraged to report all events, including those that were anticipated.

3. Clinical Endpoints

With regards to safety, the safety of Revanesse Ultra in the nasolabial folds was evaluated by frequency and percent of subjects and investigators reporting treatment-emergent adverse events (TEAEs) tabulated by treatment group, location, frequency, severity and duration after each treatment (initial treatment, touch up, retreatment at six months and touch up) throughout the study. TEAEs were assessed by a subject diary after each injection, touch up and follow up visit, and were reported by the Evaluating Investigator at each of the follow-up visits.

With regards to effectiveness, the primary efficacy variable was changed from Baseline to Visit 6/Week 24 in WSRS score. Summary statistics and 95% confidence interval (CI) were presented for the change scores for each treatment and for the difference in change scores between the two treatments (Comparator minus Test product, i.e., Comparator minus Revanesse Ultra). The 95% CI for difference between treatments was constructed assuming a normal distribution of the change scores. If the upper bound of this 95% CI was less than the prespecified non-inferiority limit of 0.50, the Test product would be claimed to be non-inferior to the Comparator product.

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

The success/failure criteria for the primary efficacy variable was change from Baseline to Week 6/Week 24 in WSRS score. If the upper bound of this 95% CI was less than the prespecified non-inferiority limit of 0.50, the Test product would be claimed to be non-inferior to the Comparator product.

B. Accountability of PMA Cohort

At the time of database lock for the main study, of 163 patients enrolled in the PMA study, 100% (163) of the patients were available for analysis at the completion of the study, the 03 March 2016 post-operative visit. The subject disposition is depicted in Table 3, Table 5 and Figure 1.

Intent-to-treat (ITT) (safety population): All 163 randomized subjects who received study product – were included in the Safety Analysis and other evaluations.

Modified intent-to-treat (mITT): All randomized subjects who met the inclusion/exclusion criteria, were randomized, received both study products, and returned for at least 1 post-injection assessment of WSRS score from both sides of the face. There were 153 subjects in this group. Efficacy analyses were performed in this group, and were considered supportive.

Per-protocol (PP): There were 125 randomized subjects who met all inclusion/exclusion criteria, received both study products, completed Visit 6/Week 24 within the specified window, had data on WSRS score from both sides of the face, and had no significant protocol violations that would have affected the treatment evaluation. Efficacy analyses were performed in this group. For the primary endpoint, the results from PP were considered definitive.

Significant protocol violations were any unforeseen events that occurred during the conduct of the trial that resulted in noteworthy study protocol violations that could have interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy (Table 4).

Four subjects refused touch up, and were not included in the PP population for the following reasons:

- three did not feel they needed the touch up
- one refused the touch up because there was no lidocaine-type numbing agent

Table 3: Subject Accountability

SYM2014-02 Main Study	Total
Enrolled	163
Screen Failures	0
Randomized	163
ITT -Safety Population	163
mITT Population	153
Per Protocol Population	125
Number of subjects that completed study and continued to Retreatment Visits (30 in retreatment group, 41 in optimal correction group)	71
Number of subjects that discontinued prematurely and were not qualified to continue to Retreatment Study (3 withdrew consent, 1 lost to follow up)	4
Number of subjects that completed study and did not continue to Retreatment Visits (accounting of subjects follows here)	88
Optimal Correction at 6 months, and therefore not qualified to enter the retreatment portion of the study	36
Subjects that did not enter Retreatment Protocol who were satisfied with the results	32
Subjects that did not enter the Retreatment Protocol for personal reasons	7
Subjects that did not enter the Retreatment Protocol who were not satisfied / disliked	8
Subjects that did not enter the Retreatment Protocol who experienced adverse events and did not continue	4
Subject with Visit 6 Out of Window- not eligible for Retreatment Protocol	1

SYM2014-02 Retreatment Study	Total
Enrolled	71
Screen Failures	0
Completed	71

Table 4: Significant Protocol Violations

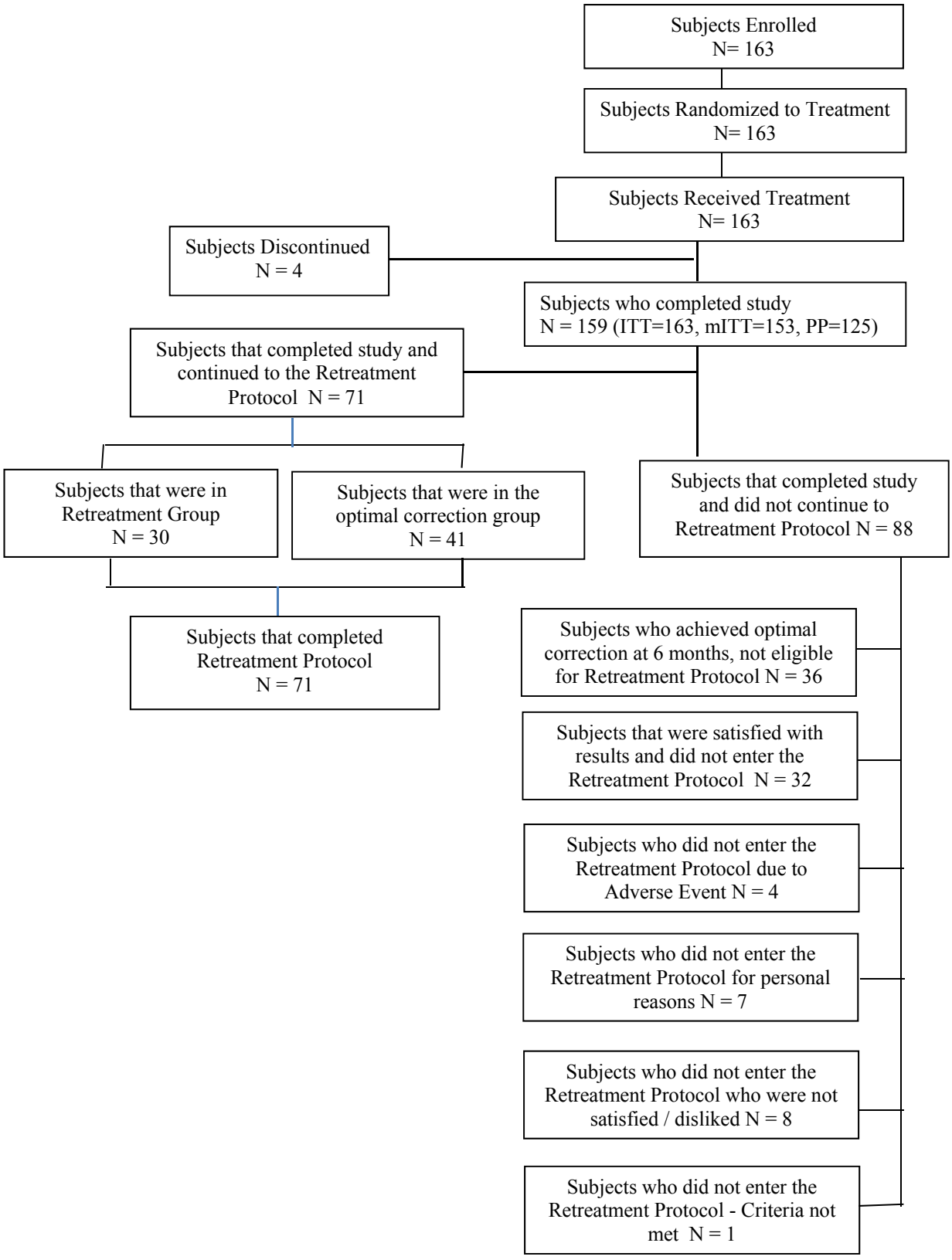
Significant Protocol Violations	Total
Did not complete Visit 6 within the specified window (including V6 as early termination)	15 (9.2%)
Touch up treatment was required but not administered	10 (6.1%)
Comparator with lidocaine was implanted instead of Comparator	9 (5.5%)
Subject refused touch up treatment	4 (2.5%)
Touch up was administered at Visit 4 instead of Visit 2	4 (2.5%)
Use of prohibited medications	3 (1.8%)
Visit 6 missed	2 (1.2%)
Violation of inclusion/exclusion criteria	1 (0.6%)

