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.

Restylane Contour is indicated for correction of temple hollowing 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.
- *Restylane Contour* is contraindicated for patients with bleeding disorders.

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 and single-session use only. 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 in cheeks and midface.
- The recommended maximum injected volume for temple treatment is up to 3 mL per temple and treatment session
- The safety and effectiveness of cannula injection of *Restylane Contour* in cheeks and midface 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.
- The safety and effectiveness of cannula and needle injection of Restylane Contour in the temple area have only been clinically evaluated in one brand of blunt tip cannula and needle, TSK STERiGLIDE™ cannula that is 25G and 1.5 inch 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.
- 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 validated 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.

[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.

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

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)

Characteristic		Statistic	Treatment Group: Group A — *Restylane Contour*	Group A — Control	Group A — Overall	Group B — *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%)
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 s supraperiosteal 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 Table 13. Subject-reported injection related events are presented in Table 5 through Table 10. Physician-reported adverse events (AEs) are presented in Table 11 through Table 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.

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					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					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 the 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 and Table 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. US study of *Restylane Contour* for the correction of temple hollowing

Study Design

Subjects were treated between March 14, 2023 and October 26, 2023. The database for this PMA supplement reflected data collected through December 11, 2024. The study included 225 patients with temple hollowing that may result from intrinsic characteristics, the natural aging process, or weight loss.

The study was a prospective, randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the safety and effectiveness of treatment with *Restylane Contour* for the correction of temple hollowing. Subjects were randomized in a 4:1 ratio as follows:

- ***Restylane Contour* Treatment group:** Subjects in this group received supraperiosteal injections of *Restylane Contour* using a needle. In addition, subjects received superficial (subdermal) injections using either a needle or a blunt cannula.
- **No Treatment Control group:** Subjects in this group did not receive any injections at baseline. However, they were offered optional treatment at 3 months.

Randomization was stratified by Fitzpatrick skin type (FST) (I-III, IV or V-VI). Subjects in the FST I-III stratum were further stratified by study center; subjects in the FST IV or FST V-VI strata were not further stratified by study center due to the smaller sample size in these groups.

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 2 (moderate) to 3 (severe) on the 4-grade Galderma Temple Volume Deficit Scale for both temples as assessed by the Blinded Evaluator and the Treating Investigator
- Written informed consent
- Willing to abstain from any other facial plastic surgical or cosmetic procedures above the subnasale line for the duration of the study.

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 hyaluronic acid (HA) gel or to Gram-positive bacterial proteins
- History of allergy or hypersensitivity to local anesthetics, such as lidocaine or other amide-type anesthetics or nerve blocking agents
- Previous facial surgery above the level of the horizontal line from subnasale that in the Treating Investigator´s opinion could interfere with the study safety and/or effectiveness assessments
- Previous permanent filler or implant, lifting threads, or autologous fat in the face regardless of time

- Any of the following procedures performed above the level of the horizontal line from subnasale: use of calcium hydroxylapatite (CaHA) or poly-L-lactic acid (PLLA) within 24 months; use of HA filler or collagen filler within 12 months; botulinum toxin treatment within 6 months; energy based aesthetic procedures within 6 months; mechanical or chemical aesthetic procedures within 6 months; cryotherapy within 6 months
- Temple hollowing due to trauma, congenital malformations or lipodystrophy
- Abnormal temple firmness, detection of any abnormal temple structure or temple symmetry, or abnormal score for monofilament/cotton wisp tests
- Poor visual acuity or any history of severely impaired/absent eye function, or any other condition with the potential to cause a decline of visual acuity.

Follow-up Schedule

After providing informed consent, eligible subjects were randomized to the Treatment group or to the Control group at baseline (Day 1).

Subjects randomized to the Treatment group were injected on Day 1. Follow-up included a telephone call 72 hours after treatment and visits 2 weeks and 1 month after treatment. Optional touch-up treatment was offered 1 month after initial treatment if deemed necessary by the Treating Investigator and the subject. If a touch-up was performed, another 72-hour follow-up telephone call and follow-up visits after 2 weeks and 1 month were scheduled. Further follow-up visits were scheduled at 3, 6, 9, 12 and 18 months after baseline.

Subjects randomized to the Control group did not receive any treatment at baseline. However, they were offered optional treatment 3 months after baseline. For the subjects who accepted this optional treatment, a follow-up telephone call was made 72 hours after treatment and follow-up visits were scheduled 2 weeks, and 1, 3, 6, 9 and 12 months after treatment. Subjects who declined optional treatment after 3 months ended their study participation at the Month 3 visit.

Effectiveness and safety data were collected for up to 18 months after baseline. Subjects were involved in the study for up to 19 months (Treatment group) or up to 16 months (Control group), including a 21-day screening period. For subjects in the Control group who did not receive treatment at 3 months, study participation lasted approximately 4 months, including the screening period.

All subjects (both in the Treatment group and subjects who received optional treatment in the Control group) received supraperiosteal injections using a needle. In addition, a needle or a cannula was used for superficial (subdermal) injections. Supraperiosteal injection was performed with the co-packed needle perpendicular to the skin 1 cm inferior to the temporal crest in a vertical line 1 cm posterior to the lateral bony orbit by a small bolus. The superficial injection was performed with the co-packed needle by small aliquots, or the co-packed cannula by retrograde fanning, across the area with volume loss. Up to 3 mL of *Restylane Contour* was used per temple and treatment session, i.e., during initial treatment and touch-up for the Treatment group or during optional treatment at month 3 for the Control group.

Clinical Endpoints

With regard to safety, the endpoints were as follows: incidence, intensity, time to onset and duration of adverse events (AEs) collected throughout the study period; incidence, intensity and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days following each treatment; subject pain assessment before and immediately after treatment, using an 11-point Numeric Pain Scale (NPS); visual function assessments at baseline (before and after infection) and at all following physical visits; temple palpation, firmness and symmetry assessments, jaw functionality, and motor and sensory tests at screening, baseline and at each physical follow-up visit.

With regard to effectiveness, the primary endpoint was the Galderma Temple Volume Deficit Scale (GTVDS, Table 14) responder rate based on the Blinded Evaluators' live assessment at 3 months after baseline. A responder was defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.

Table 14. Galderma Temple Volume Deficit Scale (GTVDS)

0	None	No to minimal volume deficit; no concavity; no bony demarcation visible.
1	Mild	Mild volume deficit; minimal to mild concavity; no to minimal bony demarcation.
2	Moderate	Moderate volume deficit; moderate concavity; visible bony demarcation.
3	Severe	Severe volume deficit; severe concavity; pronounced bony demarcation.

