REVANESSE ® VERSA™+ PROFESSIONAL DIRECTIONS FOR USE

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

DESCRIPTION

Revanesse® Versa™+ is manufactured by Prollenium Medical Technologies, and is a biocompatible, sterile, injectable hydrogel based on bioresorbable cross-linked hyaluronic acid 25 mg/mL containing 0.3% lidocaine. The gel is delivered in a pre-filled disposable glass syringe. Each box of Revanesse® Versa™+ contains two 1.0 mL or 1.2 mL syringes of Revanesse® Versa™+ along with two sterile needles.

Revanesse® Versa™+ is injected by qualified, trained doctors 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.

INDICATIONS FOR USE

Revanesse® Versa™+ 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.

CONTRAINDICATIONS

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

Revanesse® Versa™+ 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 anaesthetics of the amide type, such as lidocaine.

Revanesse® Versa™+ 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® Versa™+ 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® Versa™+.

Patients who develop hypertrophic scarring or keloid formation should not be treated with Revanesse® Versa™+.

Patients with evidence of scars at the intended treatment sites should not be treated with Revanesse® Versa™+.

Never use Revanesse® Versa™+ 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® Versa™+.

Patients with acne and / or other inflammatory diseases of the skin should not be treated with Revanesse® Versa™+.

Patients with unattainable expectations.

Patients with multiple severe allergies, allergic history including anaphylaxis, atopy, hyaluronic acid products, Streptococcal proteins or have plans to undergo desensitization therapy during treatment with Revanesse® Versa™+ should not use the product.

Revanesse® Versa™+ 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.

WARNINGS AND PRECAUTIONS

Confirm that the seal on the box has not been broken and sterility has not been compromised.

Confirm that the product has not expired.

Product is for single use only; do not re-use. If re-used, there is a risk of infection or transmission of blood borne diseases.

Revanesse Versa is a prescription product.

Revanesse Versa is a clear colorless gel. If the contents of the syringe are not clear and colorless, or if the glass syringe is compromised, contact Prollenium Medical Technologies immediately at 1-866-353-3017.

Revanesse Versa should not be used in areas that have high vascularity as there is a risk of vascular embolization. There are published reports of dermal filler use in the area of the eye resulting in ocular vessel occlusion (i.e.: blindness).

Avoid the use of Revanesse Versa when there is an active inflammatory process (pimples, hives, rashes, cysts) until the process has resolved.

Injection site reactions (for example: redness, temporary swelling, tenderness or pain) have been observed, and are short term in duration (less than seven days). Any reactions in excess of this anticipated reaction should be reported to your doctor.

All injections / transcutaneous procedures carry the risk of infection. Care must be taken to follow standard precautions for injections.

Dermal fillers have an inherent risk of keloid formation and hyperpigmentation at the injection site. Patients historically prone to these conditions should avoid dermal fillers.

If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.

Warning: Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. 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. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.

Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.

Revanesse Versa should not be mixed with any other products before implantation.

It is imperative that Revanesse Versa patients with adverse inflammatory reactions that persist for more than one week report this immediately to their doctor. Please contact the company Prollenium Medical Technologies immediately at 1-866-353-3017.

POSTMARKET SURVEILLANCE DATA

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. In some instances, patients reporting these adverse events experienced symptoms that were severe, prompting additional medical evaluation. When required, treatment included massage, cold compresses, analgesics, antibiotics, antihistamines, topical steroids, oral corticosteroids, and enzymatic degradation (with hyaluronidase) of the product.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

SYM2014-02 MAIN STUDY – ADVERSE EVENTS

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 Versa 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

PN13582 REV06

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 Versa). 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 Versa 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 Versa 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.

Of the 163 treated subjects, one or more injection-site TEAEs during the study were reported for 114 (69.9%) with Revanesse Versa 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 1. The frequency, severity and duration of TEAEs reported in ≥5% of subjects with either treatment are listed in Tables 2, 3 and 4.

After treated with Revanesse Versa, 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 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 Versa and 7.4% [12/163] with Comparator). These were injection site swelling for 1 subject with Revanesse Versa 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 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 Versa and 85.0% [470/553] with Comparator). Only 2 events with each treatment had a duration greater than 30 days, these included swelling (1 subject, Revanesse Versa, no treatment, resolved with no sequelae), injection site discomfort (1 subject, Revanesse Versa, no treatment, resolved with no sequelae), injection site mass (1 subject, Comparator, 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 Versa 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 1). Non-drug therapy was required for 14.6% (55/378) of the events with Revanesse Versa 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).

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 Versa, 47.2% [77/163] with Comparator), injection site swelling (47.2% [77/163] with Revanesse Versa, 71.2% [116/163] with Comparator), injection site pain (38.0% [62/163] with Revanesse Versa, 66.3% [108/163] with Comparator) and injection site erythema (21.5% [35/163] with Revanesse Versa, 31.9% [52/163] with Comparator) (Table 2). The

Table 1 - Overall Summary of Injection Site Treatment-Emergent Adverse Events (TEAEs) in the Main Study for Intent-to-Treat Population

	Comparator		Test: Revanesse Versa	
	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 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	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)
interrupted/discontinued				
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.

Table 2: SYM2014-02 Main Study – Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	Comparator: (N=163)	Test: Revanesse Versa (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.

PN13582 REV06

four most frequently reported injection-site TEAEs are summarized by severity in Table 3 and by duration in Table 4.

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

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 Versa injections during the treatment period (Table 5). 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.