Table 5: Subject Enrollment by Study Site

Site Number	Randomized	ITT	mITT	PP	Completed and Continued Follow-Up	Completed and Did Not Continue Follow-Up	Discontinued
01	25 (15.3%)	25 (15.3%)	24 (15.7%)	13 (10.4%)	17 (23.9%)	7 (8.0%)	1 (25.0%)
02	40 (24.5%)	40 (24.5%)	40 (26.1%)	39 (31.2%)	15 (21.1%)	25 (28.4%)	0 (0.0%)
03	58 (35.6%)	58 (35.6%)	49 (32.0%)	41 (32.8%)	19 (26.8%)	37 (42.0%)	2 (50.0%)
04	40 (24.5%)	40 (24.5%)	40 (26.1%)	32 (25.6%)	20 (28.2%)	19 (21.6%)	1 (25.0%)
Total	163	163	153	125	71	88	4

ITT: Intent-to-treat; mITT: modified ITT; PP: Per-protocol.
Percentages are based on the total number of subjects in each column.

Figure 1. Subject Accountability Flow Chart



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a dermal filler study performed in the US. The demographics and baseline characteristics of the Revanesse Ultra and control groups are presented in Table 6 and Table 7.

Table 6: SYM2014-02 Main Study Demographic and Baseline Characteristics ITT Population

Parameter	Category	Total (N = 163)
Gender	Female	156 (95.7%)
	Male	7 (4.3%)
Ethnicity	Hispanic or Latino	17 (10.4%)
	Not Hispanic or Latino	146 (89.6%)
Race	White	154 (94.5%)
	Asian	1 (0.6%)
	Native Hawaiian or Other Pacific-Islander	0 (0.0%)
	Black or African American	7 (4.3%)
	American Indian or Alaska Native	0 (0.0%)
	Other	1 (0.6%)
Age (years)	N	163
	Mean ± SD	55.4 ± 10.16
	Median	57.0
	Min, Max	30, 77
Age Groups	22 to < 40	15 (9.2%)
	40 to < 64	110 (67.5%)
	64 to < 75	35 (21.5%)
	≥ 75	3 (1.8%)
BMI*	N	163
	Mean ± SD	26.27 ± 5.374
	Median	25.00
	Min, Max	16.5, 44.1
Fitzpatrick Skin Type Classification	I	3 (1.8%)
	II	50 (30.7%)
	III	83 (50.9%)
	IV	16 (9.8%)
	V	4 (2.5%)
	VI	7 (4.3%)

* BMI = weight (lbs) / height² (in) x 703

Table 7: SYM2014-02 Retreatment Study Demographic and Baseline Characteristics

Parameter	Category	Total (N=71)
Gender	Female	66 (93.0%)
	Male	5 (7.0%)
Ethnicity	Hispanic or Latino	12 (16.9%)
	Not Hispanic or Latino	59 (83.1%)
	Not Willing to Provide	0 (0.0%)
Race	White	66 (93.0%)
	Asian	0 (0.0%)
	Native Hawaiian or Other Pacific-Islander	0 (0.0%)
	Black or African American	5 (7.0%)
	American Indian or Alaska Native	0 (0.0%)
	Other	0 (0.0%)
Age (years)	N	71
	Mean ± SD	56.1 ± 10.05
	Median	57.0
	Min, Max	30, 77
Age Groups	22 to <40	6 (8.5%)
	40 to <64	48 (67.6%)
	64 to <75	15 (21.1%)
	>=75	2 (2.8%)
BMI*	N	71
	Mean ± SD	26.42 ± 5.816
	Median	25.20
	Min, Max	16.5, 44.1
Fitzpatrick Skin Type Classification	I	0 (0.0%)
	II	27 (38.0%)
	III	30 (42.3%)
	IV	6 (8.5%)
	V	3 (4.2%)
	VI	5 (7.0%)

* BMI = weight (lbs) / height² (in) x 703

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT cohort of 163 subjects, for the 24 week evaluation in the SYM2014-02 Main Study, and 71 subjects in the SYM2014-02 Retreatment study for the 52 week evaluation. The key safety outcomes for this study are presented below. Adverse events are reported in Tables 8 to 12.

Adverse effects that occurred in the PMA clinical study:

SYM2014-02 Main Study – Adverse Events

Of the 163 treated subjects, one or more injection-site TEAEs during the study were reported for 114 (69.9%) with Revanesse Ultra treatment and 137 (84.0%) with Comparator treatment, and most events were considered by the investigator

to be possibly or probably treatment-related. A summary of injection-site TEAEs in the SYM2014-02 Main Study is provided in Table 8. The frequency, severity and duration of TEAEs reported in ≥5% of subjects with either treatment are listed in Tables 9, 10 and 11.

After treated with Revanesse Ultra, 114 subjects experienced 378 injection-site TEAEs. Most injection-site TEAEs were considered mild (70.9% [268/378]) or moderate (28.8% [109/378]); only one subject experienced injection site swelling which was reported as severe (0.3% [1/378]). There were 137 subjects who experienced 553 injection-site TEAEs in the comparator group. The proportions of injection-site TEAEs reported as mild (52.6% [291/553]), moderate (42.7% [236/553]), or severe (4.7% [26/553]). Twelve subjects had TEAEs that were reported as severe (0.6% [1/163] with Revanesse Ultra and 7.4% [12/163] with Comparator). These were injection site swelling for 1 subject with Revanesse Ultra treatment, and injection site swelling (7 subjects), injection site pain (6 subjects), injection site erythema (3 subjects), injection site hematoma (2 subjects), injection site induration (2 subjects), gingival pain (1 subject), and vascular site complication (a treatment-emergent serious adverse event, TESAE, 1 subject) with the Comparator treatment.

All injection-site TEAEs resolved during the study, most within less than 1 week (81.5% [308/378] with Revanesse Ultra and 85.0% [470/553] with Comparator). Only 2 events with each treatment had a duration greater than 30 days, including swelling (1 subject in Revanesse Ultra group, no treatment, resolved with no sequelae), injection site discomfort (1 subject in Revanesse Ultra group, no treatment, resolved with no sequelae), injection site mass (1 subject in Comparator group, no treatment, resolved with no sequelae), and 1 subject in comparator group with a serious adverse event of a possible vascular event (left lip and ala, treated with topical lidocaine, hyaluronidase, nitro paste and warm compress, followed by antibiotic, aspirin and warm compress, resolved with no sequelae).

The majority of events (76.7% [290/378] with Revanesse Ultra and 71.2% [394/553] with Comparator) did not require any treatment. The study treatment was interrupted or discontinued for only 1 subject in comparator group due to the serious adverse event of a possible vascular event (left lip and ala) (Table 8). Non-drug therapy was required for 14.6% (55/378) of the events with Revanesse Ultra and 19.7% (109/553) of the events with the Comparator, and a new over-the-counter (OTC) or prescription drug was added for 11.4% (43/378) and 12.7% (70/553) of events, respectively. No event required hospitalization (including Emergency Room visits).