The secondary effectiveness endpoints included:

- Responder rate at 3 months after baseline for the Treatment group compared to a reference standard responder rate of 50%.
- Responder rates at 6, 9, 12 and 18 months after baseline for the Treatment group; proportion of subjects, defined by having at least improved on the Global Aesthetic Improvement Scale (GAIS), on both sides of the face concurrently, as assessed by the subject and the Treating Investigator, at 3, 6, 9, 12 and 18 months after baseline for the Treatment group, or at 3, 6, 9 and 12 months after optional treatment for the Control group.
- Proportion of subjects in each response category for every question in the Subject Satisfaction Questionnaire (SSQ) at 3, 6, 9, 12 and 18 months after baseline for the Treatment group.
- Proportion of Treating Investigators in each response category for every question in the Investigator Satisfaction Questionnaire (ISQ) at 3 months after baseline for the Treatment group.
- Change from baseline in subject satisfaction using the FACE-Q™ Satisfaction with Temples questionnaire and proportion of subjects in each response category for each of the individual questions at 3, 6, 9, 12 and 18 months after baseline for the Treatment group or at baseline and at 3 months after baseline for the Control group.

- FACE-Q™ Satisfaction with Outcome Rasch-transformed total scores as well as proportion of subjects in each response category for each of the individual questions at 3, 6, 9, 12 and 18 months after baseline for the Treatment group.
- Responder rate based on the Independent Photographic Reviewer's (IPR) assessment using random pairings of baseline and post-baseline photographs from physical visits at 3 months after baseline for the Treatment and Control groups.
- Time in hours until the subject feels comfortable returning to social engagement after treatment, based on a follow-up question via telephone at 72 hours after treatment for the Treatment group.

With regard to success/failure criteria, the study success criterion was defined using the primary endpoint so that 1) the responder rate in the Treatment group would be different from the responder rate in the Control group with a 0.025 two-sided significance level and 2) the two-sided 97.5% confidence interval around the responder rate at Month 3 (for needle and/or cannula) would be completely above 50%.

Robustness of the results of the primary endpoint analysis was investigated across a number of subgroups (study site, race, ethnicity, sex at birth, age category, FST category and injection volume category). A subgroup analysis was also conducted to compare the responder rates at 3 months after baseline between subjects who received the 1-month touch-up treatment versus those who did not receive the 1-month touch-up treatment.

Accountability of PMA Cohort

At the time of database lock, of 225 subjects (181 *Restylane Contour*, 44 no treatment) patients enrolled in the PMA study and randomized, 203 (90.2%) subjects were available for analysis at the completion of the study (90.1% *Restylane Contour*, 90.9% no treatment). A summary of subject disposition is presented in Table 15. Of the 18 (9.9%) *Restylane Contour* subjects and 4 (9.1%) no-treatment subjects who did not complete the study, the most common reasons were loss to follow-up (9 [50.0%] *Restylane Contour* subjects, 2 [50.0%] no-treatment subjects) and withdrawal of consent (5 [27.8%] *Restylane Contour* subjects, 2 [50.0%] no-treatment subjects).

The intention-to-treat (ITT) population included all the subjects who were randomized.

The per-protocol population included all ITT subjects who completed the primary endpoint assessment at 3 months after baseline without any deviations considered to have a substantial impact on the primary effectiveness.

The safety population included all subjects who were treated with *Restylane Contour* or randomized to the no-treatment group (N=224).

Table 15. Summary of Subject Disposition

Category	Restylane Contour n (%)	No Treatment n (%)	Overall n (%)
Screened			253
Screen failure[1]			28 (11.1)
Randomized[1]	181 (71.5)	44 (17.4)	225 (88.9)
Completed study[2]	163 (90.1)	40 (90.9)	203 (90.2)
Did not complete study[2]	18 (9.9)	4 (9.1)	22 (9.8)
Reason did not complete study[3]			
Withdrew consent	5 (27.8)	2 (50.0)	7 (31.8)
Lost to follow-up	9 (50.0)	2 (50.0)	11 (50.0)
Adverse event	1 (5.6)	0	1 (4.5)
Other	3 (16.7)	0	3 (13.6)

1 Denominator for percentages is the number of screened subjects.
2 Denominator for percentages is the number of subjects per treatment in the intention-to-treat population.
3 Denominator for percentages is the number of subjects per treatment who did not complete the study.

Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a clinical study performed in the US among patients intending to undergo aesthetic procedures. The demographics and baseline characteristics of the study population are presented in Table 16. Demographics and baseline characteristics were generally similar between the 2 randomized groups.

The majority of subjects were female at birth (94.7%), White (89.3%), and not Hispanic or Latino (78.7%). The mean age was 56.8 years.

Among all subjects, the most common FST cohort at randomization was FST I-III (69.3%), followed by FST IV (20.4%) and FST V-VI (10.2%). Per the inclusion criteria, all subjects had moderate or severe volume deficit in the right and left temples, as assessed by the Blinded Evaluator using the GTVDS.

Table 16. Demographic and Baseline Characteristics (Intention-to-Treat Population)

Parameter	Restylane Contour (N=181)	No Treatment (N=44)	Overall (N=225)
Age at baseline (years)			
Mean (standard deviation)	56.5 (10.25)	58.1 (11.16)	56.8 (10.43)
Median	57.0	58.5	58.0
Minimum, maximum	26, 77	29, 79	26, 79
Age category at baseline, n (%)			
≤ITT population median age (58 years)	104 (57.5)	22 (50.0)	126 (56.0)
>ITT population median age (58 years)	77 (42.5)	22 (50.0)	99 (44.0)
Sex at birth, n (%)			
Female	173 (95.6)	40 (90.9)	213 (94.7)
Male	8 (4.4)	4 (9.1)	12 (5.3)
Gender identity, n (%)			
Female	173 (95.6)	40 (90.9)	213 (94.7)
Male	8 (4.4)	4 (9.1)	12 (5.3)
Race, n (%)			
White	163 (90.1)	38 (86.4)	201 (89.3)
Black/African American	15 (8.3)	4 (9.1)	19 (8.4)
Asian	4 (2.2)	1 (2.3)	5 (2.2)
Asian Indian	2 (1.1)	0	2 (0.9)
Japanese	2 (1.1)	1 (2.3)	3 (1.3)
American Indian/Alaska Native	1 (0.6)	1 (2.3)	2 (0.9)
Other	2 (1.1)	1 (2.3)	3 (1.3)
Ethnicity, n (%)			
Hispanic or Latino	37 (20.4)	11 (25.0)	48 (21.3)
Not Hispanic or Latino	144 (79.6)	33 (75.0)	177 (78.7)
FST cohort at randomization, n (%)			
I-III	127 (70.2)	29 (65.9)	156 (69.3)
IV	36 (19.9)	10 (22.7)	46 (20.4)
V-VI	18 (9.9)	5 (11.4)	23 (10.2)
Right temple GTVDS-Blinded Evaluator, n (%)			
2-Moderate	104 (57.5)	24 (54.5)	128 (56.9)
3-Severe	77 (42.5)	20 (45.5)	97 (43.1)
Left temple GTVDS-Blinded Evaluator, n (%)			
2-Moderate	103 (56.9)	24 (54.5)	127 (56.4)
3-Severe	78 (43.1)	20 (45.5)	98 (43.6)

FST=Fitzpatrick Skin Type; GTVDS=Galderma Temple Volume Deficit Scale; ITT=intention-to-treat.

