Restylane® Contour

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1 DEVICE DESCRIPTION

Restylane® Contour is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless, flexible and homogeneous soft gel composed of hyaluronic acid of bacterial origin, with a high lifting capacity. *Restylane Contour* is crosslinked with BDDE (1,4-butanediol diglycidylether). The product has a sodium hyaluronate concentration of 20 mg/mL in phosphate buffered saline at pH 7 and contains 3 mg/mL lidocaine hydrochloride.

2 INTENDED USE/INDICATIONS

Restylane Contour is indicated for use in cheek augmentation and correction of midface contour deficiencies in patients over the age of 21.

3 CONTRAINDICATIONS

- *Restylane Contour* is contraindicated for patients with severe allergies such as manifested by a history of anaphylaxis or history of multiple severe allergies.
- *Restylane Contour* may contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- *Restylane Contour* contains lidocaine and is contraindicated for patients with a history of allergies to such material or other amide type anesthetics.

4 WARNINGS

- Introduction of *Restylane Contour* 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 professional specialist should an intravascular injection occur (see Health Care Professional Instructions).
- *Restylane Contour* must not be implanted into blood vessels and should not be used in vascular rich areas. Localized superficial necrosis and scarring may occur after injection in or near vessels. It is thought to result from the injury, obstruction, or compromise of blood vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area.

- Defer use of *Restylane Contour* at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the process has been controlled.

For additional information please see Post Market Surveillance in Adverse Event section.

5 PRECAUTIONS

- *Restylane Contour* is packaged for single-patient use. Do not resterilize. Do not use if package is open or damaged.
- Health care professionals 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.
- In order to minimize the risks of potential complications, this product should only be used by health care professionals who have appropriate training, experience and knowledgeable about the anatomy at and around the site of injection in order to minimize the risks of potential complications (perforation or compression of vessels, nerves and other vulnerable structures).
- The recommended maximum injected volume per subject and treatment session is 6 mL.
- The safety and effectiveness of cannula injection of *Restylane Contour* have only been clinically evaluated in one brand of blunt tip cannulas (TSK STERiGLIDE™) that are 25-27 G and 1.5 or 2 inches in length.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- *Restylane Contour* is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- The safety of *Restylane Contour* for use during pregnancy, in breastfeeding females or in patients under 22 years has not been established.
- Injection of *Restylane Contour* in patients with pre-existing tendency towards edema formation may be associated with prominent discoloration and excessive swelling due to fluid build-up.
- Injection of *Restylane Contour* too superficially or in facial areas with limited soft tissue support, thin skin or limited soft tissue cover, may result in contour irregularities and palpable lumps.
- *Restylane Contour* should be used with caution in patients on immunosuppressive therapy.
- This product should be used with caution in patients with a tendency to form hypertrophic scars or any other healing disorders.
- *Restylane Contour* should be used with caution in patients with bleeding disorders.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants) may, as with any injection, experience increased bruising or bleeding at treatment sites.
- Avoid injecting *Restylane Contour* into areas in close proximity to permanent implants, as this could potentially aggravate latent adverse events or interfere with the aesthetic outcome of the treatment. Limited data is available on injecting *Restylane Contour* into an area where a non-permanent implant other than hyaluronic acid has been placed.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures at least until any initial swelling and redness has resolved.
- The safety of Restylane Contour with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in

controlled clinical trials. If any procedure based on active dermal response is considered after treatment with *Restylane Contour*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane Contour* is administered before the skin has healed completely after such a procedure.

- Injections of *Restylane Contour* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Post inflammatory pigmentation changes may occur after dermal filler injections in people with dark skin (Fitzpatrick Type IV-VI).
- After use, treatment syringes and needles/cannulas may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.
- Individual variation and treatment area may affect the bio-degradation of *Restylane Contour* and product might be detected in the tissue even after the clinical effect has disappeared.
- *Restylane Contour* injectable gel is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe.
- *Restylane Contour* should not be mixed with other products before implantation of the device.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer lock and needle hub connection.
- Lidocaine should be used with caution in subjects receiving agents structurally related to amide-type anesthetics, e.g. certain anti-arrhythmics, since the systemic toxic effects can be additive.
- Lidocaine should be used with caution in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function or severe renal dysfunction.

6 ADVERSE EVENTS

A. US Pivotal Study of *Restylane Contour*

Study Design

Subjects were treated between October 18, 2018 and November 25, 2019. The database for this PMA supplement reflects data collected through May 22, 2020 and included 270 subjects at 17 investigational sites in the US.

The pivotal study was a randomized, evaluator-blinded, parallel group-, comparator-controlled, multi-center study to evaluate the safety and effectiveness of treatment with *Restylane Contour* for cheek augmentation and the correction of midface contour deficiencies, versus an approved label comparator product with similar indications for use (*Juvéderm Voluma XC*). There were two treatment groups:

- **Group A** subjects were randomized to either *Restylane Contour* or Control (*Juvéderm Voluma XC*) in a 2:1 ratio (*Restylane Contour*:Control), and treated using a needle.

- **Group B** subjects received *Restylane Contour* only, using a split face design, wherein one cheek was randomized to receive treatment using a small blunt tip cannula and the other cheek was randomized to receive treatment using the co-packed needle.

Sites exclusively enrolled subjects for either Group A (210 subjects) or Group B (60 subjects).

Clinical Inclusion and Exclusion Criteria

Enrollment in the clinical study was limited to subjects who met the following key inclusion criteria:

- Males and non-pregnant, non-breastfeeding females, age 22 or older
- Grade of 2 (mild), 3 (moderate) or 4 (severe) on each side of the midface on the Medicis Midface Volume Scale (MMVS) as assessed by the Blinded Evaluator
- Written informed consent

  Subjects were not permitted to be enrolled in the clinical study if they met any of the following key exclusion criteria:

- Known/previous allergy or hypersensitivity to any injectable HA gel or to gram-positive bacterial proteins
- History of allergy or hypersensitivity to lidocaine or other amide-type anesthetics, or topical anesthetics or nerve blocking agents
- Previous use of any permanent (non-biodegradable) or semi-permanent (e.g., calcium hydroxylapatite or Poly-L-Lactic acid) facial tissue augmentation therapy, lifting threads, permanent implants or autologous fat
- Previous use of any HA based or collagen based biodegradable facial tissue augmentation therapy within 12 months prior to the baseline visit
- Abnormal score for midface function, firmness, symmetry or monofilament/cotton wisp tests
- History of other facial treatment/procedure in the previous 6 months that, in the Treating Investigator ’s opinion, would interfere with the study injections and/or study assessments or would expose the subject to undue risk by study participation.

Follow-up Schedule

In the pivotal study, qualified subjects in Group A were randomized to receive treatment with *Restylane Contour* or Control, or assigned to *Restylane Contour* treatment in Group B, for augmentation of the cheeks, on Day 1 of the study.

Subjects had scheduled visits at 2 and 4 weeks after treatment at baseline. Optional touch-up treatment was offered at Week 4 if optional correction was not achieved.

If a touch-up was performed, a second 2-week and 4-week follow-up visit was scheduled.

Subjects had in-clinic follow up visits to evaluate safety and effectiveness at 2, 4, 12, 24, 36, and 48 weeks after the last injection. At the 48-week visit after all study procedures were completed, all subjects, regardless of randomization assignment at baseline, were offered optional treatment if optimal aesthetic improvement was not maintained. If optional treatment was performed, 2, 4, and 12-week follow up visits were scheduled.

Subjects were contacted by telephone 72 hours after each treatment (i.e. initial, touch up, optional re-treatment at Week 48, as applicable) for safety follow-up.

The method of injection was at the discretion of the Treating Investigator. A sufficient amount of product was injected to achieve optimal correction of the midface, in the opinion of the Treating Investigator and subject. Optimal aesthetic result was defined as at least 1 MMVS point improvement from baseline and the best correction that could be achieved as agreed by the Treating Investigator and the subject. The maximum recommended injection volume per subject at the initial, touch-up, and re-treatment visits was 6.0 mL, for a maximum total volume of product injected of 18.0 mL.

Clinical Endpoints

With regards to safety, *Restylane Contour* in the cheek area was evaluated by: a) the incidence, intensity, and duration of predefined, expected post-treatment injection site reactions using a subject diary for 28 days after each treatment b) the incidence, intensity, duration, and onset of related AEs collected during the study, and c) cheek safety assessments as evaluated by a qualified study staff member at each visit. Vision function tests were performed before and after initial treatment and as applicable for the optional touch-up (Week 4) and re-treatment (Week 48). The vision function tests included the Snellen Visual Acuity test to assess visual acuity for distance vision; Extraocular Muscle Function test to examine the function of the eye muscle; and Confrontation Visual Field test to assess the subject's peripheral vision.

With regards to effectiveness, the primary analysis for cheek augmentation was evaluated based on demonstration of non-inferiority of *Restylane Contour* versus Control in cheek augmentation by comparing change from baseline in the Blinded Evaluator live assessment of midface fullness at 12 weeks after the last injection, using the Medicis Midface Volume Scale (MMVS) responder rates[1] (Table 1). Responders were defined as having at least 1 point improvement from baseline (as assessed by the blinded evaluator) at 12 weeks after last injection.

Table 1 Medicis Midface Volume Scale (MMVS)

Score	Description
1	Fairly full midface
2	Mild loss of fullness in midface areas
3	Moderate loss of fullness with slight hollowing below malar prominence
4	Substantial loss of fullness in the midface area, clearly apparent hollowing below malar prominence

[1] Lorenc ZP, Bank D, Kane M, Lin X, Smith S. Validation of a four-point photographic scale for the assessment of midface volume loss and/or contour deficiency. Plast Reconstr Surg 2012;130(6):1330–6.