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 Versa 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

Table 3 - 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 Versa			
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 4 - Duration of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

	Comparator				Test: Revanesse Versa			
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.

Table 5: 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 Versa (N=38)	2x Revanesse Versa (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.

PN13582 REV06

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 [Versa] + (with Lidocaine) versus Revanesse® Ultra [Versa] 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 6 (counts and proportions for the incidences of injection-site TEAEs) and Table 7 (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 Versa 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 Versa injections. For Study SYM 2014-02 Main and SYM 2016-02, each patient received an injection of Revanesse Versa 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 Versa 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.

Revanesse Versa Instructions for Use

There were 97 injections of Revanesse Versa 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 6)

There were 42 injections of Revanesse Versa 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 6)

Table 6: Combined Datasets - Summary of Injection Site Adverse Events for Revanesse Versa 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 (1.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.61%)
Injection Site Discomfort	0 (0%)	0 (0%)	2 (2.41%)	0 (0%)	2 (2.41%)	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 7: 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
Race	I (N=4) n (%)	II (N=91) n (%)	III (N=156) n (%)	IV (N=49) n (%)	I-IV (N=300) n (%)	V (N=19) n (%)	VI (N=15) n (%)	Total V-VI (N=34) n (%)	Overall Total (N=426) 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 shown to have a prevalence of hyperpigmentation, keloid and hypertrophic scarring

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 patients who had swelling from the Combined Datasets are reported in Table 6.

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 injections 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)

Clinical Study

SYM2014-02 Main Study

The study was a randomized, multicenter, double blind, split-face study in subjects seeking correction of their facial wrinkles and creases. Subjects were treated with Revanesse Versa in the NLF on one side of the face and the Comparator in the NLF on the other side of the face. The side of the face for each product was randomly assigned. 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 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 Versa). Revanesse Versa was shown to be non-inferior to the Comparator with a mean difference (Comparator minus Revanesse Versa) 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 pre-specified non-inferiority limit of 0.50. The mean change from baseline in WSRS was 1.02 with Revanesse Versa treatment and 0.91 with the Comparator treatment. Supportive results in the mITT population were similar. The mean difference (Comparator minus Revanesse Versa) 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 Versa and 0.95 with the Comparator (Table10).

SYM2014-02 Retreatment Study

Optional Retreatment at Week 24 / SYM2014-02 Retreatment: At Visit 6/Week 24, a subject could be retreated with Revanesse Versa, 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).

The demographics for the SYM2014-02 Main Study and the SYM2014-02 Retreatment Study are included in Table 8 and Table 9.

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 10.

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 10). Revanesse Versa

Table 8: SYM 2014-02 Main Study - Demographic and Baseline Characteristics for PP Subjects

Parameter	Category	Total (N=125)
Gender	Female	120 (96.0%)
	Male	5 (4.0%)
Ethnicity	Hispanic or Latino	10 (8.0%)
	Not Hispanic or Latino	115 (92.0%)
	Not Willing to Provide	0 (0.0%)
Race	White	118 (94.4%)
	Asian	1 (0.8%)
	Native Hawaiian or Other Pacific-Islander	0 (0.0%)
	Black or African American	5 (4.0%)
	American Indian or Alaska Native	0 (0.0%)
	Other	1 (0.8%)
Age (years)	N	125
	Mean ± SD	54.7 ± 9.67
	Median	55.0
	Min, Max	32, 77
Age Groups	22 to <40	11 (8.8%)
	40 to <64	92 (73.6%)
	64 to <75	20 (16.0%)
	>=75	2 (1.6%)
BMI*	N	125
	Mean ± SD	25.75 ± 5.103
	Median	24.90
	Min, Max	16.5, 42.6
Fitzpatrick Skin Type	I	3 (2.4%)
	II	38 (30.4%)
	III	63 (50.4%)
	IV	13 (10.4%)
	V	3 (2.4%)
	VI	5 (4.0%)

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

Table 9: SYM 2014-02 Retreatment Study - Demographic and Baseline Characteristics for Subjects in the Retreatment Addendum

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	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) / height (in) x 703*

PN13582 REV06

was shown to be non-inferior to Comparator with a mean difference (Comparator minus Revanesse Versa) 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 Versa treatment and 0.91 with Comparator treatment.

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 Versa and 72.8% with Comparator in the PP population, and 81.7% with Revanesse Versa and 75.8% with Comparator in the mITT population (Table 11).

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 Versa and 30.6% with Comparator in the PP population and 44.4% with Revanesse Versa and 30.7% with Comparator in the mITT population (Table 12).

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 Versa and 47.2% with Comparator in the PP population and 60.8% with Revanesse Versa and 49.7% with Comparator in the mITT population (Table 13).

SYM2014-02 Retreatment Study

Following retreatment with Revanesse Versa, subjects showed improvement in the WSRS, pGAI, and iGAI. The study did not demonstrate any safety concerns with retreatment of Revanesse Versa for men or women at least 22 years of age with NFLs with a moderate or severe WSRS score at baseline who had previously received 1 or 2 treatments with the Comparator or Revanesse Versa. 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 14).

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 Versa.

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 Versa.

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 Versa (Table 15).

The percentage of subjects in the optimal correction group with responses of much improved or very much improved on the pGAI

Table 10: 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 Versa	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.

Table 11: 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 Versa
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 12: SYM2014-02 Main Study - Secondary Efficacy: Patient Global Aesthetic Improvement (pGAI) at Visit 6/Week 24

Population	Category	Comparator: Comparator	Test: Revanesse Versa
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.