In this study, *Restylane Contour* was administered in the temple area by needle for supraperiosteal injections and by cannula or needle for subdermal (superficial) injections. The injection volumes (left and right temples combined) at each injection timepoint and for each randomized group are presented in Table 17.

Table 17. Injection Volume (mL) Administered by Injection Timepoint (Safety Population)

	Restylane Contour (N=181)			No Treatment (N=43)	
Statistic	**Initial Treatment**	**Optional Touch-up Treatment**	**Total Injected Volume**	**Initial Treatment at Month 3[1]**	**Total Injected Volume**
n	181	142	181	40	40
Mean (SD)	2.189 (0.8542)	0.919 (0.6933)	2.910 (1.2666)	2.400 (0.9229)	2.400 (0.9229)
Median	2.000	0.750	2.500	2.400	2.400
Minimum, maximum	0.80, 5.50	0.10, 4.00	1.20, 7.60	0.90, 4.00	0.90, 4.00

SD=standard deviation

1. Subjects with no treatment at baseline.

A summary of injection characteristics is presented in Table 18.

At initial treatment and at optional touch-up treatment, a 27-gauge × ½ inch ultra-thin wall needle was used for supraperiosteal injections.

A 27-gauge × ½ inch ultra-thin wall needle or a 25-gauge × 1½ inch STERiGLIDE cannula from TSK was used for subdermal (superficial) injections at initial treatment. In the *Restylane Contour* and no-treatment (at baseline) groups, subjects received subdermal injections via needle (49.2% and 37.5%, respectively) or cannula (51.4% and 62.5%, respectively). In the *Restylane Contour* and no-treatment (at baseline) groups, the most frequent injection method used for supraperiosteal injection was bolus (100% for each group). The most frequent injection methods used for subdermal injection were linear threading (47.5% and 60.0%, respectively) and fanning (35.4% and 42.5%, respectively).

Ten subjects were injected with a different injection tool at touch-up compared with the initial treatment in the subdermal layer.

No touch-up treatments were performed in the no-treatment group per protocol.

A 27-gauge × ½ inch ultra-thin wall needle or a 25-gauge × 1½ inch STERiGLIDE cannula from TSK was used for subdermal injections at optional touch-up. Subjects received subdermal injections via needle (52.6%) or cannula (47.4%). The most frequent injection method used for supraperiosteal injection at optional touch-up was bolus (99.0%). The most frequent injection methods used for subdermal injection were fanning (38.9%) and linear threading (34.7%).

Table 18. Injection Characteristics by Injection Timepoint (Safety Population)

Characteristic	Restylane Contour (N=181)		No Treatment (N=43)
	Initial Treatment	Optional Touch-up Treatment	Initial Treatment at Month 3[1]
Subjects treated, n	181	142	40
Injection depth (supraperiosteal), m/n (%)			
Supraperiosteal	180/180 (100)	104/104 (100)	39/39 (100)
Injection depth (subdermal [superficial]), m/n (%)			
Subdermal	181/181 (100)	95/95 (100)	40/40 (100)
Injection method (supraperiosteal), m/n (%)			
Bolus	180/180 (100)	103/104 (99.0)	39/39 (100)
Linear threading	0/180	0/104	1/39 (2.6)
Serial puncture	11/180 (6.1)	5/104 (4.8)	3/39 (7.7)
Injection method (subdermal [superficial]), m/n (%)			
Bolus	13/181 (7.2)	11/95 (11.6)	0/40
Linear threading	86/181 (47.5)	33/95 (34.7)	24/40 (60.0)
Serial puncture	44/181 (24.3)	23/95 (24.2)	6/40 (15.0)
Fanning	64/181 (35.4)	37/95 (38.9)	17/40 (42.5)
Tunneling	21/181 (11.6)	7/95 (7.4)	3/40 (7.5)
Injection tool (supraperiosteal), m/n (%)			
Co-packed 27G × ½" UTW needle	180/180 (100)	104/104 (100)	39/39 (100)
Injection tool (subdermal [superficial]), m/n (%)			
Co-packed 27G × ½" UTW needle	89/181 (49.2)	51/97 (52.6)	15/40 (37.5)
Cannula size (subdermal [superficial]), m/n (%)			
25G × 1½" Steriglide[2]	93/181 (51.4)	46/97 (47.4)	25/40 (62.5)

m=number of subjects who met the criterion, n=number of subjects with non-missing assessment; UTW=ultra-thin wall; 1. Subjects with no treatment at baseline; 2. TSK cannula brand.

Safety Results

The analysis of safety was based on the safety population of 224 subjects, which included all subjects who were treated with *Restylane Contour* or randomized to the no-treatment group. The key safety outcomes for this study are presented below.

Pre-identified symptoms: Subjects who received treatment were asked to record pre-identified symptoms in a diary over the first 28 days after each treatment. The symptoms that were experienced are summarized in Table 19. The percentage of subjects experiencing pre-defined, expected post-treatment events (i.e., pain, tenderness, redness, bruising, swelling, itching, or lumps/bumps) at initial treatment was similar between the *Restylane Contour* group and subjects randomized to no treatment at baseline who had optional treatment at Month 3 (84.7% and 79.5%, respectively). The percentage of subjects in the *Restylane Contour* group with expected post-treatment events at the touch-up treatment was 58.7%.

In the *Restylane Contour* group, the majority of subjects reported symptoms that were tolerable after initial treatment (range: 89.5% to 96.9%) and touch-up treatment (range: 96.3% to 100%). The most common pre-defined, expected post-treatment events after initial treatment and touch-up treatment were tenderness (71.2% and 50.0% of subjects, respectively), lumps/bumps (59.9% and 34.1% of subjects,

respectively), and swelling (55.4% and 32.6% of subjects, respectively). Only 1 (0.7%) subject reported disabling symptoms (lumps/bumps) after initial treatment; no disabling symptoms were reported after touch-up treatment.

Among subjects randomized to no treatment at baseline, the majority of subjects reported symptoms that were tolerable after initial treatment at Month 3 (range: 85.7% to 100%). The most common pre-defined, expected post-treatment events were tenderness and lumps/bumps (61.5% each), swelling (56.4%), and bruising (51.3%). No subject reported disabling symptoms.

In both the *Restylane Contour* and the no-treatment groups, the majority of subjects with pre-defined diary symptoms had resolution of their symptoms within the first 7 days after treatment.