Secondary effectiveness endpoints included: effectiveness by determining the response rate (defined as at least 1 grade improvement from baseline on MMVS on both sides of the face) at 12, 24, 36, and 48 weeks since last injection, aesthetic improvement (overall appearance), based on the GAIS; at 12, 24, 36, and 48 weeks, subjects' satisfaction after treatment using the FACE-Q Satisfaction with Outcome and Satisfaction with Cheeks scales; Independent Photographic Reviewer (IPR) assessment of improvement in midface volume by comparison of random, blinded pairings of the baseline and post-baseline photographs; and volume change over time in the area of the cheeks as measured by digital 3D photography at Weeks 12, 24, 36, and 48 visits. Assessment timepoints were measured in weeks after the last injection. One month was defined as 28 days (4 weeks).

With regard to success/failure criteria, achievement of the primary endpoint was met (non-inferiority established) if the upper limit of the Confidence Interval (CI) was below the non-inferiority margin of 0.5 units. Robustness of the results of the primary endpoint analysis was investigated across a number of subgroups (study site, FST, Age, race and ethnicity).

Accountability of PMA Cohort

At the time of database lock, of 270 patients enrolled in the PMA study, 86.7% (n=234) patients were available for analysis at the completion of the study, the 12-month follow-up visit.

In Group A, one hundred forty-two (142) subjects were randomized to *Restylane Contour* and 68 subjects were randomized to Control. For Group B, all sixty (60) subjects enrolled received treatment with *Restylane Contour.*

As noted below in Table 2, there were a total of 184 subjects in Group A that completed the study, 126 in the *Restylane Contour* treatment group and 58 in Control treatment group.

In Group B, there were a total of 50 subjects that completed the study, and five (5) subjects who discontinued early. Completion data for an additional five (5) subjects is classified as 'Missing', as one site (8604) was mandated to shut down, due to the 2020 COVID-19 pandemic, preventing the conduct of study visits or study data entry into the study database. The disposition of these 5 subjects is unknown.

Table 2 Summary of Subject Disposition: All Subjects

	Group A			**Group B**
	***Restylane Contour* (N=142)**	**Control (N = 68)**	**Group A Overall (N = 210)**	***Restylane Contour* (N=60)**
Number of Subjects Screened			235	63
Number of Subjects Randomized	142	68	210	60
Number of Subjects in the Safety Population	141	68	209	59
Number of Subjects in the ITT Population	142	68	210	60
Number of Subjects in the PP Population	136	65	201	58
Completed the Study	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Yes	126 (88.7%)	58 (85.3%)	184 (87.6%)	50 (83.3%)
No	16 (11.3%)	10 (14.7%)	26 (12.4%)	5 (8.3%)
Missing	0	0	0	5 (8.3%)
Reason for Discontinuation				
Withdrew Consent	8 (5.6%)	4 (5.9%)	12 (5.7%)	4 (6.7%)
Lost to Follow-up	5 (3.5%)	4 (5.9%)	9 (4.3%)	0
Medical Reasons	0	0	0	0
Other	3 (2.1%)	2 (2.9%)	5 (2.4%)	1 (1.7%)

The safety population included all subjects who received *Restylane Contour* or Control group based on the as-treated principle.

The Intent to Treat (ITT) population included all subjects who were randomized based on the as randomized principle.

The Per Protocol (PP) population included all subjects in the ITT population who completed the Week 12 visit without any deviations considered to have a substantial impact on the primary effectiveness outcome.

Study Population Demographics and Baseline Parameters

Study 43USV1704 was designed to enroll an ethnically diverse population by ensuring that out of 270 randomized subjects (Group A = 210; Group B = 60), at least 41 subjects (41/270 [15%]) would be FST IV–VI, with at least 27 of those subjects with FST V–VI. This goal was met as 72 subjects (72/270 [26.7%]) enrolled in the study were FST IV–VI (56 subjects randomized to *Restylane® Contour* and 16 subjects randomized to the control). Of those 72 subjects, 38 were FST V–VI (31 subjects randomized to *Restylane® Contour* and 7 subjects randomized to the control).

The demographics of the study population are presented in Table 3.

Table 3 Subject Demographics and Baseline Characteristics (Intent to Treat Population)

			Treatment Group			
			Group A			Group B
Characteristic		**Statistic**	***Restylane Contour***	**Control**	**Group A Overall**	***Restylane Contour***
Age (years)		n	142	68	210	60
		Mean (SD)	52.7 (12.61)	54.7 (11.94)	53.3 (12.41)	52.1 (9.96)
		Median	54.0	55.5	54.5	52.0
		Min, Max	(24, 79)	(24, 80)	(24, 80)	(28, 73)
Sex, n (%)						
Female		n (%)	129 (90.8%)	58 (85.3%)	187 (89.0%)	55 (91.7%)
Male		n (%)	13 (9.2%)	10 (14.7%)	23 (11.0%)	5 (8.3%)
Race, n (%)						
White		n (%)	125 (88.0%)	57 (83.8%)	182 (86.7%)	44 (73.3%)
Black or African American		n (%)	8 (5.6%)	7 (10.3%)	15 (7.1%)	13 (21.7%)
Asian		n (%)	2 (1.4%)	1 (1.5%)	3 (1.4%)	3 (5.0%)
American Indian or Alaska Native		n (%)	2 (1.4%)	0	2 (1.0%)	0
Native Hawaiian or Other Pacific Islander		n (%)	1 (0.7%)	1 (1.5%)	2 (1.0%)	0
Other		n (%)	4 (2.8%)	2 (2.9%)	6 (2.9%)	0
Ethnicity, n (%)						
Hispanic or Latino		n (%)	26 (12.4%)	5 (7.4%)	21 (14.8%)	8 (13.3%)
Not Hispanic or Latino		n (%)	184 (87.6%)	63 (92.6%)	121 (85.2%)	52 (86.7%)
Fitzpatrick Skin Types, n (%)						
I		n (%)	4 (2.8%)	1 (1.5%)	5 (2.4%)	1 (1.7%)
II		n (%)	40 (28.2%)	23 (33.8%)	63 (30.0%)	9 (15.0%)
III		n (%)	65 (45.8%)	28 (41.2%)	93 (44.3%)	27 (45.0%)
IV		n (%)	17 (12.0%)	9 (13.2%)	26 (12.4%)	8 (13.3%)
V		n (%)	8 (5.6%)	3 (4.4%)	11 (5.2%)	3 (5.0%)
VI		n (%)	8 (5.6%)	4 (5.9%)	12 (5.7%)	12 (20.0%)
Baseline MMVS Score by Blinded Evaluator, n (%)						
Left	1	n (%)	0	0	0	0
	2	n (%)	48 (33.8%)	18 (26.5%)	66 (31.4%)	19 (31.7%)
	3	n (%)	84 (59.2%)	43 (63.2%)	127 (60.5%)	34 (56.7%)
	4	n (%)	10 (7.0%)	7 (10.3%)	17 (8.1%)	7 (11.7%)

Characteristic		Statistic	Treatment Group			
			Group A			Group B
			Restylane Contour	Control	Group A Overall	*Restylane Contour*
Right	1	n (%)	0	0	0	0
	2	n (%)	47 (33.1%)	25 (36.8%)	71 (34.3%)	22 (36.7%)
	3	n (%)	84 (59.2%)	36 (52.9%)	120 (57.1%)	31 (51.7%)
	4	n (%)	11 (7.7%)	7 (10.3%)	18 (8.6%)	7 (11.7%)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.

Group A subjects treated with *Restylane Contour* and Control during the initial treatment and optional touch-up (4 weeks) received a median total injection volume of 4.00 mL and 4.63 mL respectively. Subjects in both treatment groups who opted for re-treatment at 48 weeks each received a median injection volume of 2.0 mL. Injection Characteristics for initial treatment are described in Table 4 below.

The provided 27G ½" ultra-thin wall needle was the most commonly used needle for administering *Restylane Contour* (100% of right midface treatments; 98.6% of left midface treatments) and Control (100% right midface treatments; 98.5% left midface treatments). Across both treatment groups, and sides of midface, injection were made in the subcutaneous region and the supraperiosteal zone. The suprapeiosteal zone was the most common injection depth (99.3% [*Restylane Contour*]; 97.1–98.5% [Control]). Injection techniques used were linear anterograde, linear retrograde, fanning, depot, serial puncture and fern pattern techniques. Depot was the most common injection method (70.2% [*Restylane Contour*]; 69.1% [Control]) followed by serial puncture (62.4% [*Restylane Contour*]; 61.8% [Control]) for the initial treatment.

In Group B, the median total volume of *Restylane Contour* injected into the midface for cheek augmentation (cannula plus needle) was 3.80 mL for the initial and touch-up treatment combined. The median volume injected for re-treatment at Week 48 was 1.95 mL. Injection methods used were linear anterograde, linear retrograde, fanning, depot and serial puncture techniques.

The supraperiosteal zone was the most common injection depth (52/59 [88.1%] subjects) and linear retrograde was the most common injection method (59/59 [100%]) for cannula treatments.

For initial treatments by needle, the supraperiosteal zone was the most common injection depth (all subjects). Depot and serial puncture techniques (31/59 [52.5%] subjects each) were the most common injection methods.

Table 4 Injection Characteristics: Group B (Safety Population)

Assessment	Injection Tool: Cannula			Injection Tool: Needle		
	Initial Treatment m/n (%)	Touch-Up m/n (%)	Re-Treatment m/n (%)	Initial Treatment m/n (%)	Touch-Up m/n (%)	Re-Treatment m/n (%)
Subjects Treated	**59**	**33**	**36**	**59**	**31**	**34**
Incision needle for treatment						
Co-packed with cannula	28/59 (47.5)	19/33 (57.6)	23/36 (63.9)	NA	NA	NA
Other	31/59 (52.5)	14/33 (42.4)	13/36 (36.1)	NA	NA	NA
Cannula Brand for treatment						
TSK STERiGLIDE	59/59 (100)	33/33 (100)	36/36 (100)	NA	NA	NA
Cannula Gauge for treatment						
25G	17/59 (28.8)	5/33 (15.2)	6/36 (16.7)	NA	NA	NA
27G	42/59 (71.2)	28/33 (84.8)	30/36 (83.3)	NA	NA	NA
Cannula Length for treatment						
0.1 inch	0/59	0/33	1/36 (2.8)	NA	NA	NA
1.5 inch	45/59 (76.3)	29/33 (87.9)	30/36 (83.3)	NA	NA	NA
2 inch	14/59 (23.7)	4/33 (12.1)	5/36 (13.9)	NA	NA	NA

Safety Results

The analysis of safety was based on the cohort of 268 subjects available up to the final evaluation (i.e., 12 weeks after re-treatment) at Week 48.