Table 8 - Overall Summary of Injection Site Treatment-Emergent Adverse Events (TEAEs) in the Main Study for Intent-to-Treat Population

	Comparator		Test: Revanesse Ultra	
	Subjects[1] (N=163) n (%)	Events[2] (N=553) n (%)	Subjects[1] (N=163) n (%)	Events[2] (N=378) n (%)
Overall				
	137 (84.0)	553 (100)	114 (69.9)	378 (100)
Duration				
Less than 1 week	130 (79.8)	470 (85.0)	99 (60.7)	308 (81.5)
Between 1 week and 1 month (30 days)	40 (24.5)	81 (14.6)	47 (28.8)	68 (18.0)
More than 1 month (30 days)	2 (1.2)	2 (0.4)	2 (1.2)	2 (0.5)
Severity				
Mild	52 (31.9)	291 (52.6)	65 (39.9)	268 (70.9)
Moderate	73 (44.8)	236 (42.7)	48 (29.4)	109 (28.8)
Severe	12 (7.4)	26 (4.7)	1 (0.6)	1 (0.3)
Causality				
Treatment-related*	136 (83.4)	540 (97.6)	112 (68.7)	373 (98.7)
Not treatment-related	1 (0.6)	13 (2.4)	2 (1.2)	5 (1.3)
Outcome				
Resolved	137 (84.0)	553 (100)	114 (69.9)	378 (100)
Improved	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stabilized	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worsened	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unchanged	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment Required (Action Taken)				
None	119 (73.0)	394 (71.2)	100 (61.3)	290 (76.7)
Study treatment interrupted/discontinued	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)
Non-drug therapy	43 (26.4)	109 (19.7)	26 (16.0)	55 (14.6)
New OTC or Rx drug added	35 (21.5)	70 (12.7)	22 (13.5)	43 (11.4)
Hospitalized (includes ER visits)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[1] Denominator is the number of subjects who received the corresponding treatment.
[2] Denominator is the number of adverse events reported by subjects who received the corresponding treatment.
*Treatment-related includes Possibly and Probably Related.
For Severity and Causality, subjects reporting more than one injection site TEAE associated with a treatment arm are counted only once for the treatment arm under the greatest reported severity and most likely causality, respectively.
For Duration, Outcome and Treatment Required (Action Taken), at each level of the categories, subjects reporting more than one injection site TEAE associated with a treatment arm are counted only once for the treatment arm at that category level.

The most frequently reported injection-site TEAEs, reported for 5% or more of subjects with either treatment, were injection site hematoma (50.3% [82/163] with Revanesse Ultra, 47.2% [77/163] with Comparator), injection site swelling (47.2% [77/163] with Revanesse Ultra, 71.2% [116/163] with Comparator), injection site pain (38.0% [62/163] with Revanesse Ultra, 66.3% [108/163] with

Comparator) and injection site erythema (21.5% [35/163] with Revanesse Ultra, 31.9% [52/163] with Comparator) (Table 9). The four most frequently reported injection-site TEAEs are summarized by severity in Table 10 and by duration in Table 11.

Table 9: SYM2014-02 Main Study – Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	Comparator: (N=163)	Test: Revanesse Ultra (N=163)
General Disorders and Administration Site Conditions		
Injection site erythema	52 (31.9%)	35 (21.5%)
Injection site haematoma	77 (47.2%)	82 (50.3%)
Injection site pain	108 (66.3%)	62 (38.0%)
Injection site swelling	116 (71.2%)	77 (47.2%)

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects with either treatment. Counts reflect numbers of subjects reporting one or more injection site TEAEs that map to the MedDRA (version 15.1) system organ class/preferred term. At each level of summarization (system organ class or preferred term) subjects reporting more than one injection site TEAE are only counted once.

Table 10 - Severity of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) in the Main Study by MedDRA Preferred Term for Intent-to-Treat Population

	Comparator				Test: Revanesse Ultra			
Adverse Event	Events % (n/N)[1]	Mild % (n/N)[2]	Moderate % (n/N)[2]	Severe % (n/N)[2]	Events % (n/N)[1]	Mild % (n/N)[2]	Moderate % (n/N)[2]	Severe % (n/N)[2]
INJECTION SITE ERYTHEMA	11.8% (65/553)	59.6% (31/52)	34.6% (18/52)	5.8% (3/52)	11.6% (44/378)	68.6% (24/35)	31.4% (11/35)	0.0% (0/35)
INJECTION SITE HAEMATOMA	17.2% (95/553)	41.6% (32/77)	55.8% (43/77)	2.6% (2/77)	28.0% (106/378)	59.8% (49/82)	40.2% (33/82)	0.0% (0/82)
INJECTION SITE PAIN	34.7% (192/553)	38.9% (42/108)	55.6% (60/108)	5.6% (6/108)	27.2% (103/378)	61.3% (38/62)	38.7% (24/62)	0.0% (0/62)
INJECTION SITE SWELLING	29.5% (163/553)	41.4% (48/116)	52.6% (61/116)	6.0% (7/116)	27.0% (102/378)	63.6% (49/77)	35.1% (27/77)	1.3% (1/77)

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects of any treatment group.
[1] Denominator is the number of injection site TEAEs reported by all ITT subjects who received the corresponding treatment.
[2] Denominator for percentages by severity is the number of subjects with respective TEAEs after receiving the corresponding treatment. Numerator (count of subjects) is based on the rule that subjects reporting more than one same incidence associated with a treatment arm are counted only once for the treatment arm under the greatest reported severity.

Table 11 - Duration of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

	Comparator				Test: Revanesse Ultra			
Adverse Event	Events % (n/N)[1]	<7 Days % (n/N)[2]	7-30 Days % (n/N)[2]	>30 Days % (n/N)[2]	Events % (n/N)[1]	<7 Days % (n/N)[2]	7-30 Days % (n/N)[2]	>30 Days % (n/N)[2]
INJECTION SITE ERYTHEMA	11.8% (65/553)	90.4% (47/52)	9.6% (5/52)	0.0% (0/52)	11.6% (44/378)	94.3% (33/35)	5.7% (2/35)	0.0% (0/35)
INJECTION SITE HAEMATOMA	17.2% (95/553)	68.8% (53/77)	31.2% (24/77)	0.0% (0/77)	28.0% (106/378)	61.0% (50/82)	39.0% (32/82)	0.0% (0/82)
INJECTION SITE PAIN	34.7% (192/553)	88.9% (96/108)	11.1% (12/108)	0.0% (0/108)	27.2% (103/378)	83.9% (52/62)	16.1% (10/62)	0.0% (0/62)
INJECTION SITE SWELLING	29.5% (163/553)	81.0% (94/116)	19.0% (22/116)	0.0% (0/116)	27.0% (102/378)	77.9% (60/77)	20.8% (16/77)	1.3% (1/77)

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects of any treatment group.
[1] Denominator is the number of injection site TEAEs reported by all ITT subjects who received the corresponding treatment.
[2] Denominator for percentages by duration is the number of subjects with respective TEAEs after receiving the corresponding treatment. Numerator (count of subjects) is based on the rule that subjects reporting more than one same incidence associated with a treatment arm are counted only once for the treatment arm under the longest duration.

There were 52 TEAEs reported for <5% or more of subjects with either treatment (33 Comparator, 19 Revanesse Ultra), and included gingival pain (3 Comparator, 2 Revanesse Ultra), injection site anaesthesia (2 Comparator, 1 Revanesse Ultra), discomfort (1 Comparator, 2 Revanesse Ultra), exfoliation (4 Comparator, 3 Revanesse Ultra), induration (4 Comparator, 1 Revanesse Ultra), injection site mass (8 Comparator, 5 Revanesse Ultra), injection site papule (2 Comparator, 2 Revanesse Ultra), injection site pruritis (6 Comparator, 3 Revanesse Ultra), injection site warmth (1 Comparator, 0 Revanesse Ultra), vascular complication associated with the device (1 Comparator, 0 Revanesse Ultra), and rhinorrhea (1 Comparator, 0 Revanesse Ultra).

Five subjects experienced TESAEs, one of which was considered to be related to the study treatment (possible vascular event left lip and ala with Comparator) and led to treatment interruption. No deaths were reported and no subject discontinued the study due to AEs.

Non-Injection Site TEAEs

Twenty-two subjects (13.5%) experienced non-injection site (systemic) TEAEs. The most frequently reported events were headache (3.1%) and arthralgia (1.8%). Most non-injection site TEAEs were mild or moderate. Three subjects had non-injection site TEAEs that were reported as severe: arthralgia and arthritis in the same subject, cholelithiasis, and breast cancer.