Table 13: SYM2014-02 Main Study - Secondary Efficacy: Investigator Global Aesthetic Improvement (iGAI) at Visit 6/Week 24

Population	Category	Comparator: Comparator	Test: Revanesse Versa
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.

PN13582 REV06

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 Versa (Table 15).

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 Versa (Table 16).

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 Versa (Table 16).

Table 14: SYM2014-02 Retreatment Study - Change in Wrinkle Severity Rating Scale (WSRS)

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

Treatment Arm: Study Visit	Category	Statistics	Retreatment (N=30)	Optimal Correction (N=41)	Total (N=71)
Test: Revanesse Versa:					
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
	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 7/Week 28	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.

Table 15: SYM2014-02 Retreatment Study - Patient Global Aesthetic Improvement (pGAI) by Visit

Category	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%)

Category	Statistics	Retreatment (N=30)	Optimal Correction (N=41)	Total (N=71)
Test: Revanesse Versa				
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.

Table 16: SYM2014-02 Retreatment Study - Investigator Global Aesthetic Improvement (iGAI) by Visit

Category	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%)

Category	Statistics	Retreatment (N=30)	Optimal Correction (N=41)	Total (N=71)
Test: Revanesse Versa				
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 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.

PN13582 REV06

SYM2016-02 Main Study For Revanesse ® Versa™+ – Adverse Events

Patients were treated between August 24 2016 and June 21 2017 to compare the safety and efficacy profiles of Revanesse ® Versa™+ (with lidocaine) to Revanesse Versa (previously known as Revanesse Ultra) for subjects undergoing correction of nasolabial folds (NLFs). The product without lidocaine – Revanesse Versa, was the subject of a name change request (P160042), and is currently marketed in the United States as Revanesse Versa. This study enrolled 100 patients. There were 4 investigational sites.

The study was randomized, multicenter, double-blind, split-face study in subjects seeking NLF correction. Subjects were treated with Revanesse Versa + in the NLF on one side of the face and Revanesse Versa in the NLF on the other side of the face. Where possible, subjects enrolled in the then-ongoing retreatment phase of study SYM 2014-02 were invited to participate in this study and are referred to as the subset of "rollover subjects." 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 the proportion of responders immediately after injection, where a responder was defined as a subject who had a within-subject difference (Revanesse Versa minus Revanesse Versa +) in VAS pain score of at least 10 mm on a 100-mm scale. Summary statistics were presented for VAS score for each treatment and for the within-subject difference. The proportion of responders was summarized with frequency and percentage with a 95% confidence interval (CI) constructed using a one-sample binomial exact test. If the lower bound of this 95% CI was greater than 50%, Revanesse Versa + (the test product) was to be claimed to be superior to the comparator product (Revanesse Versa). The primary endpoint was summarized by site and a Pearson's Chi-square test was performed to assess consistency of treatment effect across study sites.

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

Other efficacy variables were change in Wrinkle Severity Rating Scale (WSRS) score from baseline, patient Global Aesthetic Improvement (pGAI), and investigator Global Aesthetic Improvement (iGAI) at each scheduled post-baseline visit. Descriptive summaries were provided for each treatment and for within-subject difference.

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

Efficacy: Visual analog scale (VAS) for subject assessment of pain following injection, WSRS, Patient Global Aesthetic Improvement (pGAI), and Investigator Global Aesthetic Improvement (iGAI)

Safety: Treatment-emergent adverse events (TEAEs)

Table 1 Safety - Overall Summary of Injection Site Treatment-Emergent Adverse Events (TEAEs) for Intent-to-Treat Population

	Revanesse Versa		Revanesse® Versa™+	
	Subjects[1] (N =100)	Events[2] (N = 112)	Subjects[1] (N = 100)	Events[2] (N = 102)
Overall	52 (52.0%)	112 (100%)	53 (53.0%)	102 (100%)
Duration				
Less than 1 week	42 (42.0%)	82 (73.2%)	45 (45.0%)	67 (65.7%)
Between 1 week and month (30 days)	21 (21.0%)	30 (26.8%)	17 (17.0%)	34 (33.3%)
More than 1 month (30 days)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)[3]
Severity				
Mild	40 (40.0%)	87 (77.7%)	46 (46.0%)	87 (85.3%)
Moderate	12 (12.0%)	25 (22.3%)	6 (6.0%)	14 (13.7%)
Severe	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)[4]
Causality				
Treatment-related*	52 (52.0%)	112 (100%)	53 (53.0%)	102 (100%)
Not treatment-related	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Outcome				
Resolved	52 (52.0%)	112 (100%)	53 (53.0%)	102 (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%)
Lost to Follow-up/Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment Required (Action Taken)				
None	48 (48.0%)	92 (82.1%)	50 (50.0%)	86 (84.3%)
Study treatment interrupted/ discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-drug therapy	10 (10.0%)	17 (15.2%)	7 (7.0%)	12 (11.8%)
New OTC or Rx drug added	3 (3.0%)	4 (3.6%)	3 (3.0%)	5 (4.9%)
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.*
3. *The TEAE with duration of more than 30 days was injection site mass.*
4. *The severe TEAE was injection site bruising.*

**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.

Other: Investigator Ease of Use Assessment

Subjects meeting the inclusion and exclusion criteria were randomized to treatment with Revanesse® Versa™+ in the NLF on one side of the face and Revanesse Versa in the NLF on the other side of the face.