The key safety outcomes for this study are presented below in Table 5 through 13. Subject-reported injection related events are presented in Table 5 – 10. Physician-reported adverse events (AEs) are presented in Table 11 – 13.

Pre-defined Injection Related Events: Subjects evaluated injection site reactions (IREs) in a 28-day diary following initial treatment, and touch-up and re-treatment, if performed. The presence of pre-defined expected post-treatment events, i.e., pain, tenderness, redness, bruising and swelling, were assessed for the treated area. Subjects recorded the presence and level of intensity (i.e., none, tolerable, affects daily activities, or disabling) for each of the pre-defined events.

IRE In Group A, the majority of subjects who reported pre-defined IREs classified them as tolerable post-initial injection (114/129 [88.4%]), post-touch-up injection (82/86 [95.3%]), and post-re-treatment injection (64/73 [87.7%]) with *Restylane Contour*. The majority of Group B subjects who reported pre-defined IREs classified them as tolerable following initial treatment (cannula: 48/52 [92.3%]; needle: 48/54 [88.9%), touch-up (cannula: 26/27 [96.3%]; needle: 20/22 [90.9%]), and re-treatment (cannula: 28/29 [96.6%]; needle:27/28 [96.4%]) with *Restylane Contour*.

The majority of IREs in both Group A and B lasted 2 weeks or less after all 3 treatments (initial, optional touch-up or re-treatment).

There were no significant differences in the IREs reported in the *Restylane Contour* treatment group compared to the Control group. However a smaller proportion of subjects receiving *Restylane Contour* treatment reported commonly reported IREs in each category (pain, tenderness, redness, bruising, swelling, itching) when compared to Control subjects following initial treatment. IREs in both groups were typically reported at a lower incident rate and intensity, and shorter duration, following touch-up compared to initial treatment.

Table 5 Pre-defined Injection Related Events by Maximum Intensity Occurring in Subjects After Initial Treatment (Safety Population)

	Group A							
	Post-Initial Injection with *Restylane Contour* (N=139) n (%)				Post-Initial Injection with Control (N=66) n (%)			
Injection Related Event	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**
Any Diary Symptom	129 (92.8)	114 (82.0)	14 (10.9)	1 (0.8)	65 (98.5)	56 (86.2)	8 (12.3)	1 (1.5)
Pain (including burning)	86 (61.9)	81 (94.2)	5 (5.8)	0	52 (78.8)	48 (92.3)	4 (7.7)	0
Tenderness	120 (86.3)	114 (95.0)	6 (5.0)	0	64 (97.0)	58 (90.6)	6 (9.4)	0
Redness	82 (59.0)	78 (95.1)	4 (4.9)	0	45 (68.2)	43 (95.6)	2 (4.4)	0
Bruising	86 (61.9)	74 (86.0)	11 (12.8)	1 (1.2)	46 (69.7)	43 (93.5)	2 (4.3)	1 (2.2)
Swelling	99 (71.2)	94 (94.9)	4 (4.0)	1 (1.0)	54 (81.8)	48 (88.9)	6 (11.1)	0
Itching	20 (14.4)	20 (100.0)	0	0	9 (13.6)	9 (100.0)	0	0

	Group B							
	Post-Initial Injection with *Restylane Contour* Cannula (N=57) n (%)				Post-Initial Injection with *Restylane Contour* Needle (N=57) n (%)			
Injection Related Event	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**
Any Diary symptom	52 (91.2)	48 (92.3)	4 (7.7)	0	54 (94.7)	48 (88.9)	6 (11.1)	0
Pain (including burning)	33 (57.9)	32 (97.0)	1 (3.0)	0	38 (66.7)	36 (94.7)	2 (5.3)	0
Tenderness	50 (87.7)	49 (98.0)	1 (2.0)	0	53 (93.0)	51 (96.2)	2 (3.8)	0
Redness	27 (47.4)	25 (92.6)	2 (7.4)	0	29 (50.9)	27 (93.1)	2 (6.9)	0
Bruising	21 (36.8)	18 (85.7)	3 (14.3)	0	32 (56.1)	28 (87.5)	4 (12.5)	0
Swelling	35 (61.4)	34 (97.1)	1 (2.9)	0	38 (66.7)	36 (94.7)	2 (5.3)	0
Itching	8 (14.0)	8 (100.0)	0	0	10 (17.5)	10 (100.0)	0	0

Notes: Percentages for symptom severity columns are based on the total number of subjects who reported “Tolerable” or higher for a respective symptom in their subject diary; the total column percentages are based on the number of subjects who completed at least one diary entry and were injected.

Table 6 Pre-defined Injection Related Events by Maximum Intensity Occurring in Subjects After Optional Touch-up Treatment (Safety Population)

	Group A							
	Post-Optional Touch-Up Injection with *Restylane Contour* (N=106) n (%)				Post-Optional Touch-Up Injection with Control (N=52) n (%)			
Injection Related Event	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**
Any Diary Symptom	86 (81.1)	82 (95.3)	4 (4.7)	0	45 (86.5)	40 (88.9)	4 (8.9)	1 (2.2)
Pain (including burning)	48 (45.3)	48 (100.0)	0	0	31 (59.6)	27 (87.1)	3 (9.7)	1 (3.2)
Tenderness	78 (73.6)	78 (100.0)	0	0	43 (82.7)	39 (90.7)	3 (7.0)	1 (2.3)
Redness	49 (46.2)	48 (98.0)	1 (2.0)	0	28 (53.8)	24 (85.7)	4 (14.3)	0
Bruising	47 (44.3)	45 (95.7)	2 (4.3)	0	27 (51.9)	25 (92.6)	2 (7.4)	0
Swelling	60 (56.6)	59 (98.3)	1 (1.7)	0	28 (53.8)	24 (85.7)	4 (14.3)	0
Itching	9 (8.5)	9 (100.0)	0	0	12 (23.1)	11 (91.7)	1 (8.3)	0
	Group B							
	Post-Optional Touch=Up Injection with *Restylane Contour* Cannula (N=33) n (%)				Post-Optional Touch-Up Injection with *Restylane Contour* Needle (N=30) n (%)			
Injection Related Event	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**
Any Diary symptom	27 (81.8)	26 (96.3)	1 (3.7)	0	22 (73.3)	20 (90.9)	2 (9.1)	0
Pain (including burning)	18 (54.5)	17 (94.4)	1 (5.6)	0	16 (53.3)	16 (100)	0	0
Tenderness	24 (72.7)	23 (95.8)	1 (4.2)	0	22 (73.3)	21 (95.5)	1 (4.5)	0
Redness	12 (36.4)	12 (100.0)	0	0	15 (50.0)	15 (100.0)	0	0
Bruising	7 (21.2)	7 (100.0)	0	0	9 (30.0)	8 (88.9)	1 (11.1)	0
Swelling	22 (66.7)	22 (100.0)	0	0	18 (60.0)	17 (94.4)	1 (5.6)	0
Itching	5 (15.2)	5 (100.0)	0	0	6 (20.0)	6 (100.0)	0	0

Notes: Percentages for symptom severity columns are based on the total number of subjects who reported "Tolerable" or higher for a respective symptom in their subject diary; the total column percentages are based on the number of subjects who completed at least one diary entry and were injected.

Table 7 Pre-defined Injection Related Events by Maximum Intensity Occurring in Subjects After Re-treatment (Safety Population)

	Group A							
	Post Re-treatment Injection with *Restylane Contour* (N=82) n (%)				Post Re-treatment Injection with Control (N=40) n (%)			
Injection Related Event	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**
Any Diary symptom	73 (89.0)	64 (87.7)	8 (11.0)	1 (1.4)	38 (95.0)	32 (84.2)	6 (15.8)	0
Pain (including burning)	47 (57.3)	43 (91.5)	4 (8.5)	0	23 (57.5)	21 (91.3)	2 (8.7)	0
Tenderness	65 (79.3)	60 (92.3)	5 (7.7)	0	37 (92.5)	33 (89.2)	4 (10.8)	0
Redness	46 (56.1)	43 (93.5)	3 (6.5)	0	27 (67.5)	24 (88.9)	3 (11.1)	0
Bruising	39 (47.6)	32 (82.1)	6 (15.4)	1 (2.6)	25 (62.5)	22 (88.0)	3 (12.0)	0
Swelling	48 (58.5)	44 (91.7)	3 (6.3)	1 (2.1)	26 (65.0)	24 (92.3)	2 (7.7)	0
Itching	7 (8.5)	6 (85.7)	1 (14.3)	0	7 (17.5)	6 (85.7)	1 (14.3)	0
	Group B							
	Post Re-treatment Injection with *Restylane Contour* Cannula (N=34)				Post Re-treatment Injection with *Restylane Contour* Needle (N=32)			
Injection Related Event	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**	**Total**	**Tolerable**	**Affects Daily Activities**	**Disabling**
Any Diary symptom	29 (85.3)	28 (96.6)	1 (3.4)	0	28 (87.5)	27 (96.4)	1 (3.6)	0
Pain (including burning)	21 (61.8)	21 (100.0)	0	0	23 (71.9)	22 (95.7)	1 (4.3)	0
Tenderness	24 (70.6)	23 (95.8)	1 (4.2)	0	27 (84.4)	26 (96.3)	1 (3.7)	0
Redness	14 (41.2)	14 (100.0)	0	0	13 (40.6)	13 (100.0)	0	0
Bruising	7 (20.6)	7 (100.0)	0	0	11 (34.4)	11 (100.0)	0	0
Swelling	20 (58.8)	20 (100.0)	0	0	20 (62.5)	20 (100.0)	0	0
Itching	1 (2.9)	1 (100.0)	0	0	2 (6.3)	2 (100.0)	0	0

Notes: Percentages for symptom severity columns are based on the total number of subjects who reported "Tolerable" or higher for a respective symptom in their subject diary; the total column percentages are based on the number of subjects who completed at least one diary entry and were injected.