SYM2014-02 Retreatment Addendum

During the retreatment period no TESAEs were reported and no TEAEs led to study treatment or discontinuation. At least one injection-site TEAE was reported for 50.0% (15/30) and 48.8% (20/41) of subjects who had 1 or 2 Comparator injections during the treatment period, respectively, and 36.8% (14/38) and 66.7%

(22/33) of subjects who had 1 or 2 Revanesse Ultra injections during the treatment period (Table 12). The most frequent injection-site TEAEs were injection site hematoma, injection site swelling, and injection site pain. Non-injection site TEAEs were reported for 7 of the 71 retreated subjects (9.9%). No non injection site TEAE was reported for more than 1 subject. All non-injection site TEAEs were mild or moderate, and no non-injection site TEAEs were considered related to study product.

Table 12: SYM2014-02 Retreatment Addendum –Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject during Retreatment by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	1x Comparator (N=30)	2x Comparator (N=41)	1x Revanesse Ultra (N=38)	2x Revanesse Ultra (N=33)
Subjects with at Least One Injection Site TEAE	15 (50.0%)	20 (48.8%)	14 (36.8%)	22 (66.7%)
General disorders and administration site conditions	14 (46.7%)	19 (46.3%)	14 (36.8%)	22 (66.7%)
Injection site erythema	3 (10.0%)	6 (14.6%)	4 (10.5%)	6 (18.2%)
Injection site haematoma	8 (26.7%)	12 (29.3%)	9 (23.7%)	13 (39.4%)
Injection site mass	1 (3.3%)	1 (2.4%)	1 (2.6%)	2 (6.1%)
Injection site pain	6 (20.0%)	6 (14.6%)	6 (15.8%)	9 (27.3%)
Injection site swelling	8 (26.7%)	12 (29.3%)	11 (28.9%)	11 (33.3%)

Note: The sides of the faces are grouped by the number of injections received and the treatment arm during the treatment period (i.e., 1x includes subjects receiving injection only at Visit 1 while 2x includes subjects who also received a touch-up treatment). Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects with either treatment. Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version 15.1) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one injection site TEAE are counted only once.

During both the main study and retreatment, almost all injection site TEAEs were reported by the subjects. The only events reported by the investigators were injection site papule and vascular complication associated with the device during the main study and ocular hyperemia during retreatment. All non-injection site (i.e., systemic) TEAEs during both the main study and retreatment were reported by the subjects.

Subgroup Analyses

Subgroup analyses of Treatment-Emergent Adverse Events (TEAEs) were performed by Fitzpatrick skin phototype (grouped as I-IV, V-VI and each skin type). Subject skin type did not appear to have an effect on the distribution of TEAEs. In general, there were no significant differences between the Revanesse Ultra and comparator groups for any Fitzpatrick skin phototype (FST) subgroup in terms of injection site TEAEs, except for a higher incidence rate of swelling in FST V subjects (75%, 3/4) observed as compared to overall subjects (47.2%, 77/163). In all studies there were no incidences of hyperpigmentation, keloid or hypertrophic scar formation.

The company has provided injection related Adverse Event (AE) information to the agency in support of the injection related treatment emergent adverse event data for the Fitzpatrick Skin Type (FST) analysis as a compilation of three clinical

studies (SYM 2014-02 Main Study, SYM 2014-02 Retreatment Study, SYM 2016-02). The analysis was performed by a second Clinical Research Organization. A summary of the SYM2016-02 study titled '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' is included as part of the FST analysis. The first subject for the SYM2016-02 study was enrolled on August 25 2016. The 100th subject was enrolled at on December 22, 2016. Enrollment has been closed at all four sites. Among the 100 randomized subjects, 95 are included in the mITT population (definitive population) and 75 in the PP population (supportive population). The study included all Fitzpatrick Skin Types (FST I = 1, FST II = 14, FST III = 43, FST IV = 27, FST V = 12, FST VI = 3). Adverse events for all skin types were analyzed.

The combined analysis of the three datasets for the injection-site TEAEs in terms of FST scores are presented in Table 13 (counts and proportions for the incidences of injection-site TEAEs) and Table 14 (racial distribution within Fitzpatrick skin phototype subgroup).

For each of the three Adverse Event (AE) datasets (SYM 2014-02 Main, SYM 2014-02 Retreatment, and SYM 2016-02), the injection-site related AEs for Revanesse Ultra per injection were summarized by patient Fitzpatrick Skin Type (FST). The injection-site related AEs were also summarized by grouping the FST categories for I-IV and V-VI. If an AE occurred at any time following a specific injection, regardless of the number of times the AE was recorded in the database, it was counted only once. As such, the summaries represent the instances of occurrence of each specific AE for the number of Revanesse Ultra injections. For Study SYM 2014-02 Main and SYM 2016-02, each patient received an injection of Revanesse Ultra on one side of the face. Accordingly, the number of injections was equal to the number of patients who participated in each of these studies. For Study SYM 2014-02 Retreatment, each patient received an injection of Revanesse Ultra on both sides of the face (i.e. two injections per patient). The number of injections for the retreatment phase of SYM 2014-02 was equal to two times the number of patients who participated in this phase of the study. If a specific AE was reported for one side or the other of a patient's face, it was counted as a single occurrence for the AE. If the AE was reported as occurring on both sides of the face, it was counted as two occurrences for the AE for the retreatment phase.

Table 13: Combined Datasets - Summary of Injection Site Adverse Events for Revanesse Ultra by Fitzpatrick Skin Type
Studies SYM 2014-02 (Main Study) SYM 2014-02 Retreatment Study and SYM 2016-02 - Analysis of Injection-Related AEs by Fitzpatrick Skin Type

Skin Type System Organ Class Preferred Term[a]	I (N=4) n (%)	II (N=118) n (%)	III (N=186) n (%)	IV (N=55) n (%)	Total I-IV (N=363) n (%)	V (N=22) n (%)	VI (N=20) n (%)	Total V-VI (N=42) n (%)	Overall Total (N=405) n (%)
Number of subjects with at least one Injection Site-Related TEAE	4 (100%)	70 (59.32%)	108 (58.06%)	36 (65.45%)	218 (60.06%)	9 (40.91%)	6 (30%)	15 (35.71%)	233 (57.53%)
General Disorders And Administration Site Conditions	4 (100%)	70 (59.32%)	108 (58.06%)	36 (65.45%)	218 (60.06%)	9 (40.91%)	6 (30%)	15 (35.71%)	233 (57.53%)
Injection Site Anaesthesia	0 (0%)	0 (0%)	1 (1.2%)	0 (0%)	1 (0.66%)	0 (0%)	0 (0%)	0 (0%)	1 (0.61%)
Injection Site Discomfort	0 (0%)	0 (0%)	2 (2.41%)	0 (0%)	2 (1.32%)	0 (0%)	0 (0%)	0 (0%)	2 (1.23%)
Injection Site Erythema	1 (25%)	16 (13.56%)	34 (18.28%)	10 (18.18%)	61 (16.8%)	2 (9.09%)	3 (15%)	5 (11.9%)	66 (16.3%)
Injection Site Exfoliation	1 (33.33%)	2 (1.92%)	1 (0.7%)	0 (0%)	4 (1.44%)	0 (0%)	0 (0%)	0 (0%)	4 (1.31%)
Injection Site Haematoma	3 (75%)	45 (38.14%)	73 (39.25%)	23 (41.82%)	144 (39.67%)	5 (22.73%)	6 (30%)	11 (26.19%)	155 (38.27%)
Injection Site Induration	0 (0%)	0 (0%)	1 (1.2%)	0 (0%)	1 (0.66%)	0 (0%)	0 (0%)	0 (0%)	1 (0.61%)
Injection Site Mass	0 (0%)	4 (3.39%)	6 (3.23%)	2 (3.64%)	12 (3.31%)	0 (0%)	0 (0%)	0 (0%)	12 (2.96%)
Injection Site Pain	3 (75%)	30 (25.42%)	56 (30.11%)	15 (27.27%)	104 (28.65%)	3 (13.64%)	3 (15%)	6 (14.29%)	110 (27.16%)
Injection Site Papule	0 (0%)	0 (0%)	2 (2.41%)	0 (0%)	2 (1.32%)	0 (0%)	0 (0%)	0 (0%)	2 (1.23%)
Injection Site Pruritus	1 (25%)	0 (0%)	6 (3.23%)	4 (7.27%)	11 (3.03%)	0 (0%)	0 (0%)	0 (0%)	11 (2.72%)
Injection Site Swelling	2 (50%)	45 (38.14%)	64 (34.41%)	14 (25.45%)	125 (34.44%)	7 (31.82%)	4 (20%)	11 (26.19%)	136 (33.58%)