Table 19. Summary of Subject Diary Events by Injection Timepoint and Maximum Intensity (Safety Population)

	Restylane Contour				No Treatment at Baseline			
Characteristic	Tolerable n (%)	Affects Daily Activities n (%)	Disabling n (%)	Total n (%)	Tolerable n (%)	Affects Daily Activities n (%)	Disabling n (%)	Total n (%)
After Initial Treatment (N=177 for Restylane Contour and N=39 for No Treatment at Baseline)								
Pain (including burning)	87 (95.6)	4 (4.4)	0	91 (51.4)	15 (88.2)	2 (11.8)	0	17 (43.6)
Tenderness	120 (95.2)	6 (4.8)	0	126 (71.2)	22 (91.7)	2 (8.3)	0	24 (61.5)
Redness	63 (96.9)	2 (3.1)	0	65 (36.7)	9 (100)	0	0	9 (23.1)
Bruising	72 (93.5)	5 (6.5)	0	77 (43.5)	19 (95.0)	1 (5.0)	0	20 (51.3)
Swelling	93 (94.9)	5 (5.1)	0	98 (55.4)	22 (100)	0	0	22 (56.4)
Itching	17 (89.5)	2 (10.5)	0	19 (10.7)	6 (85.7)	1 (14.3)	0	7 (17.9)
Lumps/bumps	101 (95.3)	4 (3.8)	1 (0.9)	106 (59.9)	23 (95.8)	1 (4.2)	0	24 (61.5)
Total	136 (90.7)	13 (8.7)	1 (0.7)	150 (84.7)	28 (90.3)	3 (9.7)	0	31 (79.5)
After Touch-up Treatment (N=138 for Restylane Contour)								
Pain (including burning)	52 (96.3)	2 (3.7)	0	54 (39.1)	N/A	N/A	N/A	N/A
Tenderness	69 (100)	0	0	69 (50.0)	N/A	N/A	N/A	N/A
Redness	27 (96.4)	1 (3.6)	0	28 (20.3)	N/A	N/A	N/A	N/A
Bruising	34 (100)	0	0	34 (24.6)	N/A	N/A	N/A	N/A
Swelling	45 (100)	0	0	45 (32.6)	N/A	N/A	N/A	N/A
Itching	10 (100)	0	0	10 (7.2)	N/A	N/A	N/A	N/A
Lumps/bumps	46 (97.9)	1 (2.1)	0	47 (34.1)	N/A	N/A	N/A	N/A
Total	77 (95.1)	4 (4.9)	0	81 (58.7)	N/A	N/A	N/A	N/A

n=number of subjects who completed at least 1 diary entry and were injected; N/A=not applicable

Tolerable columns percentages were based on the total number of subjects who reported 'Tolerable' or higher for a respective symptom in their subject diary; the total column percentages were based on the number of subjects who completed at least 1 diary entry and were injected. Maximum intensity between both temples is presented.

Adverse Events: Each subject was questioned about adverse events (AEs) at each study visit following the screening visit. AE information could have also been obtained from signs and symptoms detected during each examination by the Investigator or designee, which should have included visual inspection of the treatment area or from a laboratory test, subject diaries, or spontaneous reports from subjects or their relatives.

A summary of AEs is presented in Table 20. Sixty-one (33.7%) *Restylane Contour* subjects and 10 (25.0%) subjects who received no treatment at baseline and optional treatment at Month 3 experienced at least 1 AE during the study. Nineteen (10.5%) *Restylane Contour* subjects and 2 (5.0%) subjects who received no treatment at baseline and optional treatment at Month 3 experienced an AE considered related to study product or injection procedure. Seven (3.9%) *Restylane Contour* subjects and 1 (2.5%) subject who received no treatment at baseline and optional treatment at Month 3 experienced a serious AE (SAE), each of which was considered unrelated to study product or injection procedure. One (0.6%) *Restylane Contour* subject experienced an AE leading to study discontinuation. Four (2.2%) *Restylane Contour*

subjects and 1 (2.5%) subject who received no treatment at baseline and optional treatment at Month 3 experienced an AE of special interest (AESI), with 2 (1.1%) of the *Restylane Contour* subjects experiencing serious AESIs. No subject died during the study.

Table 20. Adverse Event Overview – Initial Treatment + Touch-up (Safety Population)

Subjects with at least 1:	Restylane Contour (N=181) n (%)	No Treatment at Baseline (N=40) n (%)	Overall (N=221) n (%)
Any AE	61 (33.7)	10 (25.0)	71 (32.1)
Of which were serious	7 (3.9)	1 (2.5)	8 (3.6)
Of which led to study discontinuation	1 (0.6)	0	1 (0.5)
Any AE related to study product or injection procedure	19 (10.5)	2 (5.0)	21 (9.5)
Of which were serious	0	0	0
Any AE unrelated to both study product and injection procedure	50 (27.6)	9 (22.5)	59 (26.7)
Of which were serious	7 (3.9)	1 (2.5)	8 (3.6)
Any AESI	4 (2.2)	1 (2.5)	5 (2.3)
Of which were serious	2 (1.1)	0	2 (0.9)
Any AE ongoing at the end of the study	20 (11.0)	1 (2.5)	21 (9.5)
Subjects who did not have an AE	120 (66.3)	30 (75.0)	150 (67.9)

AE=adverse event; AESI=adverse event of special interest

Note: AESIs included all incidences of visual disturbances, jaw functionality abnormalities, and stroke, regardless of relationship to study product or seriousness.

A summary of AEs experienced by >1 subject in either group (i.e., subjects in the Restylane Contour group and subjects in the no-treatment group who received optional initial treatment at Month 3) is presented in Table 21. The most common AEs were headache (17 [9.4%] Restylane Contour subjects and 2 [5.0%] no-treatment subjects), implant site pain (12 [6.6%] Restylane Contour subjects and 2 [5.0%] no-treatment subjects), and COVID-19 (5 [2.8%] Restylane Contour subjects and 3 [7.5%] no-treatment subjects).

Table 21. Adverse Events by Preferred Term Experienced by >1 Subject in Either Group – Initial Treatment + Touch-up (Safety Population)

Preferred Term	Restylane Contour (N=181) n (%)	No Treatment at Baseline (N=40) n (%)	Overall (N=221) n (%)
Subjects with at least 1 adverse event	61 (33.7)	10 (25.0)	71 (32.1)
Headache	17 (9.4)	2 (5.0)	19 (8.6)
Implant site pain	12 (6.6)	2 (5.0)	14 (6.3)
COVID-19	5 (2.8)	3 (7.5)	8 (3.6)
Nasopharyngitis	3 (1.7)	0	3 (1.4)
Actinic keratosis	3 (1.7)	0	3 (1.4)
Back pain	2 (1.1)	0	2 (0.9)
Dry eye	2 (1.1)	0	2 (0.9)
Visual acuity reduced	2 (1.1)	0	2 (0.9)
Hypercholesterolaemia	2 (1.1)	0	2 (0.9)
Anxiety	2 (1.1)	0	2 (0.9)
Depression	2 (1.1)	0	2 (0.9)
Constipation	2 (1.1)	0	2 (0.9)

Note: Adverse events were coded using Medical Dictionary for Regulatory Activities Version 25.1. Subjects were counted once for each preferred term. This table includes adverse events from subjects randomized to *Restylane Contour* that started after randomization plus adverse events from subjects randomized to no treatment that started on/after their optional initial treatment at Month 3.