Table 8 Duration of Pre-defined Injection Related Events Occurring in Subjects After Initial Treatment (Safety Population)

	Group A									
	Post-Initial Injection with *Restylane Contour* (N=139) n (%)					Post-Initial Injection with Control (N=66) n (%)				
	Duration									
	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days
Any Symptom	129 (92.8)	34 (24.5)	22 (15.8)	45 (32.4)	28 (20.1)	65 (98.5)	14 (21.2)	13 (19.7)	23 (34.8)	15 (22.7)
Pain (including burning)	86 (61.9)	57 (66.3)	17 (19.8)	12 (14.0)	0	34 (65.4)	34 (65.4)	12 (23.1)	6 (11.5)	0
Tenderness	120 (86.3)	42 (35.0)	31 (25.8)	38 (31.7)	9 (7.5)	20 (31.3)	20 (31.3)	18 (28.1)	17 (26.6)	9 (14.1)
Redness	82 (59.0)	61 (74.4)	12 (14.6)	7 (8.5)	2 (2.4)	29 (64.4)	29 (64.4)	9 (20.0)	3 (6.7)	4 (8.9)
Bruising	86 (61.9)	24 (27.9)	14 (16.3)	29 (33.7)	19 (22.1)	16 (34.8)	16 (34.8)	7 (15.2)	16 (34.8)	7 (15.2)
Swelling	99 (71.2)	51 (51.5)	28 (28.3)	15 (15.2)	5 (5.1)	32 (59.3)	32 (59.3)	10 (18.5)	9 (16.7)	3 (5.6)
Itching	20 (14.4)	14 (70.0)	4 (20.0)	1 (5.0)	1 (5.0)	3 (33.3)	3 (33.3)	3 (33.3)	2 (22.2)	1 (11.1)
	Group B									
	Duration									
	Post-Initial Injection with *Restylane Contour* Cannula (N=57) n (%)					Post-Initial Injection with *Restylane Contour* Needle (N=57) n (%)				
	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days
Any Symptom	52 (91.2)	19 (33.3)	17 (29.8)	9 (15.8)	7 (12.3)	54 (94.7)	15 (26.3)	20 (35.1)	12 (21.1)	7 (12.3)
Pain (including burning)	33 (57.9)	25 (75.8)	7 (21.2)	1 (3.0)	0	38 (66.7)	27 (71.1)	9 (23.7)	2 (5.3)	0
Tenderness	50 (87.7)	17 (34.0)	18 (36.0)	11 (22.0)	4 (8.0)	53 (93.0)	18 (34.0)	20 (37.7)	10 (18.9)	5 (9.4)
Redness	27 (47.4)	21 (77.8)	5 (18.5)	0	1 (3.7)	29 (50.9)	21 (72.4)	8 (27.6)	0	0
Bruising	21 (36.8)	14 (66.7)	6 (28.6)	0	1 (4.8)	32 (56.1)	10 (31.3)	12 (37.5)	7 (21.9)	3 (9.4)
Swelling	35 (61.4)	23 (65.7)	9 (25.7)	2 (5.7)	1 (2.9)	38 (66.7)	19 (50.0)	15 (39.5)	3 (7.9)	1 (2.6)
Itching	8 (14.0)	5 (62.5)	2 (25.0)	1 (12.5)	0	10 (17.5)	6 (60.0)	3 (30.0)	1 (10.0)	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary.

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

Table 9 Duration of Pre-defined Injection Related Events Occurring in Subjects After Optional Touch-Up Treatment (Safety Population)

	Group A									
	Post-Optional Touch-Up Injection with *Restylane Contour* (N=106) n (%)					Post-Optional Touch-Up Injection with Control (N=52) n (%)				
	Duration									
	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days
Any Symptom	86 (81.1)	28 (26.4)	23 (21.7)	23 (21.7)	12 (11.3)	45 (86.5)	11 (21.2)	14 (26.9)	15 (28.8)	5 (9.6)
Pain (including burning)	48 (45.3)	36 (75.0)	10 (20.8)	1 (2.1)	1 (2.1)	31 (59.6)	22 (71.0)	7 (22.6)	1 (3.2)	1 (3.2)
Tenderness	78 (73.6)	34 (43.6)	28 (35.9)	13 (16.7)	3 (3.8)	43 (82.7)	16 (37.2)	14 (32.6)	11 (25.6)	2 (4.7)
Redness	49 (46.2)	32 (65.3)	8 (16.3)	7 (14.3)	2 (4.1)	27 (51.9)	19 (67.9)	7 (25.0)	1 (3.6)	1 (3.6)
Bruising	47 (44.3)	11 (23.4)	12 (25.5)	16 (34.0)	8 (17.0)	27 (51.9)	7 (25.9)	8 (29.6)	8 (29.6)	4 (14.8)
Swelling	60 (56.6)	34 (56.7)	14 (23.3)	8 (13.3)	4 (6.7)	28 (53.8)	16 (57.1)	6 (21.4)	4 (14.3)	2 (7.1)
Itching	9 (8.5)	8 (88.9)	1 (11.1)	0	0	12 (23.1)	9 (75.0)	3 (25.0)	0	0

Table 10 Duration of Pre-defined Injection Related Events Occurring in Subjects After Re-treatment (Safety Population)

	Group A									
	Post Re-treatment Injection with *Restylane Contour* (N=82) n (%)					Post Re-treatment Injection with Control (N=40) n (%)				
		Duration								
	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days
Any Diary Symptom	73 (89.0)	23 (28.0)	20 (24.4)	16 (19.5)	14 (17.1)	38 (95.0)	11 (27.5)	15 (37.5)	8 (20.0)	4 (10.0)
Pain (including burning)	47 (57.3)	26 (55.3)	15 (31.9)	6 (12.8)	0	23 (57.5)	16 (69.6)	5 (21.7)	2 (8.7)	0
Tenderness	65 (79.3)	22 (33.8)	21 (32.3)	15 (23.1)	7 (10.8)	37 (92.5)	17 (45.9)	14 (37.8)	4 (10.8)	2 (5.4)
Redness	46 (56.1)	31 (67.4)	11 (23.9)	3 (6.5)	1 (2.2)	27 (67.5)	19 (70.4)	6 (22.2)	2 (7.4)	0
Bruising	39 (47.6)	14 (35.9)	6 (15.4)	9 (23.1)	10 (25.6)	25 (62.5)	7 (28.0)	10 (40.0)	5 (20.0)	3 (12.0)
Swelling	48 (58.5)	25 (52.1)	14 (29.2)	3 (6.3)	6 (12.5)	26 (65.0)	9 (34.6)	16 (61.5)	0	1 (3.8)
Itching	7 (8.5)	4 (57.1)	2 (28.6)	1 (14.3)	0	7 (17.5)	4 (57.1)	1 (14.3)	2 (28.6)	0
	Group B									
	Post Re-treatment Injection with *Restylane Contour* Cannula (N=34) n (%)					Post Re-treatment Injection with *Restylane Contour* Needle (N=32) n (%)				
		Duration								
	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days	Total	1–3 Days	4–7 Days	8–14 Days	>14 Days
Any Diary Symptom	29 (85.3)	16 (47.1)	8 (23.5)	4 (11.8)	1 (2.9)	28 (87.5)	15 (46.9)	3 (9.4)	9 (28.1)	1 (3.1)
Pain (including burning)	21 (61.8)	16 (76.2)	5 (23.8)	0	0	23 (71.9)	17 (73.9)	6 (26.1)	0	0
Tenderness	24 (70.6)	14 (58.3)	7 (29.2)	2 (8.3)	1 (4.2)	27 (84.4)	15 (55.6)	7 (25.9)	4 (14.8)	1 (3.7)
Redness	14 (41.2)	10 (71.4)	4 (28.6)	0	0	13 (40.6)	11 (84.6)	1 (7.7)	1 (7.7)	0
Bruising	7 (20.6)	3 (42.9)	4 (57.1)	0	0	11 (34.4)	4 (36.4)	1 (9.1)	6 (54.5)	0
Swelling	20 (58.8)	11 (55.0)	5 (25.0)	4 (20.0)	0	20 (62.5)	13 (65.0)	4 (20.0)	3 (15.0)	0
Itching	1 (2.9)	0	0	1 (100)	0	2 (6.3)	1 (50.0)	0	1 (50.0)	0

*Number of subjects who completed at least one diary entry. Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms.

Device and Injection Related Events: AEs were evaluated by Investigators throughout entirety of the study. An overall summary of AEs following initial and touch-up treatment is presented in Table 11.

Of the subjects in Group A treated with *Restylane Contour* who experienced AEs, 67 events in 23/141 (16.3%) subjects were considered related to the investigational treatment or injection procedure, while for Group A subjects treated with Control, 101 related events in 17/68 subjects (25.0%) were recorded. In Group B, 2/59 subjects (3.4%) experienced AEs related to investigational treatment or injection procedure; of these, one event in one subject (1.7%) was considered related to side treated by cannula injection, and one event in one subject (1.7%) had an AE considered related, but not to a specific side.

There were three (3) SAEs during the study experienced by 2 subjects in Group A Control subjects (2.9%) that were not related the investigational treatment or procedure (severe intestinal obstruction, pneumonia, pancreatic carcinoma).

While no subjects treated with *Restylane Contour* in Group A or Group B experienced late-onset related AEs (i.e., >21 days after initial or re-treatment), two (2) subjects in Group A treated with Control did have late onset AEs. There were no ongoing related AEs at the end of the study. After initial treatment with *Restylane Contour*, most related AEs in Group A resolved within approximately 3 days, and within 2 weeks (14 days) following re-treatment.