Note: 'Injection Site Bruising' presented as 'Injection Site Haematoma'
Data for subjects in FST I-IV and V-VI are presented in the table, in addition to presenting the data for each individual skin type, as individuals with higher FST have been shown to have a prevalence of hyperpigmentation, keloid and hypertrophic scarring

Table 14: Summary of Racial Distribution within Fitzpatrick Skin Type - Combined Datasets
Studies SYM 2014-02 (Main Study) SYM 2014-02 Retreatment Study and SYM 2016-02 - Analysis of Injection-Related AEs by Fitzpatrick Skin Type

	Skin Type				Total	Skin Type		Total	Overall
	I	II	III	IV	I-IV	V	VI	V-VI	Total
	(N=4)	(N=91)	(N=156)	(N=49)	(N=300)	(N=19)	(N=15)	(N=34)	(N=426)
Race	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
White	4 (100%)	91 (100%)	156 (100%)	44 (89.8%)	295 (98.33%)	14 (73.68%)	0 (0%)	14 (41.18%)	309 (72.54%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.26%)	0 (0%)	1 (2.94%)	1 (0.23%)
Black or African American	0 (0%)	0 (0%)	0 (0%)	3 (6.12%)	3 (1%)	4 (21.05%)	15 (100%)	19 (55.88%)	22 (5.16%)
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	1 (2.04%)	1 (0.33%)	0 (0%)	0 (0%)	0 (0%)	1 (0.23%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other (Cuban)	0 (0%)	0 (0%)	0 (0%)	1 (6.25%)	1 (0.66%)	0 (0%)	0 (0%)	0 (0%)	1 (0.61%)

Note: Race is self-reported, middle-Eastern descent is usually identifies as "white" unless the subject chooses to specify otherwise
Data for subjects in FST I-IV and V-VI are presented in the table, in addition to presenting the data for each individual skin type, as individuals with higher FST have been sbown to have a prevalence of hyperpigmentation, keloid and hypertrophic scarring

There were 97 injections of Revanesse Ultra in the Fitzpatrick Skin Type IV-VI category, with 308 injections in the I-III category. The percentage of incidences of each type of adverse event was greater for the I-III FST (pale to cream white or yellowish) than for the IV-VI FST (olive or light brown skin to very dark brown). (Table 13)

There were 42 injections of Revanesse Ultra in the Fitzpatrick Skin Type V-VI with 363 injections in the I-IV category. The percentage of incidences of each AE was greater for the I-IV FST (pale to olive or light brown) than for the V-VI FST (brown to very dark brown). (Table 13).

The incidence of swelling for the Combined Analysis (SYM 2014-02 Main, SYM 2014-02 Retreatment, and SYM 2016-02) are reported as the number of injection sites that had swelling below. The number of pateints who had swelling from the Combined Datasets are reported in Table 13.

The incidence of swelling for the Combined Analysis (SYM 2014-02 Main, SYM 2014-02 Retreatment, and SYM 2016-02) was greatest in the FST I:

I 50.00% (There were 4 injections in FST I skin type of which 2 had swelling)
II 38.14% (There were 118 injections in FST II skin type of which 45 had swelling)
III 34.41% (There were 186 injections in FST III skin type of which 64 had swelling)
IV 25.45% (There were 55 injections in FST IV skin type of which 14 had swelling)
V 31.82% (There were 22 injections in FST V skin type of which 7 had swelling)
VI 20.00% (There were 20 injections in FST VI skin type of which 4 had swelling)

The incidence of injection site swelling in the Main Study (SYM 2014-02 Main) was greatest in FST V, of the four injections in patients that were FST V there were three incidences of swelling at the injection site:

I 66.67% (There were 3 injections in FST I skin type of which 2 had swelling)
II 50% (There were 50 injections in FST II skin type of which 25 had swelling)
III 45.78% (There were 83 injections in FST III skin type of which 38 had swelling)
IV 43.75% (There were 16 injections in FST IV skin type of which 7 had swelling)
V 75% (There were 4 injections in FST V skin type of which 3 had swelling)
VI 28.57% (There were 7 injections in FST VI skin type of which 2 had swelling)

In the Retreatment Study (SYM 2014-02 Retreatment) the most injection site swelling was observed in the FST IV with 4 incidences out of 12 injections:

I 0% (There were 0 injections in FST I skin type of which 0 had swelling)
II 31.48% (There were 54 injections in FST II skin type of which 17 had swelling)
III 30% (There were 60 injections in FST III skin type of which 18 had swelling)
IV 33.33% (There were 12 injections in FST IV skin type of which 4 had swelling)
V 16.67% (There were 6 injections in FST V skin type of which 1 had swelling)
VI 20% (There were 10 injections in FST VI skin type of which 2 had swelling)

2. Effectiveness Results

The analysis of effectiveness was based on the 125 evaluable patients at the 24-week time point. Key effectiveness outcomes are presented in Table 15.

Primary Endpoints

The analysis of effectiveness (SYM2014-02 Main Study) was based on the Per Protocol analysis set which includes 125 evaluable patients at the 24 week time point (Tables 15). Revanesse Ultra was shown to be non-inferior to Comparator with a mean difference (Comparator minus Revanesse Ultra) in the change from baseline in WSRS score at Visit 6/Week 24 in the PP population of -0.11, with a 95% CI of -0.225 to 0.001. The upper bound of this 95% CI was less than the prespecified non-inferiority limit of 0.50. The mean change from baseline in WSRS was 1.02 with Revanesse Ultra treatment and 0.91 with Comparator treatment.

Table 15: SYM2014-02 Main Study - Primary Efficacy: Change from Baseline to Visit 6/Week 24 in Wrinkle Severity Rating Scale (WSRS)

Population	Statistics	Comparator	Test: Revanesse Ultra	Difference: Comparator minus Test
Per-Protocol (PP)	N	125	125	125
	Mean ± SD	0.91 ± 0.762	1.02 ± 0.689	-0.11 ± 0.638
	95% CI of Mean	(0.777, 1.047)	(0.902, 1.146)	(-0.225, 0.001)
	Median	1.00	1.00	0.00
	Min, Max	-1.0, 3.0	0.0, 3.0	-2.0, 1.0
Modified Intent-to-Treat (mITT)	N	153	153	153
	Mean ± SD	0.95 ± 0.746	1.09 ± 0.692	-0.14 ± 0.608
	95% CI of Mean	(0.835, 1.073)	(0.981, 1.202)	(-0.234, -0.040)
	Median	1.00	1.00	0.00
	Min, Max	-1.0, 3.0	0.0, 3.0	-2.0, 1.0

CI = confidence interval; SD = standard deviation

Note: The results from PP are considered definitive and those from mITT supportive. Missing efficacy data were imputed via the last observation carried forward (LOCF) method in the mITT analysis.