A summary of AEs related to study product or injection procedure is presented in Table 22. The only AEs considered related to study product or injection procedure were implant site pain (12 [6.6%] *Restylane Contour* subjects and 2 [5.0%] subjects who received no treatment at baseline and optional treatment at Month 3) and headache (10 [5.5%] *Restylane Contour* subjects).

Reported terms for implant site pain included descriptions such as “jaw pain,” “implant site pain,” “jaw ache,” “jaw muscle soreness,” “tenderness with chewing while opening and closing mouth,” “jaw pain when eating, opening and closing mouth,” “bilateral back part of the jaw stiffness, hard to open mouth, uncomfortable,” “jaw hurts when chewing,” “jaw tenderness,” “sore jaw when yawning,” and “tenderness (temples).” In the majority of cases, the probable root cause was indicated to be the local tissue response following needle puncture at the injection site.

Of the 14 subjects who experienced implant site pain, all events resolved without any action taken and the majority were considered not related to study product and related to injection procedure. The duration of events ranged from 1 to 5 days.

Table 22. Related Adverse Events by Preferred Term - Initial Treatment + Touch-up (Safety Population)

Preferred Term	Restylane Contour (N=181) n (%)	No Treatment at Baseline (N=40) n (%)	Overall (N=221) n (%)
Subjects with at least 1 related adverse event	19 (10.5)	2 (5.0)	21 (9.5)
Implant site pain	12 (6.6)	2 (5.0)	14 (6.3)
Headache	10 (5.5)	0	10 (4.5)

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.1. Subjects were counted once for each preferred term. Related adverse events have a relationship of reasonable possibility to study product or injection procedure.

No subject experienced an AE with late onset (>21 days after the most recent treatment).

All AEs related to study product or injection procedure were mild or moderate in intensity regardless of injection tool used. Of the 21 (9.5%) subjects who had an AE related to study product or injection procedure, no action was required for 20 subjects and medication was given (paracetamol) for 1 event of mild implant site pain in 1 subject.

Overall, the mean time to onset of AEs related to study product or injection procedure was 0.6 days for headache to 0.7 days for implant site pain following the most recent treatment. The mean duration of AEs related to study product or injection procedure was 2.6 days for implant site pain and 3.3 days for headache.

One (0.6%) *Restylane Contour* subject experienced SAEs leading to premature study discontinuation (lung carcinoma cell type unspecified stage IV, transient ischaemic attack and cerebrovascular accident). Each of these SAEs was considered severe and unrelated to study product or injection procedure.

Four (2.2%) *Restylane Contour* subjects and 1 (2.5%) subject who received no treatment at baseline and optional treatment at Month 3 experienced at least 1 AE of special interest (AESI). All AESIs were considered mild in intensity, except for the SAEs that led to premature study discontinuation of the subject described above. All AESIs were considered not related to study product or injection procedure.

Subjects who experienced SAEs are presented in Table 23.

Table 23. Subjects with Serious Adverse Events (Safety Population)

Subject number	Age/Gender/ Race	Preferred term	Start day/ end day	Days to onset/ Last treatment	Intensity	Related to study product/ injection procedure	Outcome
Randomized to *Restylane Contour* at baseline							
8478-007	66/Female/White	Sepsis	398/419	397/Initial	Severe	No/No	Recovered
8478-009	55/Female/White	Appendicitis	135/208	102/Optional TU	Severe	No/No	Recovered
		Diverticulitis intestinal perforated	283/288	250/ Optional TU	Severe	No/No	Recovered
8478-017	58/Female/White	Loss of consciousness	460/460	424/Optional TU	Severe	No/No	Recovered
		Facial bones fracture	460/462	424/Optional TU	Severe	No/No	Recovered
		Subdural haematoma	460/462	424/Optional TU	Severe	No/No	Recovered
8482-001	69/Female/White	Retinal tear[1]	26/ongoing	25/Initial	Severe	No/No	Not resolved/ ongoing
8648-012	75/Female/Black/ African American	Back pain	77/127	43/Optional TU	Severe	No/No	Recovered
		Pulmonary embolism	168/171	134/ Optional TU	Severe	No/No	Recovered
8774-006	67/Female/White	Lung carcinoma cell type unspecified stage IV[2]	131/ongoing	96/Optional TU	Severe	No/No	Not resolved/ ongoing
		Transient ischaemic attack[1,2]	148/152	113/Optional TU	Severe	No/No	Recovered
		Cerebrovascular accident[1,2]	155/161	120/ Optional TU	Severe	No/No	Recovered with sequelae: aphasia
8774-007	67/Female/White	Coronary artery disease	415/420	379/Optional TU	Severe	No/No	Recovered
Randomized to no treatment at baseline and received optional *Restylane Contour* treatment at Month 3							
8679-001	44/Male/Black/ African American	Appendicitis	83/84	13/Optional Month 3	Severe	No/No	Recovered
		Anal fistula	120/293	50/Optional Month 3	Severe	No/No	Recovered

TU=touch-up

[1] Event was an adverse event of special interest.

[2] Event led to study discontinuation.

Device deficiencies: One subject in the *Restylane Contour* group experienced a device deficiency (i.e., needle/cannula disconnected) during the study. No AE was reported for this subject due to the deficiency.

Other safety assessments: Mean left and right temple Numeric Pain Scale (NPS) scores post-injection at initial treatment were 0.7 and 0.8, respectively, in the *Restylane Contour* group and 0.4 and 0.4, respectively, in subjects randomized to no treatment at baseline. No clinically meaningful results were reported from visual function assessments, temple palpation, firmness and symmetry assessments, motor and sensory tests, or jaw functionality tests.

C. 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
- short duration of effect
- erythema
- inflammation
- ischemia and necrosis including pallor, livedo reticularis, due to unintentional intravascular injection or embolization
- bruising/hematoma
- presumptive bacterial infections/abscess formation including purulent discharge and pustules
- injection site reactions including warmth, burning sensation and exfoliation
- hypersensitivity/angioedema
- discoloration
- neurological symptoms including hypoesthesia, paresthesia, nerve compression and facial nerve paralysis
- device dislocation
- eye disorders including eye pain, eyelid oedema, ocular discomfort, blurred vision
- granuloma/foreign body reaction
- asymmetry/deformity
- pruritus
- symptoms of reactivation of herpes infection
- skin atrophy/scarring/scab
- blisters/vesicles
- urticaria
- rash
- extrusion of device
- acne
- encapsulation
- muscle disorders including muscle edema
- dermatitis

- non-dermatological events including headache, dizziness, influenza-like symptoms such as chills, pyrexia and malaise, nausea, seizure 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.

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.

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

7 CLINICAL STUDIES

A. US 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 24 and for Group B in Table 25.

Table 24. 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 25. 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 26 through Table 28.

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 26. 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 27. 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 28. 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.