Mean duration of related AEs for Group A *Restylane Contour* subjects was 7.2 days for initial and 18.5 days for re-treatment. For Control treatment subjects, mean duration of related AEs was 4.5 days for initial and 4.7 days for re-treatment, respectively. After initial and retreatment with in Group A *Restylane Contour*, three related AEs (3/67 or 4.5%) lasted 40 days or longer. These events included one event each of blepharospasm, swelling of eyelid and intravascular embolic injury, out of which action including medical and non-pharmacological treatment was administered for the vascular embolic injury only. All events were resolved without sequelae. After initial treatment with *Restylane Contour* (by cannula), one Group B subject experienced a related AE (catheter site erythema) which had a duration of 169 days, however, the event resolved spontaneously (i.e., without any treatment). The only other related AE in one Group B subject resolved on the same day as onset.

The severity and duration of treatment related AEs occurring in ≥ 2% of subjects in Group A are summarized in Table 12 - 13. Common related AEs in Group A included implant site pain, bruising, oedema, swelling and erythema. Related events of implant site pain typically lasted 7 days or less; implant site bruising typically lasted less than 21 days, and implant site oedema, swelling and erythema each typically lasted less than 7 days.

Treatment-related AEs occurring in < 2% of subject after initial and touch-up treatment, for both treatment groups, included blepharospasm, hypoaesthesia teeth, toothache, implant site pruritis, implant site reaction, facial pain, implant site paraesthesia, implantation complication, headache and syncope.

Midface Safety Assessments: During all on-site visits, safety assessments including subject's midface sensation (monofilament and cotton wisp tests), firmness, symmetry, function (puff cheeks, broad smile, and chewing motion), and mass formation tests were performed. After the Day 1 treatment visit, device palpability was also performed at each on-site visit.

All Group A subjects were found to have normal midface firmness assessments at all visits throughout the study. While the majority of Group B subjects had normal assessments, 1 subject (1/56 [1.8%]) was found to have mildly abnormal midface firmness at Visit 4 (Week 4), however, the firmness returned to normal at the next visit. Midface symmetry was assessed as normal or mildly abnormal at all visits throughout the study for both Group A and Group B subjects. Midface function assessments were assessed as normal throughout the study for Group B subjects and all but one Group A subject. One Group A subject (1/84 [1.2%]) had difficulty smiling broadly due to a mildly swollen cheek after re-treatment. The subject's smile was assessed as normal at the next visit. All Group A and B subjects were found to have normal midface sensation at all visits throughout the study.

For device palpability, in all Group A and Group B subjects, the midface was found to have a normal expected feel upon palpation at all visits throughout the study. No Group A or B subjects developed any mass formations throughout the course of the study.

Additional Safety Assessments

Vision Function: Two subjects experienced a visual acuity change that was categorized as an AE (unrelated to investigational treatment or injection procedure). No extraocular muscle abnormalities or disturbances in the quadrants of the visual field were identified in Group A or Group B subjects.

Pain Assessment: Mean pain scores (pre and post injection) were low (below 2.5) throughout the study, across both Group A treatment groups (*Restylane Contour* and Control), as well as across both Group B treatment groups (cannula and needle), where a score of 0 on the 11-point NPS corresponded to no pain and 10 corresponded to worse pain imaginable.

Table 11 Summary of Related Adverse Events After Initial/Re-treatment, Group A (Safety Population)

	Group A							
	Initial Treatment with *Restylane Contour* (N=141)		Re-treatment with *Restylane Contour* (N=92)		Initial Treatment with Control (N=68)		Re-treatment with Control (N=45)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
AEs Overall	61 (43.3)	135	15 (16.3)	24	40 (58.8)	134	12 (26.7)	27
Any AE Related to Study Product or Injection Procedure								
Total	21 (14.9)	57	6 (6.5)	10	13 (19.1)	79	8 (17.8)	22
Mild	18 (12.8)	53	6 (6.5%)	10	8 (11.8)	72	6 (13.3)	16
Moderate	3 (2.1)	4	0	0	4 (5.9)	6	2 (4.4)	6
Severe	0	0	0	0	1 (1.5)	1	0	0
Action Required								
None	19 (13.5)	52	4 (4.3)	8	10 (14.7)	74	8 (17.8)	22
Medication	2 (1.4)	5	2 (2.2)	2	2 (2.9)	4	0	0
Non-Pharmacological	0	0	1 (1.1)	1	1 (1.5)	1	0	0
Withdrawal	0	0	0	0	0	0	0	0
Onset								
Mean Onset of Related AEs (Days)	0.5		3.0		6.1		2.0	
Minimum (Days)	0		0		0		0	
Maximum (Days)	5		14		319		36	
Mean Duration of Related AEs (Days)	7.2		18.5		4.5		4.7	
Minimum (Days)	1		3		1		1	
Maximum (Days)	80		46		36		17	
Median Duration of Related AEs (days)	3		14		3		4	
	Subjects n (%)	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Events**
Unrelated AEs	50 (35.5)	78	11 (12.0)	14	32 (47.1)	55	4 (8.9)	5
Serious AEs	0	0	0	0	2 (2.9)	3	0	0
No AEs	80 (56.7)	NA	77 (83.7)	NA	28 (41.2)	NA	33 (73.3)	NA

NA=Not applicable;
Initial treatment is considered the time after the first treatment up until optional re-treatment, or end of study. Re-treatment is considered to be the time after optional re-treatment until the end of the study.

Table 12 Treatment Related Adverse Events Occurring ≥ 2% of Subjects by Maximum Severity after Initial/Re-treatment, Group A (Safety Population)

		Group A							
		Initial Treatment with *Restylane Contour* (N=141)		Re-treatment with *Restylane Contour* (N=92)		Initial Treatment with Control (N=68)		Re-treatment with Control (N=45)	
System Organ Class/ *Preferred Term*	**Severity**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**
Any Related AE	Total	21(14.9%)	57	6 (6.5%)	10	13(19.1%)	79	8 (17.8%)	22
	Mild	18(12.8%)	53	6 (6.5%)	10	8 (11.8%)	72	6 (13.3%)	16
	Moderate	3 (2.1%)	4	0	0	4 (5.9%)	6	2 (4.4%)	6
	Severe	0	0	0	0	1 (1.5%)	1	0	0
Eye disorders	Total	1 (0.7%)	1	1 (1.1%)	1	0	0	2 (4.4%)	2
	Mild	1 (0.7%)	1	1 (1.1%)	1	0	0	2 (4.4%)	2
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Blepharospasm	Total	0	0	1 (1.1%)	1	0	0	1 (2.2%)	1
	Mild	0	0	1 (1.1%)	1	0	0	1 (2.2%)	1
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Swelling of eyelid	Total	1 (0.7%)	1	0	0	0	0	1 (2.2%)	1
	Mild	1 (0.7%)	1	0	0	0	0	1 (2.2%)	1
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
General disorders and administration site conditions	Total	18(12.8%)	51	4 (4.3%)	7	12(17.6%)	77	6 (13.3%)	20
	Mild	15(10.6%)	47	4 (4.3%)	7	7 (10.3%)	70	4 (8.9%)	14
	Moderate	3 (2.1%)	4	0	0	4 (5.9%)	6	2 (4.4%)	6
	Severe	0	0	0	0	1 (1.5%)	1	0	0
Implant site pain	Total	6 (4.3%)	16	0	0	9 (13.2%)	36	4 (8.9%)	13

		Group A							
		Initial Treatment with *Restylane Contour* (N=141)		Re-treatment with *Restylane Contour* (N=92)		Initial Treatment with Control (N=68)		Re-treatment with Control (N=45)	
System Organ Class/ *Preferred Term*	**Severity**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**
	Mild	5 (3.5%)	15	0	0	7 (10.3%)	33	3 (6.7%)	9
	Moderate	1 (0.7%)	1	0	0	2 (2.9%)	3	1 (2.2%)	4
	Severe	0	0	0	0	0	0	0	0
Implant site bruising	Total	5 (3.5%)	5	3 (3.3%)	5	1 (1.5%)	1	1 (2.2%)	1
	Mild	4 (2.8%)	4	3 (3.3%)	5	1 (1.5%)	1	0	0
	Moderate	1 (0.7%)	1	0	0	0	0	1 (2.2%)	1
	Severe	0	0	0	0	0	0	0	0
Implant site oedema	Total	3 (2.1%)	6	0	0	5 (7.4%)	15	2 (4.4%)	4
	Mild	3 (2.1%)	6	0	0	4 (5.9%)	13	2 (4.4%)	4
	Moderate	0	0	0	0	1 (1.5%)	2	0	0
	Severe	0	0	0	0	0	0	0	0
Implant site erythema	Total	2 (1.4%)	6	0	0	5 (7.4%)	11	1 (2.2%)	1
	Mild	2 (1.4%)	6	0	0	4 (5.9%)	10	0	0
	Moderate	0	0	0	0	1 (1.5%)	1	1 (2.2%)	1
	Severe	0	0	0	0	0	0	0	0
Implant site swelling	Total	3 (2.1%)	4	0	0	2 (2.9%)	2	0	0
	Mild	3 (2.1%)	4	0	0	1 (1.5%)	1	0	0
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	1 (1.5%)	1	0	0
Implant site haemorrhage	Total	1 (0.7%)	2	0	0	3 (4.4%)	4	0	0
	Mild	1 (0.7%)	2	0	0	3 (4.4%)	4	0	0
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Injection site nodule	Total	2 (1.4%)	4	0	0	2 (2.9%)	3	0	0
	Mild	2 (1.4%)	4	0	0	2 (2.9%)	3	0	0

		Group A							
		Initial Treatment with *Restylane Contour* (N=141)		Re-treatment with *Restylane Contour* (N=92)		Initial Treatment with Control (N=68)		Re-treatment with Control (N=45)	
System Organ Class/ *Preferred Term*	**Severity**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Implant site hypoaesthesia	Total	1 (0.7%)	1	0	0	2 (2.9%)	2	0	0
	Mild	1 (0.7%)	1	0	0	2 (2.9%)	2	0	0
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Implant site induration	Total	0	0	0	0	2 (2.9%)	3	0	0
	Mild	0	0	0	0	2 (2.9%)	3	0	0
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Injection site papule	Total	0	0	0	0	0	0	1 (2.2%)	1
	Mild	0	0	0	0	0	0	1 (2.2%)	1
	Moderate	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Nervous system disorders	Total	2 (1.4%)	2	1 (1.1%)	1	2 (2.9%)	2	0	0
	Mild	2 (1.4%)	2	1 (1.1%)	1	2 (2.9%)	2	0	0