At each visit, investigator and subject evaluations of the treated areas were performed and recorded. Visits occurred at:

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

Visit 2/Week 2 (± 2 days) interim visit, touch-up if the Investigator Global Aesthetic Improvement (iGAI) score was 3 or 4

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

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

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

Every subject received Revanesse Versa + on one side of the face and Revanesse Versa on the other side of the face.

Of the 100 treated subjects, 102 injection site TEAEs were reported by 53 subjects (53.0%) with Revanesse Versa + treatment and 112 TEAEs were reported by 52 subjects (52.0%) with Revanesse Versa treatment. These TEAEs were reported by subjects throughout the 6 months study. The most frequently reported injection site TEAEs were bruising (32.0% Revanesse Versa +, 31.0% Revanesse Versa), swelling (21.0% Revanesse Versa +, 17.0% Revanesse Versa), and pain (17.0% Revanesse Versa +, 21.0% Revanesse Versa). One injection site TEAE was considered severe, injection site bruising with Revanesse Versa + (not a rollover subject). Non-injection site (systemic) TEAEs were reported for 5 subjects (5.0%), and no systemic TEAE was reported for more than 1 subject. One subject (not a rollover subject) experienced an SAE of worsening right knee

PN13582 REV06

Table 2 Safety- Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	All TEAEs		Reported by Subject		Reported by Investigator	
	Revanesse Versa (N=100)	Revanesse Versa+ (N=100)	Revanesse Versa (N=100)	Revanesse Versa+ (N=100)	Revanesse Versa (N=100)	Revanesse Versa+ (N=100)
Subjects with at Least One Injection Site TEAE	52 (52.0%)	53 (53.0%)	52 (52.0%)	53 (53.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	52 (52.0%)	53 (53.0%)	52 (52.0%)	53 (53.0%)	0 (0.0%)	0 (0.0%)
APPLICATION SITE PAIN	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE BRUISING	31 (31.0%)	32 (32.0%)	31 (31.0%)	32 (32.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE ERYTHEMA	12 (12.0%)	15 (15.0%)	12 (12.0%)	15 (15.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE MASS	2 (2.0%)	1 (1.0%)	2 (2.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE PAIN	21 (21.0%)	17 (17.0%)	21 (21.0%)	17 (17.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE PRURITUS	7 (7.0%)	3 (3.0%)	7 (7.0%)	3 (3.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE SWELLING	17 (17.0%)	21 (21.0%)	17 (17.0%)	21 (21.0%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
HEADACHE	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version 18.1) 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.

Table 3 Safety - Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population – Subset of Rollover Subjects

System Organ Class Preferred Term	All TEAEs		Reported by Subject		Reported by Investigator	
	Revanesse Versa (N=17)	Revanesse Versa+ (N=17)	Revanesse Versa (N=17)	Revanesse Versa+ (N=17)	Revanesse Versa (N=17)	Revanesse Versa+ (N=17)
Subjects with at Least One Injection Site TEAE	10 (58.8%)	9 (52.9%)	10 (58.8%)	9 (52.9%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (58.8%)	9 (52.9%)	10 (58.8%)	9 (52.9%)	0 (0.0%)	0 (0.0%)
INJECTION SITE BRUISING	4 (23.5%)	5 (29.4%)	4 (23.5%)	5 (29.4%)	0 (0.0%)	0 (0.0%)
INJECTION SITE ERYTHEMA	4 (23.5%)	4 (23.5%)	4 (23.5%)	4 (23.5%)	0 (0.0%)	0 (0.0%)
INJECTION SITE PAIN	8 (47.1%)	4 (23.5%)	8 (47.1%)	4 (23.5%)	0 (0.0%)	0 (0.0%)
INJECTION SITE PRURITUS	1 (5.9%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE SWELLING	6 (35.3%)	7 (41.2%)	6 (35.3%)	7 (41.2%)	0 (0.0%)	0 (0.0%)

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version 18.1) 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.

pain (arthralgia), which was considered unlikely related to study product. No deaths were reported and no subject discontinued the study due to AEs.

Among the 17 treated subjects in the subset of rollover subjects, 23 injection site TEAEs were reported by 9 subjects (52.9%) with Revanesse Versa + treatment and 31 TEAEs were reported by 10 subjects (58.8%) with Revanesse Versa treatment. The most frequently reported injection site TEAEs were bruising (29.4% Revanesse Versa +, 23.5% Revanesse Versa), swelling (41.2% Revanesse Versa +, 35.3% Revanesse Versa), and pain (23.5% Revanesse Versa +, 47.1% Revanesse Versa).

The frequency, severity and duration of TEAEs reported in subjects with either treatment are listed in Tables 1, 2 and 3.