Change from baseline in WSRS = WSRS at Visit 1 – WSRS at Visit 6. A positive score indicates improvement. The 95% confidence intervals were constructed assuming a normal distribution of the change scores.

Secondary Endpoints

The treatment success rate at Visit 6/Week 24, defined as at least a 1-grade improvement in WSRS score from baseline, was 78.4% with Revanesse Ultra and 72.8% with Comparator in the PP population, and 81.7% with Revanesse Ultra and 75.8% with Comparator in the mITT population (Table 16).

The percentage of subjects with Patient Global Aesthetic Improvement (pGAI) at Visit 6/Week 24 responses of much improved or very much improved was 44.4% with Revanesse Ultra and 30.6% with Comparator in the PP population and 44.4% with Revanesse Ultra and 30.7% with Comparator in the mITT population (Table 17).

The percentage of subjects with the Investigator Global Aesthetic Improvement (iGAI) at Visit 6/Week 24 responses of much improved or very much improved was 59.2% with Revanesse Ultra and 47.2% with Comparator in the PP population and 60.8% with Revanesse Ultra and 49.7% with Comparator in the mITT population (Table 18).

Table 16: SYM2014-02 Main Study -Treatment Success (as at least a 1-grade improvement in WSRS from baseline **)** at Visit 6/Week 24

Population	Category	Comparator:	Test: Revanesse Ultra
Per-Protocol (PP)	N	125	125
	n (%) of Subjects with Treatment Success*	91 (72.8%)	98 (78.4%)
Modified Intent-to-Treat (mITT)	N	153	153
	n (%) of Subjects with Treatment Success*	116 (75.8%)	125 (81.7%)

Missing efficacy data were imputed via the last observation carried forward (LOCF) method in the mITT analysis.
*Treatment success at Visit 6/Week 24 was defined as at least a 1-grade improvement in WSRS from baseline.

Table 17: SYM2014-02 Main Study - Secondary Efficacy: Patient Global Aesthetic Improvement (pGAI) at Visit 6/Week 24

Population	Category	Comparator: Comparator	Test: Revanesse Ultra
Per-Protocol (PP)	N	124	124
	1 = Worse	1 (0.8%)	0 (0.0%)
	2 = No Change	30 (24.2%)	25 (20.2%)
	3 = Improved	55 (44.4%)	44 (35.5%)
	4 = Much Improved	32 (25.8%)	47 (37.9%)
	5 = Very Much Improved	6 (4.8%)	8 (6.5%)
Modified Intent-to-Treat (mITT)	N	153	153
	1 = Worse	1 (0.7%)	0 (0.0%)
	2 = No Change	33 (21.6%)	29 (19.0%)
	3 = Improved	72 (47.1%)	56 (36.6%)
	4 = Much Improved	39 (25.5%)	60 (39.2%)
	5 = Very Much Improved	8 (5.2%)	8 (5.2%)

Missing efficacy data were imputed via the last observation carried forward (LOCF) method in the mITT analysis.

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Table 18: SYM2014-02 Main Study - Secondary Efficacy: Investigator Global Aesthetic Improvement (iGAI) at Visit 6/Week 24

Population	Category	Comparator: Comparator	Test: Revanesse Ultra
Per-Protocol (PP)	N	125	125
	1 = Worse	1 (0.8%)	0 (0.0%)
	2 = No Change	6 (4.8%)	2 (1.6%)
	3 = Improved	59 (47.2%)	49 (39.2%)
	4 = Much Improved	26 (20.8%)	43 (34.4%)
	5 = Very Much Improved	33 (26.4%)	31 (24.8%)
Modified Intent-to-Treat (mITT)	N	153	153
	1 = Worse	1 (0.7%)	0 (0.0%)
	2 = No Change	8 (5.2%)	2 (1.3%)
	3 = Improved	68 (44.4%)	58 (37.9%)
	4 = Much Improved	35 (22.9%)	51 (33.3%)
	5 = Very Much Improved	41 (26.8%)	42 (27.5%)

Missing efficacy data were imputed via the last observation carried forward (LOCF) method in the mITT analysis.

SYM2014-02 Retreatment Study

Following retreatment with Revanesse Ultra, subjects showed improvement in the WSRS, pGAI, and iGAI. The study did not demonstrate any safety concerns with retreatment of Revanesse Ultra for men or women at least 22 years of age with NLFs with a moderate or severe WSRS score at baseline who had previously received 1 or 2 treatments with the Comparator or Revanesse Ultra. The retreatment group showed greater improvement than the optimal correction group. The majority of subjects were evaluated on the pGAI and the iGAI as much improved or very much improved at Visit 7/ Week 28, and as at least improved at Visit 8/ Week 52 (Table 19).

Subjects from both the retreatment group and the optimal correction groups achieved similar WSRS scores at Visit 8/Week 52, with a mean WSRS score of 2.4 for each group. The retreatment group showed a greater improvement in WSRS score while the optimal correction group maintained their WSRS score.

For WSRS scores in the retreatment group, mean change from Visit 6/Week 24 to Visit 7/ Week 28 (i.e., Visit 6/Week 24 - Visit 7/ Week 28) and from Visit 6/Week 24 to Visit 8/Week 52 (Visit 6/Week 24 - Visit 8/Week 52), respectively, was 0.8 and 0.8 for subjects treated originally with The Comparator, and 0.8 and 0.6 for subjects treated originally with Revanesse Ultra.

In the optimal correction group, mean change from Visit 6/Week 24 to Visit 7/Week 28 and from Visit 6/Week 24 to Visit 8/Week 52, respectively, was 0.5 and 0.0 for subjects

treated originally with The Comparator, and 0.4 and 0.1 for subjects treated originally with Revanesse Ultra.

Table 19: SYM2014-02 Retreatment Study - Change in Wrinkle Severity Rating Scale (WSRS) by Visit

Treatment Arm: Study Visit	Category	Statistics	Retreatment (N=30)	Optimal Correction (N=41)	Total (N=71)
Comparator:					
Visit 6/Week 24	Observed Value	N	30	41	71
		Mean ± SD	3.2 ± 0.61	2.4 ± 0.50	2.7 ± 0.67
		Median	3.0	2.0	3.0
		Min, Max	2, 4	2, 3	2, 4
Visit 7/Week 28	Observed Value	N	30	41	71
		Mean ± SD	2.4 ± 0.77	1.9 ± 0.62	2.1 ± 0.73
		Median	2.0	2.0	2.0
		Min, Max	1, 4	1, 3	1, 4
	Change from Week 24	N	30	41	71
		Mean ± SD	0.8 ± 0.71	0.5 ± 0.55	0.6 ± 0.64
		Median	1.0	1.0	1.0
		Min, Max	-1, 2	-1, 1	-1, 2
Visit 8/Week 52	Observed Value	N	30	41	71
		Mean ± SD	2.4 ± 0.63	2.4 ± 0.89	2.4 ± 0.79
		Median	2.0	2.0	2.0
		Min, Max	1, 4	1, 4	1, 4
	Change from Week 24	N	30	41	71
		Mean ± SD	0.8 ± 0.63	0.0 ± 0.69	0.3 ± 0.75
		Median	1.0	0.0	0.0
		Min, Max	-1, 2	-1, 1	-1, 2
Test: Revanesse Ultra:					
Visit 6/Week 24	Observed Value	N	30	41	71
		Mean ± SD	3.0 ± 0.49	2.2 ± 0.54	2.6 ± 0.65
		Median	3.0	2.0	3.0
		Min, Max	2, 4	1, 3	1, 4
Visit 7/Week 28	Observed Value	N	30	41	71
		Mean ± SD	2.2 ± 0.73	1.9 ± 0.61	2.0 ± 0.69
		Median	2.0	2.0	2.0
		Min, Max	1, 4	1, 3	1, 4
Visit 7/Week 28	Change from Week 24	N	30	41	71
		Mean ± SD	0.8 ± 0.71	0.4 ± 0.63	0.6 ± 0.69
		Median	1.0	0.0	1.0
		Min, Max	-1, 2	-1, 1	-1, 2
Visit 8/Week 52	Observed Value	N	30	41	71
		Mean ± SD	2.4 ± 0.68	2.2 ± 0.74	2.3 ± 0.72
		Median	2.0	2.0	2.0
		Min, Max	1, 4	1, 4	1, 4
	Change from Week 24	N	30	41	71
		Mean ± SD	0.6 ± 0.72	0.1 ± 0.69	0.3 ± 0.74
		Median	1.0	0.0	0.0
		Min, Max	-1, 2	-1, 1	-1, 2

Note: The retreatment group included subjects whose WSRS scores at Visit 6 had returned to baseline for one or both sides of the face. The optimal correction group included subjects whose WSRS scores at Visit 6 had not returned to baseline for either side of the face. Change from Week 24 = WSRS at Visit 6 - WSRS at Visit 7/8. A positive score indicates improvement.