Initial treatment was considered the time after first treatment up until optional re-treatment, or end of study.
Re-treatment was considered to be the time after optional re-treatment up until the end of the study

Table 13 Treatment Related AEs Occurring ≥ 2% of Subjects by Duration after Initial/Re-treatment, Group A (Safety Population)

Adverse event	Group A *Restylane Contour*											
	Initial Treatment with *Restylane Contour* (N=141)						Re-treatment with *Restylane Contour* (N=92)					
SOC *Preferred term*	Subjects n (%)	Events n	≤ 7 Days n (%)	8-14 Days n (%)	15-30 Days n (%)	> 30 Days n (%)	Subjects n (%)	Events n	≤ 7 Days n (%)	8-14 Days n (%)	15-30 Days n (%)	> 30 Days n (%)
General disorders and administration site conditions												
Implant site bruising	5 (3.5)	5	3 (60.0)	0	2 (40.0)	0 (0.0)	3 (3.3)	5	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)
Implant site oedema	3 (2.1)	6	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implant site pain	6 (4.3)	16	10 (62.5)	4 (25.0)	2 (12.5)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implant site swelling	3 (2.1)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse event	Group A Control											
	Initial Treatment with Control (N=68)						Re-treatment with Control (N=45)					
SOC *Preferred term*	Subjects n (%)	Events n	≤ 7 Days n (%)	8-14 Days n (%)	15-30 Days n (%)	> 30 Days n (%)	Subjects n (%)	Events n	≤7 Days n (%)	8-14 Days n (%)	15-30 Days n (%)	> 30 Days n (%)
Eye disorders												
Blepharospasm	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling of eyelid	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions												
Implant site bruising	1 (1.5)	1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (2.2)	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implant site erythema	5 (7.4)	11	10 (90.9)	1 (9.1)	0 (0.0)	0 (0.0)	1 (2.2)	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implant site haemorrhage	3 (4.4)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implant site hypoaesthesia	2 (2.9)	2	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implant site induration	2 (2.9)	3	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implant site oedema	5 (7.4)	15	14 (93.3)	1 (6.7)	0 (0.0)	0 (0.0)	2 (4.4)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)

Implant site pain	9 (13.2)	36	33 (91.7)	0 (0.0)	2 (5.6)	1 (2.8)	4 (8.9)	13	12 (92.3)	0 (0.0)	1 (7.7)	0 (0.0)
Implant site swelling	2 (2.9)	2	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site nodule	2 (2.9)	3	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site papule	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Nervous system disorders												
Headache	1 (1.5)	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	1 (1.5)	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Initial treatment was considered the time after first treatment up until optional re-treatment, or end of study. Re-treatment was considered to be the time after optional re-treatment up until the end of the study. The percentages by duration are based on the number of events for the corresponding treatment-related adverse event.

B. Post-Market Surveillance

The adverse event reports received from post-marketing surveillance (voluntary reporting and published literature) for the use of *Restylane Contour* with and without lidocaine from worldwide sources most commonly included reports of transient swelling/edema and with immediate onset or delayed onset, up to several weeks after treatment.

The following events were also reported in decreasing order of frequency:

- mass formation/induration
- pain/tenderness
- papules/nodules
- erythema
- inflammation
- short duration of effect
- presumptive bacterial infections and abscess formation
- bruising/hematoma
- ischemia and necrosis including pallor, due to unintentional intravascular injection or embolisation
- injection site reactions including warmth, burning sensation and exfoliation
- hypersensitivity/angioedema
- neurological symptoms including hypoaesthesia and paraesthesia
- granuloma/foreign body reaction
- device dislocation
- deformity/asymmetry
- discoloration
- eye disorders including eye pain and eyelid oedema
- symptoms of reactivation of herpes infection
- pruritus
- blisters/vesicles
- rash
- atrophy/scarring
- acne
- dermatitis
- encapsulation
- extrusion of device
- urticaria
- non-dermatological events including headache, discomfort, nausea and
- other dermatological events including chapped lips and hyperhidrosis

When required, treatments for these events included corticosteroids, antibiotics, antihistamines, analgesics, NSAIDs, vasodilation agent, drainage or enzymatic degradation (with hyaluronidase) of the product.

Reports of serious adverse events for *Restylane Contour* with and without lidocaine are rare. The most commonly reported serious adverse events from post-marketing surveillance were ischemia/necrosis, infection/abscess and hypersensitivity/angioedema.

Serious ischemia/necrosis was mostly reported with immediate onset up to a few days following the injection. The outcomes of ischemia/necrosis cases were mainly recovered or were recovering at the time of last contact. The treatments included hyaluronidase, analgesics, corticosteroids, vasodilation agent, antihistamine and aspirin.

Serious infection/abscess was reported with onset up to a week or a delayed onset up to a year following the injection. The outcome was mainly recovered or recovering at the time of last contact. The treatments included antibiotics, antihistamine, corticosteroids, hyaluronidase and drainage.

Serious hypersensitivity/angioedema was mostly reported with immediate onset up to a few days following the injection. Almost all patients had recovered at the time of last contact. The treatments included antihistamine, analgesic, corticosteroids, hyaluronidase and sodium chloride.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discolouration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolization. Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments with dermal fillers have been reported. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, antibiotics, local wound care, drainage, surgery and hyperbaric oxygen.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions, infections should be excluded and treated if necessary since inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended.

The prolonged use of any medication, e.g., corticosteroids or antibiotics in treatment of adverse events has to be carefully assessed, since this may carry a risk for the patient. In case of persistent or recurrent inflammatory symptoms, consider removal of the product by aspiration/drainage, extrusion or enzymatic degradation (use of hyaluronidase has been described in scientific publications). Before any removal procedure is performed, the swelling may be reduced by using e.g. NSAID for 2-7 days or a short course of corticosteroids for less than 7 days, in order to more easily palpate any remaining product.

Adverse reactions should be reported to Galderma Laboratories, L.P. at 1-855-425-8722.

Clinical Studies

Pivotal Study of *Restylane Contour*

Study Design

A randomized, evaluator-blinded, parallel-group, comparator-controlled, multi-center study was conducted to evaluate the safety and effectiveness of *Restylane Contour* versus an approved label comparator product for cheek augmentation and the correction of midface contour deficiencies.

Subject Demographics

In total, 270 subjects were randomized and treated in Group A or Group B. Subject demographics for Group A are presented in Table 14 and for Group B in Table 15.

Table 14 Demographic and Baseline Characteristics: Group A (ITT Population)

Parameter/Category	Group A		
	Restylane Contour **(N=142)**	**Control (N=68)**	**Overall (N=210)**
Age (years), n	142	68	210
Mean (SD)	52.7 (12.61)	54.7 (11.94)	53.3 (12.41)
Median	54.0	55.5	54.5
Min, Max	(24, 79)	(24, 80)	(24, 80)
Sex, n (%)			
Female	129 (90.8)	58 (85.3)	187 (89.0)
Male	13 (9.2)	10 (14.7)	23 (11.0)
Race, n (%)			
White	125 (88.0)	57 (83.8)	182 (86.7)
Black or African American	8 (5.6)	7 (10.3)	15 (7.1)
Asian	2 (1.4)	1 (1.5)	3 (1.4)
American Indian or Alaska Native	2 (1.4)	0	2 (1.0)
Native Hawaiian or Other Pacific Islander	1 (0.7)	1 (1.5)	2 (1.0)
Other	4 (2.8)	2 (2.9)	6 (2.9)
Ethnicity, n (%)			
Hispanic or Latino	21 (14.8)	5 (7.4)	26 (12.4)
Not Hispanic or Latino	121 (85.2)	63 (92.6)	184 (87.6)
Fitzpatrick Skin Types, n (%)			
I	4 (2.8)	1 (1.5)	5 (2.4)
II	40 (28.2)	23 (33.8)	63 (30.0)
III	65 (45.8)	28 (41.2)	93 (44.3)
IV	17 (12.0)	9 (13.2)	26 (12.4)
V	8 (5.6)	3 (4.4)	11 (5.2)
VI	8 (5.6)	4 (5.9)	12 (5.7)

Table 15 Demographic and Baseline Characteristics: Group B (ITT Population)

Parameter/Category	Group B
	Restylane Contour **(N=60)**
Age (years), n	60
Mean (SD)	52.1 (9.96)
Median	52.0
Min, Max	(28, 73)
Sex, n (%)	
Female	55 (91.7)
Male	5 (8.3)
Race, n (%)	
White	44 (73.3)
Black or African American	13 (21.7)
Asian	3 (5.0)
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Other	0
Ethnicity, n (%)	
Hispanic or Latino	8 (13.3)
Not Hispanic or Latino	52 (86.7)
Fitzpatrick Skin Types, n (%)	
I	1 (1.7)
II	9 (15.0)
III	27 (45.0)
IV	8 (13.3)
V	3 (5.0)
VI	12 (20.0)

Effectiveness Results

The analysis of effectiveness was based on the cohort of 210 subjects in Group A and 60 subjects in Group B available up to the Week 48 evaluation. A total of 9 subjects in Group A (one not treated, 5 randomized to *Restylane Contour*, and 3 subjects randomized to Control) and 2 subjects in Group B (one not treated) were excluded from the per protocol analysis population due to deviations considered to have substantial impact on the primary effectiveness outcome. Key effectiveness outcomes are presented in Table 16 through Table 18.

Study Endpoints

Primary Endpoint: The primary effectiveness analysis for Group A was a test of non-inferiority of *Restylane Contour* to Control. The Blinded Evaluator rated the subject's midface area for severity of contour deficiencies using the 4-point MMVS for the right and left side of the face. The change in score from baseline at Week 12 was the response variable. Scoring was based on a visual live assessment at defined time points, and not in comparison to the baseline appearance. The primary effectiveness analysis for Group B was a test of non-inferiority *Restylane Contour* administered with a cannula to *Restylane Contour* administered with a needle.