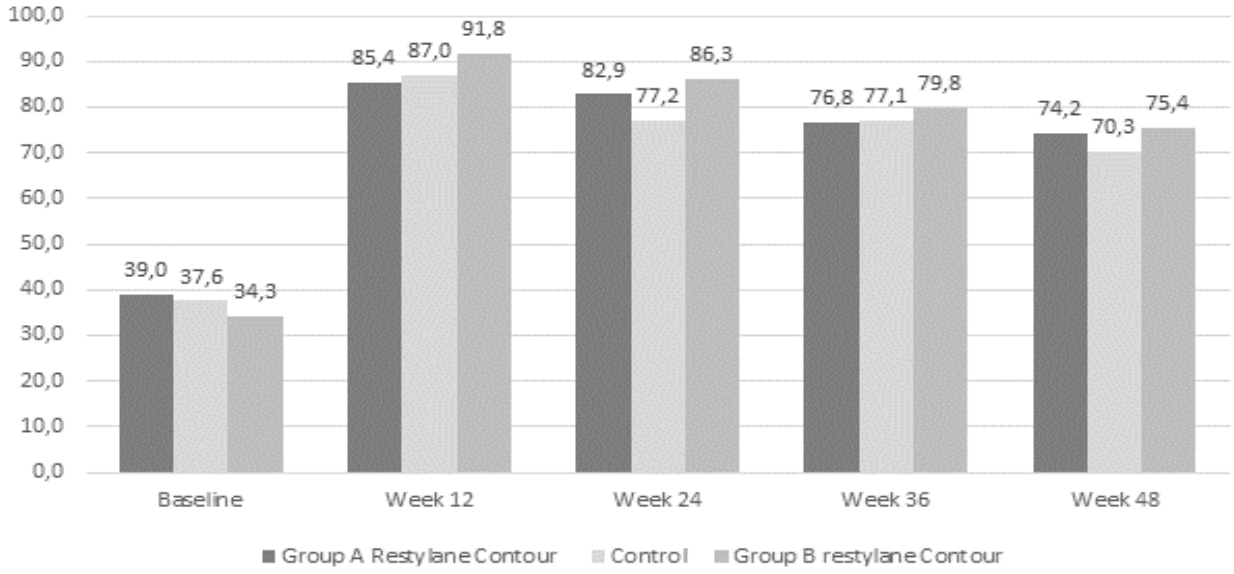


Figure 1. Summary of Change FACE-Q Satisfaction with Cheeks Rasch Transformed Total Score over Time, Group A and Group B, ITT Population

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.

B. US Study of *Restylane Contour* for the correction of temple hollowing

Study Design

The study was a prospective, randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the safety and effectiveness of treatment with *Restylane Contour* for the correction of temple hollowing. Subjects were randomized in a 4:1 ratio as follows:

- ***Restylane Contour* Treatment group:** Subjects in this group received supraperiosteal injections of *Restylane Contour* using a needle. In addition, subjects received superficial (subdermal) injections using either a needle or a blunt cannula.
- **No Treatment Control group:** Subjects in this group did not receive any injections at baseline. However, they were offered optional treatment at 3 months.

Randomization was stratified by Fitzpatrick skin type (FST) (I-III, IV or V-VI). Subjects in the FST I-III stratum were further stratified by study center; subjects in the FST IV or FST V-VI strata were not further stratified by study center due to the smaller sample size in these groups.

Subject Demographics

In total, 225 subjects were randomized to the Treatment group or to the Control group. Subject demographics for each group are presented in Table 16.

Effectiveness Results

The analysis of effectiveness was based on the 181 evaluable subjects in the Treatment group at 3, 6, 9, 12 and 18 months after baseline and on the 44 evaluable subjects in the Control group at 3, 6, 9 and 12 months after optional treatment.

Study Endpoints

Primary Endpoint: The primary effectiveness endpoint was the responder rate based on the Blinded Evaluators' live assessment of the Galderma Temple Volume Deficit Scale (GTVDS) at 3 months after baseline. A responder was defined as a subject with at least a 1-point improvement from baseline in both temples concurrently on the GTVDS.

As shown in Table 29 the responder rate at Month 3 was significantly higher in the *Restylane Contour* group than in the no-treatment group for both needle (87.6% versus 9.1%, respectively; $p<0.001$) and cannula (95.7% versus 9.1%, respectively; $p<0.001$) injection tools used for subdermal injections and overall (91.2% versus 9.1%, respectively; $p<0.001$).

Both study success criteria for the primary effectiveness endpoint were met: 1) the 2 Chi-square tests for needle and cannula subdermal injection tools resulted in p-values ($p<0.001$) below the significance level of 0.025 and 2) the corresponding 2-sided 97.5% CI around the responder rate at Month 3 (for needle and cannula subdermal injection tools) was completely above 50% (lower limit of 80.6% for needle and 91.8% for cannula).

Table 29. Responder Rate Based on the Galderma Temple Volume Deficit Scale (Blinded Evaluator) at Month 3 (Multiple Imputation – Intention-to-Treat Population)

Statistic	Restylane Contour (N=181)	No Treatment (N=44)
Total		
Responder rate, m/n (%)[1]	(91.2)	(9.1)
97.5% confidence interval[2]	86.85, 95.47	0.73, 19.27
Treatment difference (*Restylane Contour* - no treatment), %[2,3]		82.1
97.5% confidence interval		70.78, 91.54
P-value[4]		<0.001
Needle for subdermal (superficial) injections		
Responder rate, m/n (%)[1]	(87.6)	(9.1)
97.5% confidence interval[2]	80.56, 94.29	0.73, 19.27
Treatment difference (*Restylane Contour* - no treatment), %[2,3]		78.5
97.5% confidence interval		65.73, 89.11
P-value[4]		<0.001
Cannula for subdermal (superficial) injections		
Responder rate, m/n (%)[1]	(95.7)	(9.1)
97.5% confidence interval[2]	91.84, 100	0.73, 19.27
Treatment difference (*Restylane Contour* - no treatment), %[2,3]		86.6
97.5% confidence interval		75.69, 96.22
P-value[4]		<0.001

[1] Responder rate was defined as the number and percentage of subjects with at least 1-grade improvement from baseline based on the GTVDS in both temples concurrently, as assessed by the Blinded Evaluator.

[2] 97.5% confidence interval for responder rates and difference were calculated using the normal approximation (Wald) method.

[3] Difference=*Restylane Contour* responder rate – no-treatment responder rate.

[4] P-value was from a Chi-square test of responder rates between the *Restylane Contour* and no-treatment groups.

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

Responder rate, as assessed by the Blinded Evaluator, at Month 3 after baseline for the treatment group compared to a reference standard responder rate of 50%: The responder rate at Month 3 was superior (p<0.001) to the reference standard responder rate of 50% overall (91.9%) and for both needle (88.0%) and cannula (96.7%) injection tools used for subdermal injections.

Responder rates, as assessed by the Blinded Evaluator, at 6, 9 and 12 months after baseline for the treatment group: The responder rate was, overall, 94.6% at Month 6, 92.8% at Month 9 and 91.6% at Month 12. The responder rate was similar between needle and cannula for subdermal injections at Month 6 (92.3% and 96.6%, respectively), Month 9 (90.0% and 95.4%, respectively), and Month 12 (91.1% and 93.0%, respectively).