Clinical Study SYM2016-02

The study was randomized, multicenter, double-blind, split-face study in subjects seeking NLF correction. Subjects were treated

Table 4 Safety -Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

System Organ Class Preferred Term	Treatment Group	FST I (N=1)	FST II (N=14)	FST III (N=43)	FST IV (N=27)	Pooled FST I-IV (N=85)	FST V (N=12)	FST VI (N=3)	Pooled FST V-VI (N=15)
Subjects with at Least One Injection Site TEAE	R. Versa	1 (100%)	10 (71.4%)	20 (46.5%)	16 (59.3%)	47 (55.3%)	5 (41.7%)	-	5 (33.3%)
	R. Versa+	1 (100%)	10 (71.4%)	23 (53.5%)	14 (51.9%)	48 (56.5%)	4 (33.3%)	1 (33.3%)	5 (33.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	R. Versa	1 (100%)	10 (71.4%)	20 (46.5%)	16 (59.3%)	47 (55.3%)	5 (41.7%)	-	5 (33.3%)
	R. Versa+	1 (100%)	10 (71.4%)	23 (53.5%)	14 (51.9%)	48 (56.5%)	4 (33.3%)	1 (33.3%)	5 (33.3%)
APPLICATION SITE PAIN	R. Versa	-	-	-	1 (3.7%)	1 (1.2%)	-	-	-
	R. Versa+	-	-	-	1 (3.7%)	1 (1.2%)	-	-	-
INJECTION SITE BRUISING	R. Versa	-	5 (35.7%)	13 (30.2%)	10 (37.0%)	28 (32.9%)	3 (25.0%)	-	3 (20.0%)
	R. Versa+	1 (100%)	9 (64.3%)	12 (27.9%)	5 (18.5%)	27 (31.8%)	4 (33.3%)	1 (33.3%)	5 (33.3%)
INJECTION SITE ERYTHEMA	R. Versa	-	1 (7.1%)	5 (11.6%)	4 (14.8%)	10 (11.8%)	2 (16.7%)	-	2 (13.3%)
	R. Versa+	-	2 (14.3%)	7 (16.3%)	5 (18.5%)	14 (16.5%)	1 (8.3%)	-	1 (6.7%)
INJECTION SITE MASS	R. Versa	-	2 (14.3%)	-	-	2 (2.4%)	-	-	-
	R. Versa+	-	1 (7.1%)	-	-	1 (1.2%)	-	-	-
INJECTION SITE PAIN	R. Versa	-	6 (42.9%)	6 (14.0%)	6 (22.2%)	18 (21.2%)	3 (25.0%)	-	3 (20.0%)
	R. Versa+	-	5 (35.7%)	6 (14.0%)	4 (14.8%)	15 (17.6%)	2 (16.7%)	-	2 (13.3%)
INJECTION SITE PRURITUS	R. Versa	1 (100%)	-	3 (7.0%)	3 (11.1%)	7 (8.2%)	-	-	-
	R. Versa+	1 (100%)	-	-	2 (7.4%)	3 (3.5%)	-	-	-
INJECTION SITE SWELLING	R. Versa	-	3 (21.4%)	8 (18.6%)	3 (11.1%)	14 (16.5%)	3 (25.0%)	-	3 (20.0%)
	R. Versa+	-	4 (28.6%)	10 (23.3%)	4 (14.8%)	18 (21.2%)	3 (25.0%)	-	3 (20.0%)
NERVOUS SYSTEM DISORDERS	R. Versa	-	1 (7.1%)	-	-	1 (1.2%)	-	-	-
	R. Versa+	-	1 (7.1%)	-	-	1 (1.2%)	-	-	-
HEADACHE	R. Versa	-	1 (7.1%)	-	-	1 (1.2%)	-	-	-
	R. Versa+	-	1 (7.1%)	-	-	1 (1.2%)	-	-	-

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version18.1) 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.

with Revanesse Versa + in the NLF on one side of the face and Revanesse Versa in the NLF on the other side of the face. Where possible, subjects enrolled in the then-ongoing retreatment phase of study SYM 2014-02 were invited to participate in this study and are referred to as the subset of "rollover subjects." 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 the proportion of responders immediately after injection, where a responder was defined as a subject who had a within-subject difference (Revanesse Versa minus Revanesse Versa +) in VAS pain score of at least 10 mm on a 100-mm scale. Summary statistics were presented for VAS score for each treatment and for the within-subject difference. The proportion of responders was summarized with frequency and percentage with a 95% confidence interval (CI) constructed using a one-sample binomial exact test. If the lower bound of this 95% CI was greater than 50%, Revanesse Versa + (the test product) was to be claimed to be superior to the comparator product (Revanesse Versa). The primary endpoint was summarized by site and a Pearson's Chi-square test was performed to assess consistency of treatment effect across study sites.

In the modified intent-to-treat (mITT[1]) population for all subjects, the mean VAS score immediately after injection was 26.2 with Revanesse Versa + and 39.4 with Revanesse Versa, and the mean within-subject difference (Revanesse Versa – Revanesse Versa +) was 13.17. The proportion of responders (95% CI) was 54.7% (44.2% to 65.0%) (Table 2).

For the 17 rollover subjects, the mean VAS score immediately after injection in the identical mITT and per-protocol (PP[2]) populations was 30.5 with Revanesse Versa + and 53.9 with Revanesse Versa, and the mean within-subject difference was 23.42. The proportion of responders (95% CI) was 58.3% (27.7% to 84.8%), which did not meet the superiority criterion (Table 2a).

All effectiveness analyses were performed for both the mITT and PP populations. For the primary endpoint, the results from mITT were considered definitive and those from PP supportive. The demographics for the SYM2016-02 are included in Table 8 and Table 9.

1. mITT: All randomized subjects who met the inclusion/exclusion criteria, were randomized, received both study products, and had VAS pain score immediately post injection from both sides of the face.

2. PP: All randomized subjects who met all inclusion/exclusion criteria, received both study products, completed Visit 5/Week 24 within the specified window, had data on pain score from both sides of the face immediately post injection and at 15, 30, 45, and 60 minutes post injection at Visit 1/Day1; had data on pain score at 2 weeks post injection (prior to touch-up if required); and had no significant protocol violations that would affect the treatment evaluation.