The study met its primary endpoint, demonstrating non-inferiority between *Restylane Contour* and Control for cheek augmentation and correction of midface contour deficiencies in Group A subjects. Additionally, improvements in Blinded Evaluator MMVS between baseline and Week 12 for Group B for both *Restylane Contour* injected by needle and *Restylane Contour* injected by cannula met the requirements for the primary endpoint.

The robustness of the results of the primary endpoint analyses were investigated across a number of subgroups (Study site, FST, Age, Race and Ethnicity). Results of the subgroup analyses did not raise questions about the effectiveness in these subgroups. Sensitivity analyses of the primary endpoint for Group A using the PP population and ITT population without imputation (i.e., observed cases only) also showed non-inferiority of *Restylane Contour* compared to Control. For Group B, sensitivity analyses also showed non-inferiority between *Restylane Contour* injected by needle and *Restylane Contour* injected by cannula.

Table 16 Summary of Change from Baseline to Week 12 in MMVS (ITT and PP Population)

Group A							
Population (Imputation)	**Group 1: *Restylane Contour***		**Group 2: Control**		**Difference (Group 1 – Group 2)**		
	LS Mean	**95% CI**	**LS Mean**	**95% CI**	**LS Mean**	**SE**	**95% CI**
ITT (Hot deck*)	-1.4	-1.48, -1.32	-1.3	-1.44, -1.20	-0.1	0.07	-0.22, 0.06
PP (Observed)	-1.4	-1.51, -1.35	-1.3	-1.44, -1.20	-0.1	0.07	-0.26, 0.03

Group B				
Change from Baseline to Visit 5 (Week 12)	***Restylane Contour* Cannula**	***Restylane Contour* Needle**	**Difference**	**95% CI**
n	60	60	60	
Mean (SD)	-1.3 (0.75)	-1.3 (0.74)	-0.1 (0.39)	(-0.15, 0.05)
Median	-1.0	-1.0	0	
Min, Max	(-3, 1)	(-3, 1)	(-1, 1)	

Missing MMVS values at Week 12 were handled using the hot deck imputation method. Non-inferiority margin=0.5.
CI=Confidence Interval; LS=Least Square; SE=Standard error

Secondary Effectiveness Analyses: The following secondary endpoints were evaluated to assess secondary effectiveness.

Blinded Evaluator MMVS, Over Time: For Group A, the majority of subjects treated with *Restylane Contour* achieved a 1-grade or greater improvement from baseline in MMVS on both sides of the face concurrently, as assessed by the Blinded Evaluator, at each of the timepoints.

Table 17 Responder Rates using the MMVS as Assessed by Blinded Evaluator at Each Visit: Observed Cases (ITT Population) Group A

Visit Category	Statistic	Group A	
		Restylane Contour **(N=142)**	**Control (N=68)**
Visit 5 (Week 12)	m/n (%)	125/137 (91.2)	57/65 (87.7)
At Least 1-Grade Improvement	95% CI	(85.20, 95.39)	(77.18, 94.53)
Visit 6 (Week 24)	m/n (%)	116/131 (88.5)	49/59 (83.1)
At Least 1-Grade Improvement	95% CI	(81.82, 93.45)	(71.03, 91.56)
Visit 7 (Week 36)	m/n (%)	93/129 (72.1)	51/61 (83.6)
At Least 1-Grade Improvement	95% CI	(63.52, 79.63)	(71.91, 91.85)
Visit 8 (Week 48)	m/n (%)	81/129 (62.8)	41/63 (65.1)
At Least 1-Grade Improvement	95% CI	(53.84, 71.14)	(52.03, 76.66)

Table 18 Responder Rates using the MMVS as Assessed by Blinded Evaluator at Each Visit: Observed Cases (ITT Population) Group B

Group B			
Visit	**Statistic**	***Restylane Contour*** **Cannula**	***Restylane Contour*** **Needle**
Visit 5 (Week 12)	m/n (%)	52/58 (89.7)	52/58 (89.7)
	95% CI	(78.83, 96.11)	(78.83, 96.11)
Visit 6 (Week 24)	m/n (%)	45/55 (81.8)	50/55 (90.9)
	95% CI	(69.10, 90.92)	(80.05, 96.98)
Visit 7 (Week 36)	m/n (%)	46/56 (82.1)	49/56 (87.5)
	95% CI	(69.60, 91.09)	(75.93, 94.82)
Visit 8 (Week 48)	m/n (%)	34/55 (61.8)	36/55 (65.5)
	95% CI	(47.73, 74.59)	(51.42, 77.76)

Subject and Treating Investigator GAIS: Independently of each other, the investigator and the subject evaluated the degree of improvement from baseline in the appearance of the subject's

midface area using the GAIS at each post-baseline visit. The majority of subjects (76.9–94.9%) in Group A who were treated with *Restylane Contour* reported aesthetic improvements (improved, much improved or very much improved) in the midface area across the Week 12, Week 24, Week 36 and Week 48 assessments using the GAIS. Similarly, across the same time points, Treating Investigators scored 86.9–97.8% of subjects in the *Restylane Contour* group as improved, using the GAIS.

In Group B, the proportion of subjects who reported aesthetic improvements (improved, much improved or very much improved) in the midface across the Week 12, Week 24, Week 36 and Week 48 assessments using the GAIS was very similar for *Restylane Contour* injected by cannula (90.7–98.2%) and *Restylane Contour* injected by needle (88.9–96.6%). Across the same timepoints, Treating Investigators scored 92.6–100% of subjects as improved using the GAIS, with no differences between *Restylane Contour* injected by cannula and *Restylane Contour* injected by needle at any visit.

Independent Photographic Reviewer's Assessment of Improvement of Midface Volume: Across all timepoints and for both sides of the face, the IPR (blinded to study treatment and visit name/date) considered the majority of Group A subjects treated with *Restylane Contour* (59.5–69.6%) and Control subjects (58.6–66.2%) to have achieved an improvement in cheek augmentation, based on comparison of random pairings of baseline and post-baseline photographs. Additionally, the IPR's left-side vs. right-side assessments were similar within each group at all visits (all ≤ 3.1 percentage-point differences).

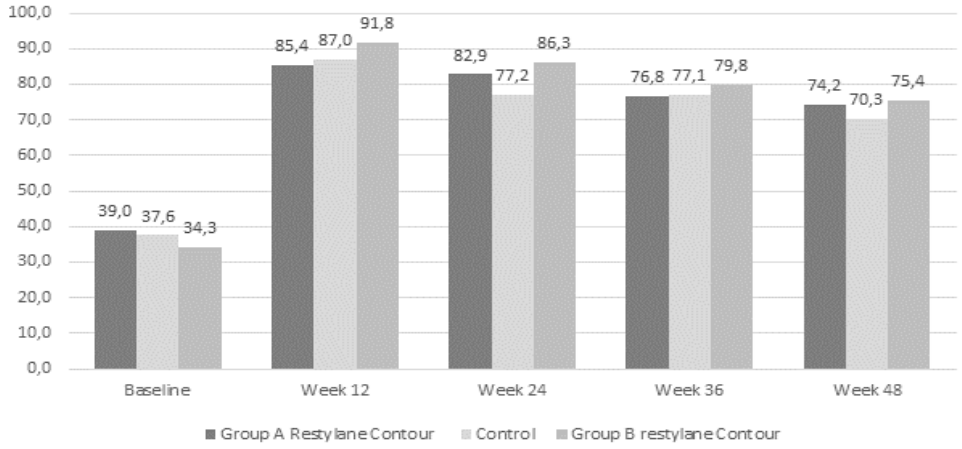
Likewise, for Group B, the IPR (blinded to study treatment and visit name/date) considered similar proportions of cheek augmentations by cannula (58.6–74.1%) and needle (56.9–68.5%) to reflect an improvement across all timepoints, based on comparison of random pairings of baseline and post-baseline photographs. There were no notable differences between the injection tools for any of the visits based on the IPR assessments (all ≤ 5.6 percentage-point differences).

3D Photography, Midface Volume Changes: Subjects treated with *Restylane Contour* showed mean increases from baseline in total midface volume of 3.3-2.7 mL [left side]; and 3.2-2.6 mL [right side].

Subject FACE-Q Questionnaire, Satisfaction with Cheeks: The FACE-Q questionnaire was used to assess treatment outcome from the subject's perspective at baseline, 12, 24, 36, and 48 weeks after randomization.

Mean total scores were similar between the treatment groups at baseline (Group A *Restylane Contour* [39.0], Group A Control [37.6], and Group B *Restylane Contour* [34.3]) on the 100-point scale), as shown in **Figure 1**. At Week 12, the mean total scores increased similarly across treatment groups (Group A [85.4] and Group B [91.8] *Restylane Contour*, as shown in **Figure 1**.

Figure 1: Summary of Change FACE-Q Satisfaction with Cheeks Rasch Transformed Total Score over Time, Group A and Group B, ITT Population



Subgroup Analyses

Safety: Exploratory safety analyses by subgroup (i.e., study site, age, median injection volume of ≤ 2.7 mL and > 2.7 mL, and FST) were evaluated.

A total of 10 of 13 Group A study sites had subjects who experienced related AEs; there were no obvious reporting trends for related AEs amongst the sites. Only 2 subjects from Group B experienced related AEs during the study, and the subjects were from different sites.

This study stratified subjects by FST group (I-III, IV, or V-VI). Combining *Restylane Contour* and Control Group A subjects together within each FST subgroup, reporting rates for related AEs were highest in the FST IV group following initial treatment: 16.4% vs. 26.9% vs. 4.3% for FST I-–III vs. IV vs. V-–VI skin types, respectively. Of the 7 FST IV subjects reporting related AEs, there were 4 Control and 3 *Restylane Contour* subjects. The 1 FST V-VI subject to report a related AE received Control treatment. The AE rates were similar amongst the FST groups following re-treatment: 11.0% (6 subjects each *Restylane Contour* and Control) vs. 7.1% (1 subject, Control) vs. 7.1% (1 subject, Control) for FST I-–III vs. IV vs. V-–VI skin types, respectively. Only 2 subjects from Group B experienced related AEs during the study, and the subjects were in different FST subgroups (FST I-III and FST IV).