Responder rate, as assessed by the Blinded Evaluator, at 18 months after baseline for the treatment group: The responder rate was 86.1% at Month 18 overall and similar between needle and cannula injection tools used for subdermal injections at Month 18 (84.3% and 88.4%, respectively).

A summary of the responder rate as assessed by the Blinded Evaluator over time in the treatment group is presented graphically in Figure 2.

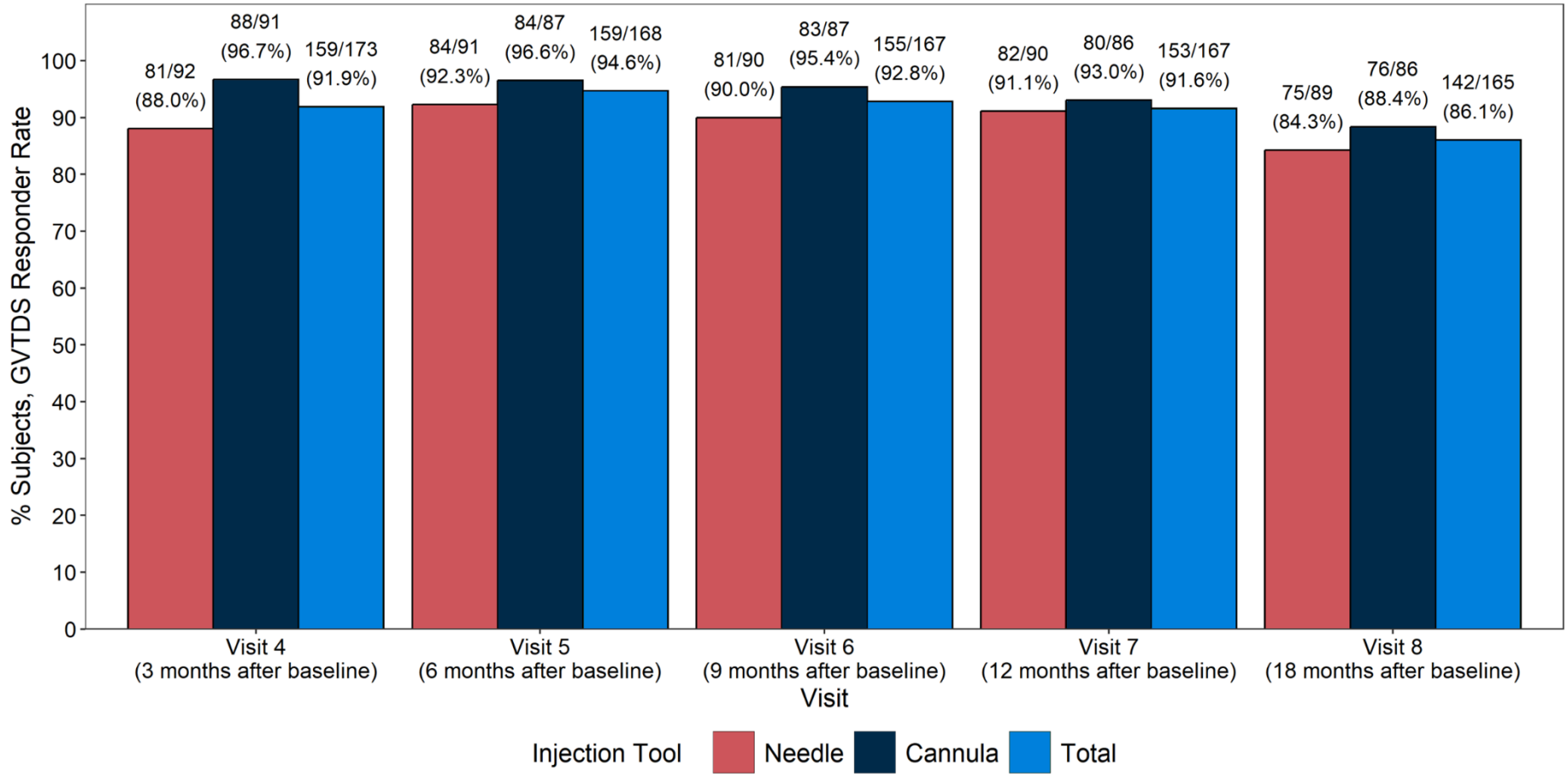


Figure 2. Responder Rate Based on the Galderma Temple Volume Deficit Scale by Visit (Blinded Evaluator) – Treatment Group (Observed Cases – Intention-to-Treat Population)

Proportion of subjects having at least "Improved" (improved, much improved, or very much improved) on the Global Aesthetic Improvement Scale (GAIS), on both sides of the face (each temple) concurrently, as assessed by the subject and the Treating Investigator, respectively, at 3, 6, 9, 12 and 18 months after baseline for the treatment group: GAIS improvement rates as assessed by the subject ranged from 80.6% at Month 18 to 96.0% at Month 3 in the treatment group. GAIS improvement rates as assessed by the Treating Investigator ranged from 88.5% at Month 18 to 100% at Month 3 in the Restylane Contour group.

Proportion of subjects having at least "Improved" on the GAIS, on both sides of the face (each temple) concurrently, as assessed by the subject and the Treating Investigator, respectively, at 3, 6, 9, 12 and 18 months after optional treatment for the no-treatment group: GAIS improvement rates as assessed by the subject ranged from 81.6% at 9 and 12 months to 92.3% at 3 months after optional treatment. GAIS improvement rates as assessed by the Treating Investigator ranged from 92.1% at 9 and 12 months to 97.4% at 3 months after optional treatment.

Proportion of subjects in each response category for every question in the Subject Satisfaction Questionnaire (SSQ) at 3, 6, 9, 12 and 18 months after last treatment for the treatment group: The majority of subjects in the treatment group would recommend the treatment to a friend (Month 3 to Month 18 range: 92.1% to 95.2%) and would choose to receive the treatment again (Month 3 to Month 18 range: 90.3% to 92.2%). Almost all subjects (97.1%) in the treatment group were satisfied with how quickly they could go back to social engagements at Month 3.

Proportion of Treating Investigators in each response category for every question in the Investigator Satisfaction Questionnaire (ISQ) at 3 months after baseline for the treatment group: Almost all Treating Investigators responded as "agree" or "strongly agree" that the treatment results were natural looking (99.4%), that they were satisfied with how the product enabled them to correct the temple hollowing (97.7%), and that they liked how the subject looked after treatment (99.4%).

Change from baseline in subject satisfaction using the FACE-Q™ Satisfaction with Temples questionnaire and proportion of subjects in each response category for each of the individual questions, at 3, 6, 9, 12 and 18 months after baseline for the treatment group and at 3 months after baseline for the no-treatment control group: Based on the change from baseline in the FACE-Q™ Satisfaction with Temples Questionnaire Rasch-transformed total scores, subjects in the treatment group were satisfied with their temples at all post-baseline visits from Month 3 through Month 18 (mean increase from baseline range: 52.1 to 58.6), whereas subjects randomized to no treatment at baseline had a mean change from baseline at Month 3 of -1.9.