The percentage of subjects in the retreatment group with responses of much improved or very much improved on the pGAI score at Visit 6/Week 24, Visit 7/Week 28, and Visit 8/Week 52, respectively, was 33.3%, 60.0%, and 26.7% for subjects treated originally with The Comparator, and 40.0%, 63.3%, and 33.3% for subjects treated originally with Revanesse Ultra (Table 20).

The percentage of subjects in the optimal correction group with responses of much improved or very much improved on the pGAI score at Visit 6/Week 24, Visit 7/Week 28, and Visit 8/Week 52, respectively, was 24.4%, 65.9%, and 39.0% for subjects treated originally with The Comparator, and 48.8%, 68.3%, and 58.5% for subjects treated originally with Revanesse Ultra (Table 20).

Table 20: SYM2014-02 Retreatment Study - Patient Global Aesthetic Improvement (pGAI) by Visit

Treatment Arm Study Visit	Statistics	Retreatment (N=30)	Optimal Correction (N=41)	Total (N=71)
Comparator:				
Visit 6/Week 24	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	7 (23.3%)	9 (22.0%)	16 (22.5%)
	3 = Improved	13 (43.3%)	22 (53.7%)	35 (49.3%)
	4 = Much Improved	10 (33.3%)	9 (22.0%)	19 (26.8%)
	5 = Very Much Improved	0 (0.0%)	1 (2.4%)	1 (1.4%)
Visit 7/Week 28	N	30	41	71
	1 = Worse	1 (3.3%)	0 (0.0%)	1 (1.4%)
	2 = No Change	1 (3.3%)	3 (7.3%)	4 (5.6%)
	3 = Improved	10 (33.3%)	11 (26.8%)	21 (29.6%)
	4 = Much Improved	11 (36.7%)	19 (46.3%)	30 (42.3%)
	5 = Very Much Improved	7 (23.3%)	8 (19.5%)	15 (21.1%)
Visit 8/Week 52	N	30	41	71
	1 = Worse	1 (3.3%)	1 (2.4%)	2 (2.8%)
	2 = No Change	8 (26.7%)	8 (19.5%)	16 (22.5%)
	3 = Improved	13 (43.3%)	16 (39.0%)	29 (40.8%)
	4 = Much Improved	1 (3.3%)	12 (29.3%)	13 (18.3%)
	5 = Very Much Improved	7 (23.3%)	4 (9.8%)	11 (15.5%)
Test: Revanesse Ultra				
Visit 6/Week 24	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	6 (20.0%)	8 (19.5%)	14 (19.7%)
	3 = Improved	12 (40.0%)	13 (31.7%)	25 (35.2%)
	4 = Much Improved	12 (40.0%)	20 (48.8%)	32 (45.1%)
	5 = Very Much Improved	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 7/Week 28	N	30	41	71
	1 = Worse	1 (3.3%)	1 (2.4%)	2 (2.8%)
	2 = No Change	1 (3.3%)	2 (4.9%)	3 (4.2%)
	3 = Improved	9 (30.0%)	10 (24.4%)	19 (26.8%)
	4 = Much Improved	9 (30.0%)	18 (43.9%)	27 (38.0%)
	5 = Very Much Improved	10 (33.3%)	10 (24.4%)	20 (28.2%)
Visit 8/Week 52	N	30	41	71
	1 = Worse	0 (0.0%)	2 (4.9%)	2 (2.8%)
	2 = No Change	7 (23.3%)	6 (14.6%)	13 (18.3%)
	3 = Improved	13 (43.3%)	9 (22.0%)	22 (31.0%)
	4 = Much Improved	4 (13.3%)	19 (46.3%)	23 (32.4%)
	5 = Very Much Improved	6 (20.0%)	5 (12.2%)	11 (15.5%)

Note: The retreatment group included subjects whose WSRS scores at Visit 6 had returned to baseline for one or both sides of the face. The optimal correction group included subjects whose WSRS scores at Visit 6 had not returned to baseline for either side of the face.

The percentage of subjects in the retreatment group with responses of much improved or very much improved on the iGAI score at Visit 6/Week 24, Visit 7/Week 28, and Visit 8/Week 52, respectively, was 16.7%, 83.3%, and 43.3% for subjects treated originally with The Comparator, and 23.3%, 86.7%, and 43.3% for subjects treated originally with Revanesse Ultra (Table 21).

The percentage of subjects in the optimal correction group with responses of much improved or very much improved on the iGAI score at Visit 6/Week 24, Visit 7/Week 28, and Visit 8/Week 52, respectively, was 43.9%, 85.4%, and 58.5% for subjects treated originally with The Comparator, and 58.5%, 90.2%, and 61.0% for subjects treated originally with Revanesse Ultra (Table 21).

Table 21: SYM2014-02 Retreatment Study - Investigator Global Aesthetic Improvement (iGAI) by Visit

Treatment Arm Study Visit	Statistics	Retreatment (N=30)	Optimal Correction (N=41)	Total (N=71)
Comparator:				
Visit 6/Week 24	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	3 (10.0%)	1 (2.4%)	4 (5.6%)
	3 = Improved	22 (73.3%)	22 (53.7%)	44 (62.0%)
	4 = Much Improved	4 (13.3%)	13 (31.7%)	17 (23.9%)
	5 = Very Much Improved	1 (3.3%)	5 (12.2%)	6 (8.5%)
Visit 7/Week 28	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	1 (3.3%)	0 (0.0%)	1 (1.4%)
	3 = Improved	4 (13.3%)	6 (14.6%)	10 (14.1%)
	4 = Much Improved	9 (30.0%)	12 (29.3%)	21 (29.6%)
	5 = Very Much Improved	16 (53.3%)	23 (56.1%)	39 (54.9%)
Visit 8/Week 52	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	8 (26.7%)	7 (17.1%)	15 (21.1%)
	3 = Improved	9 (30.0%)	10 (24.4%)	19 (26.8%)
	4 = Much Improved	6 (20.0%)	11 (26.8%)	17 (23.9%)
	5 = Very Much Improved	7 (23.3%)	13 (31.7%)	20 (28.2%)
Test: Revanesse Ultra				
Visit 6/Week 24	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	1 (3.3%)	0 (0.0%)	1 (1.4%)
	3 = Improved	22 (73.3%)	17 (41.5%)	39 (54.9%)
	4 = Much Improved	7 (23.3%)	18 (43.9%)	25 (35.2%)
	5 = Very Much Improved	0 (0.0%)	6 (14.6%)	6 (8.5%)
Visit 7/Week 28	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3 = Improved	4 (13.3%)	4 (9.8%)	8 (11.3%)
	4 = Much Improved	7 (23.3%)	14 (34.1%)	21 (29.6%)
	5 = Very Much Improved	19 (63.3%)	23 (56.1%)	42 (59.2%)
Visit 8/Week 52	N	30	41	71
	1 = Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2 = No Change	8 (26.7%)	6 (14.6%)	14 (19.7%)
	3 = Improved	9 (30.0%)	10 (24.4%)	19 (26.8%)
	4 = Much Improved	5 (16.7%)	12 (29.3%)	17 (23.9%)
	5 = Very Much Improved	8 (26.7%)	13 (31.7%)	21 (29.6%)

Note: The retreatment group includes subjects whose WSRS scores at Visit 6 returned to baseline for either side or both sides of the face. The optimal correction group includes subjects whose WSRS scores at Visit 6 did not return to baseline for either side of the face.