Combining *Restylane Contour* and Control subjects together within each injection volume subgroup, reporting rates for related AEs were highest in the > median injection volume group following initial treatment, with 12.0% (12/100) subjects in the ≤ median injection volume group experiencing 1 or more related AEs compared with 20.2% (22/109) subjects in the > median injection volume group. The AE reporting rates for re-treatment were similar between the groups: 9.1% (5/55) subjects in the ≤ median injection volume group experienced 1 or more related AEs

compared with 11.0% (9/82) subjects in the > median injection volume group. Only 2 subjects from Group B experienced related AEs during the study, and the subjects were in the same injection volume subgroup (> median injection volume).

Results of the subgroup analysis by age did not raise questions about the safety in these subgroups. In Group A, the age groups 30-50 years, and >50 years had similar overall AE reporting rates for both the Restylane Contour and Control groups. The 20-29 years in the Restylane Contour group had similar AE reporting rates to the other age groups, but the Control group only had 1 subject; therefore, there was insufficient data to determine a trend.

The 30-50 years age group had the highest rate of related AEs in both the Restylane Contour (10/42 or 23.8%) and Control subjects (8/22 or 36.4%).

The Group B age group of 20-29 had only 1 subject who reported no AEs; therefore, there was insufficient data to determine trends with the other age groups. The other age groups (30-50 years and >50 years) had similar related AE reporting rates (30-50 years: 1/23 [4.3%]; >50 years: 1/35 [2.9%]).

Effectiveness: To evaluate the consistency of the primary effectiveness analysis, results across different subgroups (i.e., study site, FST, age, race and ethnicity) demonstrated that the results at Week 12 were consistent with the primary analysis based on the difference of means in the MMVS. Results of the subgroup analyses did not raise questions about the effectiveness in these subgroups.

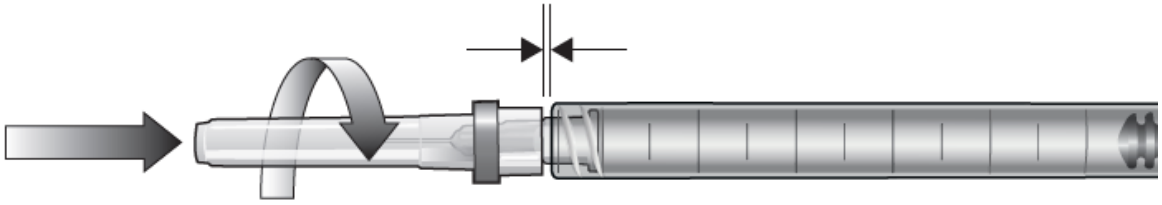
7 INSTRUCTIONS FOR USE

A. To Attach the Co-Packed Needle to Syringe

Use surgical gloves, remove the cap from the needle and the tip cap from the syringe. Hold firmly around the syringe barrel and grasp the needle shield with the other hand. Screw the needle tight onto the syringe by simultaneously pushing and rotating firmly until the needle is completely locked. To ensure proper assembly, minimize the gap between the needle shield and the syringe. See the figure below.

Remove the needle shield just before injection by pulling it straight out. Do not rotate.

Note: Improper assembly may cause leakage or needle disconnection.



B. Health Care Professional Instructions

1. *Restylane Contour* is a cross-linked formulation resulting in a robust injectable gel that can be injected using a 27 G needle or a blunt tip TSK STERiGLIDE cannula (25-27 G, length 1.5 or 2 inches) for correction of midface contour deficiencies and cheek augmentation.

2. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully appraised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to achieve and maintain the desired level of correction.

3. Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing.

4. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

    - ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines[1]

    - identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection

    - conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits

5. Aseptic technique and standard practice to prevent cross-infections should be observed at all times including the use of disposable gloves during the injection procedure. All traces of make-up below the level of the lower orbital rim should be removed prior to any injection. The treatment site should be cleaned with a suitable antiseptic solution.

6. To avoid breakage of the needle/cannula, do not attempt to bend or otherwise manipulate it before or during treatment. If needle/cannula gets bent, discard it and complete the procedure with a replacement needle/cannula. Do not re-shield used needles/cannula. Recapping by hand is a hazardous practice and should be avoided. Discard unshielded needles in approved sharps collectors.

7. Before injection, press the plunger rod carefully until a small droplet is visible at the tip of the needle and the plunger is at the 1 mL graduation mark.

8. If a needle is used, after insertion and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify the needle is not in a blood vessel. When using a cannula, an entry point is made in the skin with an incision needle of appropriate size.

9. Inject slowly by gently pressing down on the plunger rod with the thumb or palm of the hand. Do not apply excessive pressure to the syringe at any time. Presence of scar tissue may impede advancement of the needle/cannula. If resistance is encountered the needle/cannula should be partially withdrawn and repositioned or fully withdrawn and checked for function and replaced if needed.

10. The injection technique may vary based on the subject's treatment needs and the health care professional's experience and preference. The techniques may include Linear antegrade threading, Linear retrograde threading, Serial puncture, Depot, Fan technique or Other.

11. *Restylane Contour* should be injected in the supraperiosteal zone or subcutaneous region of the midface. Care should be taken to avoid intramuscular injection. It is recommended to change needle/cannula for each new treatment site.

12. It is important that the injection is stopped just before the needle/cannula is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.

13. It is recommended that the dose should not exceed 6 mL per treatment session. The recommended maximum injected volume per subject and treatment (touch-up volume included) is 12 mL.

14. Correct to 100% of the desired volume effect. Do not overcorrect.

15. 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.[1]

16. After each injection, the midface should be observed to assess the degree of enhancement and the uniformity of the implant. The area should be gently palpated to ensure an even deposition of the implant. Palpated "skip areas" (areas not containing product) should be treated with additional implant material or by gentle massage of the area until a uniform implant is palpable.

17. When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection should occur, the area should be firmly massaged between fingers to obtain optimal results. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period. Ice should be used with caution if the area is still numb from anaesthetic to avoid thermal injury.

18. Patients may experience treatment site responses, which typically resolve within 1 to 2 weeks.

19. The health care practitioner should instruct the patient to promptly report any problems associated with the use of *Restylane Contour*.

1. Jones, Derek; Fitzgerald, Rebecca; Cox, Sue Ellen; et al. Preventing and Treating Adverse Events of Injectable Fillers: Evidence-Based Recommendations from the American Society for Dermatologic Surgery Multidisciplinary Task Force, Dermatologic Surgery: February 2021 - Volume 47 - Issue 2 - p 214-226

C. Patient Instructions

- Patients should avoid heat (sun bathing, sauna, steam baths, etc.) or extreme temperatures until any signs of local inflammation have disappeared.

- The patient should be asked to avoid touching or shaving the treated area and not to apply any creams or cosmetics in the treated area before the skin has healed completely in order to prevent infections or elicit an inflammatory reaction.

- If the treated area is swollen, an ice pack may be applied to the site for a short period.

8 HOW SUPPLIED

Restylane Contour is supplied in individual treatment syringes with needles as indicated on the carton. The volume in each syringe is as stated on the syringe label and on the carton. The content of the syringe is sterile. Do not resterilize. Do not use if package is open or damaged.

SHELF LIFE AND STORAGE

Restylane Contour must be used prior to the expiration date on the package. Store at a temperature of up to 25ºC/77ºF. Do not freeze. Protect from sunlight. Refrigeration is not required.

Restylane Contour injectable gel has a clear appearance. In the event that a syringe contains material that is not clear, do not use the syringe; notify Galderma Laboratories, L.P. immediately at 1-855-425-8722.

Do not use if the package is damaged or if expiry date or lot number is missing or illegible. Immediately return the damaged product to Galderma Laboratories, L.P.

To place an order, contact Galderma Laboratories, L.P. at 1-855-425-8722

Rx only

U.S. Patent 8,357,795; 8,450,475; 8,822,676

SYMBOL GLOSSARY

SYMBOL	STANDARD	STANDARD TITLE	SYMBOL TITLE	EXPLANATORY TEXT
	ISO 15223-1 Ref. No. 5.1.1	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Manufacturer	Indicates the medical device manufacturer, as defined in EU Directive 90/385/EEC, 93/42/EEC and 98/79/EC.
	ISO 15223-1 Ref. No. 5.1.4	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Use-by date	Indicates the date after which the medical device is not to be used.
	ISO 15223-1 Ref. No. 5.1.5	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Batch code	Indicates the manufacturer's batch code so that the batch or lot can be identified.
	ISO 15223-1 Ref. No. 5.1.6	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Catalogue number	Indicates the manufacturer's catalogue number so that the medical device can be identified.
	ISO 15223-1 Ref. No. 5.2.4	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Sterilized using irradiation	Indicates a medical device that has been sterilized using irradiation.
	ISO 15223-1 Ref. No. 5.4.2	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Do not re-use	Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure.
	ISO 15223-1 Ref. No. 5.4.4	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Caution	Indicates the need for the user to consult the instructions for use for the important cautionary information such as warnings and precautions that cannot, for a variety of reasons, be presented on the medical device itself.

SYMBOLS NOT DERIVED FROM STANDARDS

SYMBOL	REFERENCE	REFERENCE TITLE	SYMBOL TITLE	EXPLANATORY TEXT
	21 CFR 801.15(c)(1)(i)F	Labeling - Medical devices; prominence of required label statements; use of symbols in labeling.	Prescription use only	Caution: Federal law restricts this device to sale by or on the order of a physician or properly licensed practitioner.
	21 CFR 801.109	Labeling – Prescription devices.		
	Medical Device Directive 93/42/EEC, Article 17	CE marking	CE marking	Signifies European technical conformity. 0123 is the notified body number for the TSK needles

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All other trademarks are the property of their respective owners.

Revised: xxx 202X
Part Number: XX-XXXXX