Effectiveness Results

All effectiveness analyses were performed for both the mITT population (95 subjects) and PP population (75 subjects). The primary endpoint was the proportion of responders immediately after injection. The secondary endpoints were the proportion of responders at 15, 30, 45, and 60 minutes post injection and at 2 weeks post injection (prior to touch-up). The effectiveness results from the mITT population were considered definitive and those from the PP population were considered supportive. Key effectiveness outcomes are presented in Table 2.

Primary Endpoints

The analysis of effectiveness (SYM2016-02) was based on the proportion of responders immediately after injection, where a responder was defined as a subject who had a within-subject difference (Revanesse Versa minus Revanesse Versa +) in VAS pain score of at least 10 mm on a 100-mm scale (Tables 2). In the mITT population for all subjects, the mean VAS score immediately after

PN13582 REV06

injection was 26.2 with Revanesse Versa + and 39.4 with Revanesse Versa, and the mean within-subject difference (Revanesse Versa – Revanesse Versa +) was 13.17. The proportion of responders (95% CI) was 54.7% (44.2% to 65.0%). The proportion of responders did not meet the superiority criteria. However, there was a clinically relevant difference in pain reduction between Revanesse® Versa™+ and Revanesse Versa.

Secondary Endpoints

The secondary efficacy endpoints were the proportion of responders at 15, 30, 45, and 60 minutes post injection and at 2 weeks post injection (prior to touch-up if required). Upon the significance of the primary efficacy outcome, secondary endpoints were analyzed using a hierarchical approach. If success was achieved at 15 minutes, 30 minutes was evaluated; if success was achieved at 30 minutes, 45 minutes was evaluated; if success was achieved at 45 minutes, 60 minutes was evaluated; and if success was achieved at 60 minutes, 2 weeks post-injection was evaluated. The mean VAS scores decreased over time for both treatments. After 30 minutes, most subjects exhibited a VAS pain score < 10 for both sides of the face, so fewer subjects over time had a VAS score large enough to yield a 10 mm difference to meet the responder definition.

For the secondary endpoints among all mITT subjects, the mean VAS score was numerically lower with Revanesse Versa + at 15, 30, 45, and 60 minutes post injection at Visit 1/Day 1, and the proportion of responders at those time points was 31.6%, 16.8%, 6.3%, and 3.2%, respectively. The proportion of responders at 2 weeks post injection was 0%.

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

The differences between the treatments for the exploratory endpoints, WSRS, pGAI, and iGAI, were small for both the mITT and PP populations.

Table 1 Demographic and Baseline Characteristics (ITT Population)

Parameter	Category	Total (N = 100)	Rollover Subset (N = 17)
Gender	Female	93 (93.0%)	17 (100.0%)
	Male	7 (7.0%)	0 (0.0%)
Ethnicity	Hispanic or Latino	38 (38.0%)	1 (5.9%)
	Not Hispanic or Latino	62 (62.0%)	16 (94.1%)
	Not Willing to Provide	0 (0.0%)	0 (0.0%)
Race	White	89 (89.0%)	16 (94.1%)
	Asian	0 (0.0%)	0 (0.0%)
	Native Hawaiian or Other Pacific-Islander	0 (0.0%)	0 (0.0%)
	Black or African American	10 (10.0%)	1 (5.9%)
	American Indian or Alaska Native	1 (1.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
Age (years)	N	100	17
	Mean ± SD	56.3 ± 11.44	63.4 ± 6.21
	Median	58.0	62.0
	Min, Max	30, 83	53, 78
Age Groups	18 to < 40	8 (8.0%)	0 (0.0%)
	40 to < 64	65 (65.0%)	11 (64.7%)
	64 to < 75	21 (21.0%)	5 (29.4%)
	≥ 75	6 (6.0%)	1 (5.9%)
BMI*	N	100	17
	Mean ± SD	24.83 ± 3.334	24.31 ± 3.306
	Median	24.70	22.80
	Min, Max	18.9, 33.1	19.8, 31.1
Fitzpatrick Skin Type Classification	I	1 (1.0%)	0 (0.0%)
	II	14 (14.0%)	3 (17.6%)
	III	43 (43.0%)	12 (70.6%)
	IV	27 (27.0%)	1 (5.9%)
	V	12 (12.0%)	1 (5.9%)
	VI	3 (3.0%)	0 (0.0%)

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

Table 2 Primary Efficacy: Proportion of Responders Immediately After Injection at Visit 1/Day 1

Population	Statistics	Revanesse Versa	Revanesse Versa +	Difference: Versa minus Versa+
Modified Intent-to-Treat				
VAS Score	N	95	95	95
	Mean ± SD	39.4 ± 25.45	26.2 ± 24.51	13.17 ± 23.983
	Median	35.0	20.0	13.00
	Min, Max	0, 98	0, 94	-49.0, 92.0
Proportion of Responders	n (%)			52 (54.7%)
	95% Confidence Interval			(44.2%, 65.0%)[1]
	P-value for Interaction			0.295[2]
Per-Protocol (PP)				
VAS Score	N	75	75	75
	Mean ± SD	40.3 ± 25.95	26.0 ± 23.71	14.27 ± 23.126
	Median	38.0	21.0	14.00
	Min, Max	0, 98	0, 93	-42.0, 92.0
Proportion of Responders	n (%)			40 (53.3%)
	95% Confidence Interval			(41.4%, 64.9%)[1]
	P-value for Interaction			0.636[2]

CI = confidence interval; SD = standard deviation

Note: The results from mITT are considered definitive and those from PP supportive.