3. Subgroup Analyses

Not available.

4. 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 four investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not available.

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

The results of this randomized, multicenter, double-blind, split-face study demonstrate that Revanesse Ultra is safe and non-inferior to Comparator in subjects undergoing correction of NLFs.

Revanesse Ultra was shown to be non-inferior to Comparator with a mean difference (Comparator minus Revanesse Ultra) in the change from baseline in WSRS score at Visit 6/Week 24 in the PP population of -0.11, with a 95% CI of -0.225 to 0.001. The upper bound of this 95% CI was less than the prespecified non-inferiority limit of 0.50.

The mean change from baseline in WSRS was 1.02 with Revanesse Ultra treatment and 0.91 with Comparator treatment.

Supportive results in the mITT population were similar. The mean difference (Comparator minus Revanesse Ultra) in the change from baseline WSRS score at Visit 6/Week 24 was -0.14, with a 95% CI of -0.234 to -0.040. The mean change from baseline in WSRS score was 1.09 with Revanesse Ultra and 0.95 with Comparator. The treatment success rate at Visit 6/Week 24, defined as at least a 1-grade improvement in WSRS score from baseline, was 78.4% with Revanesse Ultra and 72.8% with Comparator in the PP population, and 81.7% with Revanesse Ultra and 75.8% with Comparator in the mITT population.

The percentage of subjects with pGAI responses of much improved or very much improved was 44.4% with Revanesse Ultra and 30.6% with Comparator in the PP population and 44.4% with Revanesse Ultra and 30.7% with Comparator in the mITT population.

Following retreatment with Revanesse Ultra, subjects showed improvement in the WSRS, pGAI, and iGAI. The retreatment group showed greater improvement than the optimal correction group. The majority of subjects were evaluated on the pGAI and the iGAI as much improved or very much improved at Visit 7/ Week 28, and as at least improved at Visit 8/ Week 52.

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.

Safety Conclusions: Comparable safety profiles between Revanesse Ultra and Comparator were demonstrated concerning the nature, severity or frequency of injection site TEAEs. Non- injection site TEAEs were infrequent. Retreatment with Revanesse Ultra demonstrated an acceptable adverse event profile.

SYM2014-02 Main Study

- Of the 163 treated subjects, one or more injection-site TEAEs during the study were reported for 114 (69.9%) with Revanesse Ultra treatment and 137 (84.0%) with Comparator treatment.
- The most frequently reported injection site TEAEs were injection site hematoma (50.3% Revanesse Ultra, 47.2% Comparator), injection site swelling (47.2% Revanesse Ultra, 71.2% Comparator), and injection site pain (38.0% Revanesse Ultra, 66.3% Comparator).
- Injection-site TEAEs considered severe were reported for 12 subjects (0.6% Revanesse Ultra, 7.4% Comparator). Non-injection site TEAEs were reported

for 22 subjects (13.5%), with headache (3.1%) and arthralgia (1.8%) the most frequently reported.

- Five subjects experienced TESAEs, one of which was considered to be related to the study treatment (possible vascular event left lip and ala with Comparator) and led to treatment interruption. No deaths were reported and no subject discontinued the study due to AEs.
- All injection site TEAEs resolved during the study, most within less than 1 week (85.0% Comparator, 81.5% Revanesse Ultra). Only 2 events with each treatment had a duration greater than 30 days, these included swelling (1 subject, Revanesse Ultra), injection site discomfort (1 subject, Revanesse Ultra), injection site mass (1 subject, Comparator), and 1 subject in comparator group with a serious adverse event of a possible vascular event (left lip and ala).
- Subject skin type did not appear to have an effect on the distribution of AEs. In general, there were no significant differences between the Revanesse Ultra and comparator groups for any Fitzpatrick skin phototype subgroup in terms of injection site TEAEs, except for a higher incidence rate of swelling in FST V subjects (75%, 3/4) observed as compared to overall subjects (47.2%, 77/163).

SYM2014-02 Retreatment Study

- During the retreatment period no TESAEs were reported and no TEAEs led to discontinuation.
- At least one injection-site TEAE was reported for 50.0% and 48.8% of subjects who had 1 or 2 Comparator injections during the treatment period, respectively, and 36.8% and 66.7% of subjects who had 1 or 2 Revanesse Ultra injections during the treatment period.
- The most frequent injection-site TEAEs were injection site hematoma, injection site swelling, and injection site pain.
- Non-injection site TEAEs were reported for 7 of the 71 retreated subjects (9.9%).
- No non-injection site TEAE was reported for more than 1 subject.
- There were no treatment related deaths or serious adverse events.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. The main study results of this randomized, multicenter, double-blind, split-face study demonstrate that Revanesse Ultra is safe and non-inferior to Comparator in subjects undergoing correction of NLFs. In the retreatment study, following retreatment with Revanesse Ultra, subjects showed improvement in the WSRS, pGAI, and iGAI. The study demonstrated an acceptable adverse event profile with retreatment of Revanesse Ultra for men or women at least 22 years of age with NLFs with a moderate or severe

WSRS score at baseline who had previously received 1 or 2 treatments with Comparator or Revanesse Ultra.

Additional factors to be considered in determining probable risks and benefits for the Revanesse Ultra device included

1. Patient Perspectives
   Patient perspectives considered during the review included:
   Despite the frequency of adverse events, patients are willing to accept the probable risk of these harmful events as shown through patient-reported outcomes. The majority of patients (81%, 124/153) treated with Revanesse Ultra in the mITT group responded their patient Global Aesthetic Improvement (pGAI) improved at week 24, with responses of "improved", "much improved" and "very much improved" in 36.6% (56/153), 39.2% (60/153) and 5.2% (8/153), respectively.

   When subjects in the SYM2014-02 study were invited to participate in a Retreatment Study (SYM2014-02 Retreatment), of the 163 subjects in ITT population in the study, 4 subjects discontinued prematurely and were not qualified to continue to Retreatment Study (3 withdrew consent, 1 lost to follow up). Of the remaining 159 subjects, 71 elected to be treated again with Revanesse Ultra on one or both sides of the face; 88 did not continue the retreatment protocol. Most subjects (77.3%, 68/88) did not enter the retreatment protocol because they had reached optimal correction or were satisfied with the results at 6 months. The remaining subjects did not continue for the following reasons:

   - 7 Subjects did not enter the Retreatment Protocol for personal reasons
   - 8 Subjects did not enter the Retreatment Protocol were not satisfied / disliked
   - 1 Subject with Visit 6 Out of Window- not eligible for Retreatment Protocol
   - 4 Subjects did not enter the Retreatment Protocol who experienced adverse events and did not wish to continue

The information related to the safety profile and the risks associated with Revanesse Ultra are included in the product labeling, permitting the patient to make an informed decision related to the use of this product.

In conclusion, given the available information above, the data support the use of Revanesse Ultra for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, and the probable benefits outweigh the probable risks.

D. Overall Conclusions

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.

Revanesse Ultra was determined to be non-inferior to The Comparator as demonstrated by the primary efficacy criterion in the PP population. This was supported by the primary efficacy criterion in the mITT population.

The adverse event profile is sufficiently well understood for patients to make informed decisions about device use. Comparable safety profiles between Revanesse Ultra and the Comparator were demonstrated concerning the nature, severity or frequency of injection site TEAEs. Non-injection site TEAEs were infrequent.

XIV. CDRH DECISION

CDRH issued an approval order on 8/04/2017.

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.