FACE-Q™ Satisfaction with Outcome Rasch-transformed total scores as well as proportion of subjects in each response category for each of the individual questions at 3, 6, 9, 12 and 18 months after baseline for the treatment group: Based on the FACE-Q™ Satisfaction with Outcome Questionnaire Rasch-transformed total scores, subjects in the treatment group were satisfied with their treatment outcome at all visits from Month 3 through Month 18 (mean range: 74.1 to 79.6).

Responder rate based on the Independent Photographic Reviewer's (IPR) assessment using random pairings of baseline and post-baseline photographs from physical visits at 3 months after baseline for the treatment and no-treatment groups: The responder rate for the treatment and no-treatment groups was **74.4**% and **24.4**%, respectively.

Time in hours until the subject felt comfortable returning to social engagement after treatment, based on a follow-up question via telephone at 72 hours after treatment for the treatment group: The median time to feeling comfortable returning to social engagement was 5.4 hours after initial treatment and 3.6 hours after optional touch-up treatment.

Subgroup Analyses

Safety: The percentage of subjects who experienced an AE related to study product or injection procedure was compared between different subgroups. Due to relatively small sample sizes across the study sites (N=6 to 23), no meaningful conclusions could be made by comparing sites. The percentage of subjects who experienced an AE related to study product or injection procedure was 15.7% (16/102) among subjects whose subdermal injection tool was needle, 3.7% (4/109) among those whose subdermal injection tool was cannula, and 10.0% (1/10) for subjects injected with both needle and cannula subdermally. For the 10 subjects who were injected with a different injection tool at touch-up compared with initial treatment in the subdermal layer, no safety concerns were observed. The percentage of subjects who experienced an AE related to study product or injection procedure was 13.2% (20/152) in subjects with FST I-III and 1.4% (1/69) in subjects with FST IV-VI. Due to the small number of Black/African American subjects (N=17) compared with White subjects (N=193) in this analysis, no meaningful conclusions by race could be made. All subjects who experienced related AEs were not Hispanic or Latino. Due to the small number of subjects whose sex at birth was male (N=12) compared with subjects whose sex at birth was female (N=209), no meaningful conclusions by sex at birth could be made. The percentage of subjects who experienced an AE related to study product or injection procedure was similar between subjects whose age was lower than or equal to the median age (10.4% [13/125]) and those whose age was higher than the median age (8.3% [8/96]). The percentage was higher among subjects whose injection volume was higher than the median injection volume (15.1% [16/106]) than among those whose injection volume was lower than or equal to the median injection volume (4.3% [5/115]).

Effectiveness: The statistical testing performed on the primary effectiveness endpoint was repeated on the following subgroups: study site, race, ethnicity, sex at birth, age category, FST category and injection volume category. In addition, a subgroup analysis was conducted to compare the responder rates at 3 months after baseline between subjects who received the 1-month touch-up treatment versus those who did not receive the 1-month touch-up treatment.

The treatment difference in Month 3 responder rate based on the GTVDS (i.e., primary effectiveness endpoint) favored *Restylane Contour* treatment, with either needle or cannula injection tool used for subdermal injections, over no treatment for all subgroups. Statistical significance was reached for all subgroups except Black/African American race, partially due to the small sample size for this subgroup (N=20) in this analysis.

Due to relatively small sample sizes across the study sites (N=6 to 23), no meaningful conclusions could be made by comparing sites. However, most study sites showed a treatment effect that was consistent with that observed for the primary analysis.

A high GTVDS responder rate was observed at Month 3 in the *Restylane Contour* group for subjects whose median total injection volume prior to Month 3 was ≤2.5 mL via needle injection (88.9%) or via cannula injection (98.1%) and for subjects whose median total injection volume prior to Month 3 was >2.5 mL via needle injection (86.5%) or via cannula injection (95.1%).

In the *Restylane Contour* group, no difference in responder rate at Month 3 was observed between subjects who received the 1-month touch-up treatment and those who did not receive the 1-month

touch-up treatment. The responder rate at Month 3 for subjects who received the 1-month touch-up treatment via needle was 87.5% versus 88.2% for subjects who did not receive touch-up treatment (p=0.671). The responder rate at Month 3 for subjects who received the 1-month touch-up treatment via cannula was 97.2% versus 90.9% for subjects who did not receive touch-up treatment (p=0.312).

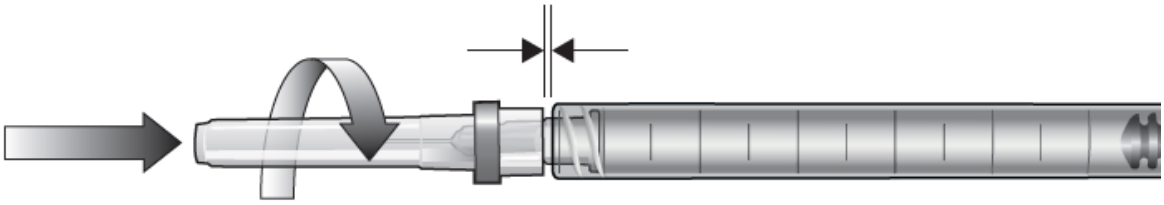
8 INSTRUCTIONS FOR USE

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. When injecting Restylane Contour for correction of temple hollowing the co-packed TSK 27G ½" UTW needle) and/or cannula (TSK STERiGLIDE 25G x 1½") can be used.

2. Educational resources are available through gainconnect.com., which provides training on the anatomy of the treatment area, effective patient assessment, and appropriate injection techniques. Health care professionals may contact Galderma for educational and training resources specific to the temple indication.

3. 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.

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

5. 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

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. *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.

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

14. 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.

15. For cheeks and midface 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.

16. For temple treatment it is recommended that the dose should not exceed 3 mL per temple and

treatment session. The recommended maximum injected volume per subject and treatment (touch-up volume included) is 12 mL.

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

18. 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.[2]

19. After each injection, treated areas 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.

20. 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.

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

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

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.

[2] 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

9 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.

10 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.

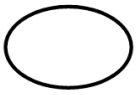
Do not use if the package is damaged or if expiry date or lot number is missing or illegible. Immediately return the damaged product to Galderma Laboratories, L.P.

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
	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. 5.2.11	Medical Devices – Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Single sterile barrier system	Indicates a single sterile barrier system
	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 that caution is necessary when operating the device or control close to where the symbol is placed, or that the current situation needs operator awareness or operator action in order to avoid undesirable consequences.

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 Regulation (EU) 2017/745, Article 20	CE marking of conformity	CE marking	Signifies European technical conformity. 0123 is the notified body number for the needles.
	Inmetro Ordinance No. 84, February 10, 2021 and Inmetro Ordinance No. 385, September 17, 2021	Hypodermic needles for Inmetro conformity	INMETRO mark	Brazilian technical requirements for conformity of hypodermic needles for single usage. TÜV Rheinland is the name of the certification body.

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