Responder (to Revanesse Versa +) is defined as a subject who had a within-subject difference (Revanesse Versa minus Revanesse Versa +) in VAS pain score of at least 10 mm on a 100-mm scale.

1 The 95% confidence intervals were constructed using a one-sample binomial exact text.

2 P-value for testing treatment effect by site interaction is from Fisher's exact test.

PN13582 REV06

Table 2a Primary Efficacy: Proportion of Responders Immediately After Injection at Visit 1/Day 1 for Subset of Rollover Subjects

Population	Statistics	Revanesse Versa	Revanesse Versa +	Difference: Versa minus Versa+
Modified Intent-to-Treat				
VAS Score	N	12	12	12
	Mean ± SD	53.9 ± 30.52	30.5 ± 30.20	23.42 ± 33.563
	Median	63.0	22.0	18.50
	Min, Max	9, 98	0, 93	-42.0, 92.0
Proportion of Responders	n (%)			7 (58.3%)
	95% Confidence Interval			(27.7%, 84.8%)[1]
	P-value for Interaction			1.000[2]

Population	Statistics	Revanesse Versa	Revanesse Versa +	Difference: Versa minus Versa+
Per-Protocol (PP)				
VAS Score	N	12	12	12
	Mean ± SD	53.9 ± 30.52	30.5 ± 30.20	23.42 ± 33.563
	Median	63.0	22.0	18.50
	Min, Max	9, 98	0, 93	-42.0, 92.0
Proportion of Responders	n (%)			7 (58.3%)
	95% Confidence Interval			(27.7%, 84.8%)[1]
	P-value for Interaction			1.000[2]

CI = confidence interval; SD = standard deviation Note: The results from mITT are considered definitive and those from PP supportive. Responder (to Revanesse Versa +) is defined as a subject who had within-subject difference (Revanesse Versa minus Revanesse Versa +) in VAS pain score of at least 10 mm on a 100-mm scale.

1 The 95% confidence intervals were constructed using a one-sample binomial exact text.

2 P-value for testing treatment effect by site interaction is from Fisher's exact test.

Table 3 Other Efficacy: Wrinkle Severity Rating Scale (WSRS) by Visit for Per Protocol Population

Study Visit	Category	Revanesse Versa	Revanesse Versa +	Difference: Versa minus Versa+
Visit 1/Day 1	N	75	75	
	1 = Absent	0 (0.0%)	0 (0.0%)	
	2 = Mild	0 (0.0%)	0 (0.0%)	
	3 = Moderate	40 (53.3%)	40 (53.3%)	
	4 = Severe	35 (46.7%)	35 (46.7%)	
	5 = Extreme	0 (0.0%)	0 (0.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			0.00 ± 0.000
Visit 2/Week 2	N	75	75	
	1 = Absent	18 (24.0%)	16 (21.3%)	
	2 = Mild	27 (36.0%)	28 (37.3%)	
	3 = Moderate	24 (32.0%)	26 (34.7%)	
	4 = Severe	6 (8.0%)	5 (6.7%)	
	5 = Extreme	0 (0.0%)	0 (0.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			-0.03 ± 0.434
Visit 3/Week 4	N	75	75	
	1 = Absent	20 (26.7%)	22 (29.3%)	
	2 = Mild	50 (66.7%)	48 (64.0%)	
	3 = Moderate	5 (6.7%)	5 (6.7%)	
	4 = Severe	0 (0.0%)	0 (0.0%)	
	5 = Extreme	0 (0.0%)	0 (0.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			0.03 ± 0.283
Visit 4/Week 12	N	75	75	
	1 = Absent	20 (26.7%)	20 (26.7%)	
	2 = Mild	46 (61.3%)	46 (61.3%)	
	3 = Moderate	9 (12.0%)	9 (12.0%)	
	4 = Severe	0 (0.0%)	0 (0.0%)	
	5 = Extreme	0 (0.0%)	0 (0.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			0.00 ± 0.232
Visit 5/Week 24	N	75	75	
	1 = Absent	16 (21.3%)	14 (18.7%)	
	2 = Mild	45 (60.0%)	47 (62.7%)	
	3 = Moderate	10 (13.3%)	11 (14.7%)	
	4 = Severe	4 (5.3%)	3 (4.0%)	
	5 = Extreme	0 (0.0%)	0 (0.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			-0.01 ± 0.260

Missing values are not imputed for the summary. A positive mean value in difference is in favor of Revanesse® Versa™+.

Shelf Life & Storage

Expiry is indicated on each individual package. Store between 2°-25° C, and protect from direct sun light and freezing. Do not use the product beyond the stated expiration date. Confirm that the seal on the box has not been broken and sterility has not been compromised. Confirm that the product has not expired. Product is for single use only; do not re-use. If re-used, there is a risk of infection or transmission of blood borne diseases.

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

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

MANUFACTURER

Prollenium Medical Technologies, Inc.
138 Industrial Parkway North, Aurora, ON
L4G 4C3, Canada
Phone: 1-866-353-3015

PN13582 REV06

Table 4 Other Efficacy: Patient Global Aesthetic Improvement (pGAI) by Visit for Per Protocol Population

Study Visit	Category	Revanesse Versa	Revanesse Versa +	Difference: Versa minus Versa+
Visit 2/Week 2	N	75	75	
	1 = Worse	0 (0.0%)	0 (0.0%)	
	2 = No Change	4 (5.3%)	4 (5.3%)	
	3 = Improved	23 (30.7%)	25 (33.3%)	
	4 = Much Improved	28 (37.3%)	25 (33.3%)	
	5 = Very Much Improved	20 (26.7%)	21 (28.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			0.01 ± 0.348
Visit 3/Week 4	N	75	75	
	1 = Worse	0 (0.0%)	0 (0.0%)	
	2 = No Change	1 (1.3%)	1 (1.3%)	
	3 = Improved	16 (21.3%)	12 (16.0%)	
	4 = Much Improved	27 (36.0%)	29 (38.7%)	
	5 = Very Much Improved	31 (41.3%)	33 (44.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			-0.08 ± 0.395
Visit 4/Week 12	N	75	75	
	1 = Worse	0 (0.0%)	0 (0.0%)	
	2 = No Change	3 (4.0%)	3 (4.0%)	
	3 = Improved	24 (32.0%)	23 (30.7%)	
	4 = Much Improved	24 (32.0%)	24 (32.0%)	
	5 = Very Much Improved	24 (32.0%)	25 (33.3%)	
	N of subjects with data from both sides			75
	Mean ± SD			-0.03 ± 0.328
Visit 5/Week 24	N	75	75	
	1 = Worse	0 (0.0%)	0 (0.0%)	
	2 = No Change	6 (8.0%)	6 (8.0%)	
	3 = Improved	20 (26.7%)	20 (26.7%)	
	4 = Much Improved	25 (33.3%)	28 (37.3%)	
	5 = Very Much Improved	24 (32.0%)	21 (28.0%)	
	N of subjects with data from both sides			75
	Mean ± SD			0.04 ± 0.448

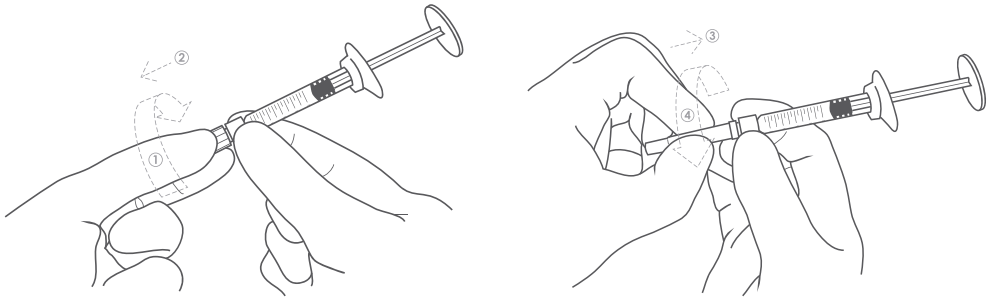
Missing values are not imputed for the summary. A negative mean value in difference is in favor of Revanesse® Versa™+.

Table 5 Other Efficacy: Investigator Global Aesthetic Improvement (iGAI) by Visit for Per Protocol Population

Study Visit	Category	Revanesse Versa	Revanesse Versa +	Difference: Versa minus Versa+
Visit 2/Week 2	N	75	75	
	1 = Worse	1 (1.3%)	1 (1.3%)	
	2 = No Change	2 (2.7%)	2 (2.7%)	
	3 = Improved	26 (34.7%)	29 (38.7%)	
	4 = Much Improved	7 (9.3%)	3 (4.0%)	
	5 = Very Much Improved	39 (52.0%)	40 (53.3%)	
	N of subjects with data from both sides			75
	Mean ± SD			0.03 ± 0.545
Visit 3/Week 4	N	75	75	
	1 = Worse	0 (0.0%)	0 (0.0%)	
	2 = No Change	0 (0.0%)	0 (0.0%)	
	3 = Improved	8 (10.7%)	7 (9.3%)	
	4 = Much Improved	19 (25.3%)	19 (25.3%)	
	5 = Very Much Improved	48 (64.0%)	49 (65.3%)	
	N of subjects with data from both sides			75
	Mean ± SD			-0.03 ± 0.162
Visit 4/Week 12	N	75	75	
	1 = Worse	0 (0.0%)	0 (0.0%)	
	2 = No Change	0 (0.0%)	0 (0.0%)	
	3 = Improved	11 (14.7%)	11 (14.7%)	
	4 = Much Improved	27 (36.0%)	26 (34.7%)	
	5 = Very Much Improved	37 (49.3%)	38 (50.7%)	
	N of subjects with data from both sides			75
	Mean ± SD			-0.01 ± 0.201
Visit 5/Week 24	N	75	75	
	1 = Worse	0 (0.0%)	0 (0.0%)	
	2 = No Change	5 (6.7%)	5 (6.7%)	
	3 = Improved	16 (21.3%)	18 (24.0%)	
	4 = Much Improved	25 (33.3%)	23 (30.7%)	
	5 = Very Much Improved	29 (38.7%)	29 (38.7%)	
	N of subjects with data from both sides			75
	Mean ± SD			0.03 ± 0.162

Missing values are not imputed for the summary. A negative mean value in difference is in favor of Revanesse® Versa™+.

ASSEMBLY OF NEEDLE TO SYRINGE:



Patents 8,450,475; 8,357,795; 8,822,676; 9,089,519; 9,238,013; 9,358,322; 10,391,202; 10,485,896

PN13582 REV06